Received:
16 November 2016

Revised:
25 January 2017

Accepted:
6 March 2017

<https://doi.org/10.1259/bjr.20160873>

Cite this article as:

Christou A, Ghiatas A, Priovolos D, Veliou K, Bougias H. Accuracy of diffusion kurtosis imaging in characterization of breast lesions. *Br J Radiol* 2017; **90**: 20160873.

FULL PAPER

Accuracy of diffusion kurtosis imaging in characterization of breast lesions

¹ALEXANDRA CHRISTOU, MD, ²ABRAHAM GHIATAS, MD, PhD, ³DIMITRIOS PRIOVOLOS, ⁴KONSTANTIA VELIOU, MD and ⁵HARALAMBOS BOUGIAS

¹Department of Medical Imaging, Doncaster and Bassetlaw Hospitals NHS Foundation Trust, Doncaster, UK

²Department of Medical Imaging, Director and owner of Global Teleradiology Services, Athens, Greece

³Department of Medical Imaging, at Iaso Maternity Hospital, Athens, Greece

⁴Department of Medical Imaging, at Chatzikosta General Hospital of Ioannina, Ioannina, Greece

⁵Department of Medical Imaging, University Hospital of Ioannina, Ioannina, Greece

Address correspondence to: Dr Alexandra Christou

E-mail: alexandrachristou@gmail.com

Objective: The aim of this study was to evaluate the accuracy of diffusion kurtosis in the characterization and differentiation of breast lesions.

Methods: 49 females with 53 breast lesions underwent breast MRI. The MRI magnetic field is 1.5 T, and the protocol is standard MRI sequences, dynamic sequences pre- and post-contrast agent administration and diffusion images. Diffusion kurtosis imaging (DKI) was applied as part of our standard breast MRI protocol. Two experienced radiologists on breast MRI, blinded to the final diagnosis, reviewed the parametric maps and placed a volume of interest on all slices including each lesion. Kurtosis [K apparent (K_{app})] and corrected apparent diffusion coefficient [D apparent (D_{app})] median values were then calculated from the whole-lesion histogram analysis. Receiver-operating characteristic analysis was used to determine the most effective cut-off values for the differentiation between benign and malignant pathologies. Histological analysis of the breast lesions was performed, and further comparative analysis of the

results was performed to investigate the accuracy of the method.

Results: Benign ($n = 19$) and malignant lesions ($n = 34$) had mean diameters of 20.8 mm (10.1–31.5 mm) and 26.4 mm (10.5–42.3 mm), respectively. The lowest and the highest kurtosis values (K_{app}) of malignant lesions were significantly higher than those of benign lesions. A cut-off of 0.71 provided specificity of 93.7% and sensitivity 97.1%, and the area under the curve (AUC) was 0.976 ($p < 0.0001$). The lowest and the highest D_{app} values of malignant lesions were lower than those of benign lesions. A cut-off value of $1.57 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ provided specificity of 93.7% and sensitivity of 91.2% with AUC of 0.949 ($p < 0.0001$).

Conclusion: DKI is an accurate additional tool for the characterization and differentiation of breast lesions with high K_{app} and D_{app} sensitivity and specificity rates.

Advances in knowledge: DKI is able to distinguish benign from malignant breast pathologies. DKI increases the specificity of breast MRI.

INTRODUCTION

Breast MRI is a well-established method for the evaluation of breast pathologies. It is widely used as a supplementary modality to mammography and ultrasound, mainly for local staging of recently diagnosed breast cancers and recently as a screening tool for patients at a high risk.^{1–6}

Dynamic contrast-enhanced (DCE)-MRI using gadolinium contrast material offers high sensitivity in detecting breast lesions, and thus it has been widely used in the past decades to locate breast cancers, to show the extent of the disease and to demonstrate small multifocal breast tumours. The sensitivity ranges in literature between 89% and 100%. However, it suffers from low specificity in characterization

and differentiation of breast lesions, as certain types of benign breast lesions enhance in a way similar to malignant cancers (reportedly around 75%).^{7–11}

The rationale behind contrast enhancement of breast tumours is probably the proliferating activity of the hyperplastic or neoplastic parenchymal cells, in addition to the vessel density associated with tumour angiogenesis. Therefore, it is not always possible to distinguish benign from malignant lesions on the basis of only contrast enhancement patterns and morphological features.^{12,13}

Diffusion-weighted imaging provides a non-contrast MRI sequence and has a high sensitivity in the detection of changes

in the microscopic cellular local biologic environment.^{14–19} In the Gaussian diffusion model, it is assumed that water molecules diffuse uniformly, as in a bucket of water. However, the real tissue contains complex cellular structures, and thus the water molecules within an imaging voxel (typically $2 \times 2 \times 2$ mm) diffuse through a highly heterogeneous environment, leading to deviation from the Gaussian distribution.

Diffusion kurtosis imaging (DKI) model includes an excess kurtosis term (K) to capture this deviation from the Gaussian distribution. Higher kurtosis values imply more impediments to normal diffusion and greater complexity within the imaged system.²⁰ It is believed that physiologic and morphologic alterations associated with breast tumour tissues may result in changes in the DKI parameters; thus, DKI providing information and indications of microstructural changes may be a valuable additional technique to conventional diffusion techniques for the characterization of the breast tumours.^{21,22}

Our study aimed to show the potential role of DKI in the characterization and differentiation of the breast lesions.

METHODS AND MATERIALS

Subjects

We prospectively enrolled 49 females with mean age 54 years (37–71 years) with 53 breast lesions between December 2014 and April 2015.

Our institutional MRI unit is 1.5 T unit equipped with a four-channel dedicated double breast coil. All females included in the study were examined in the same MRI unit. DKI was applied as a part of our standard breast MRI protocol in combination with DCE-MRI in all cases.

Whenever appropriate, we performed the scan during the second week of the menstrual cycle for the pre-menopausal females.

The main referral indications were pre-operative local staging of the tumour and clarification of suspicious findings on conventional imaging (mammography and ultrasound) or clinical examination.

Informed consent was obtained. The research was initially approved by the director of the breast imaging department and our institution. Ethical approval was also obtained.

Imaging protocol

Patients were placed in prone position.

The conventional imaging protocol included an axial fat-suppressed T_2 weighted turbo spin-echo sequence [repetition time (TR)/echo time (TE): 4000 ms/97 ms; matrix: 320×320 pixels; slice thickness: 4 mm]; a three-dimensional T_1 weighted non-fat-suppressed sequence (TR/TE: 8.6 ms/4.6 ms; matrix: 320×320 pixels; slice thickness: 1.5 mm); and a T_1 weighted fat-suppressed DCE sequence with one pre-contrast and six post-contrast acquisitions in the axial plane (dynamic scan duration: 1 min, slice thickness: 1.5 mm).

DKI was obtained before dynamic images. DKI is a diffusion-weighted (DW) image. A two-dimensional spin-echo echoplanar imaging sequence (TR/TE: 5800 ms/80 ms; matrix: 192×192 pixels; slice thickness: 4 mm; distance factor: 0%; acquisition voxel size: $1.7 \times 1.7 \times 4$ mm; band width: 1370 Hz/pixel, spectral attenuated inversion recovery fat suppression) in the axial plane was used. In order to maintain a sufficient signal-to-noise (SNR) ratio, five averages were chosen for all b -values. The acquisition time was 3.40 min. Diffusion gradients in three orthogonal directions with b -values of 0, 400 s mm^{-2} , 800 s mm^{-2} , 1100 s mm^{-2} and 1300 s mm^{-2} were applied.

Image analysis

All breast MR images were interpreted on a workstation by two experienced radiologists with 15 and 5 years' experience, respectively (AG and AC). The radiologists reviewed the images individually, and when there was disagreement consensus was reached. The operator was blinded to the final diagnosis.

Subtracted and T_2 weighted images were used primarily to identify and morphologically characterize the lesions. DCE breast MRI was used to visualize the initial enhancement and to further evaluate the enhancement of the pathologies.

The characterization of the breast pathologies and the final report was based on the morphological and kinetic features of breast lesions according to the Breast Imaging Reporting and Data System lexicon.

The post-processing analysis was performed using image analysis of a free software named FireVoxel; <https://files.nyu.edu/hr18/public/projects.html>. This software allowed placement of three-dimensional volumes of interest encompassing multiple slices. The diffusion-weighted imaging sequence chosen for volume of interest drawing was the b -value image series where the tumour was best visualized; regions of interest were then pasted to the K apparent (K_{app}) and D apparent (D_{app}) maps. DW images were co-registered to b_0 image for motion correction, and then the parametric maps were calculated pixel by pixel according the formula.¹ The median K_{app} and D_{app} values were then calculated from the histogram from the whole lesion (Figures 1–4).

The associated equation for the DKI is the following:

$$S = S_0 \times \exp\left(-b \times D + 1/6 \times b^2 \times D_{\text{app}}^2 \times K_{\text{app}}\right), \quad (1)$$

where D_{app} and K_{app} are the corrected apparent diffusion coefficient and kurtosis, respectively, $S(b)$ is the DW signal with a certain b -value and S_0 is the non-DW signal.

The evaluation of breast lesions was then made using the diffusion kurtosis parametric maps (K_{app} and D_{app}).

The time required for the image analysis was estimated as <2 min.

In order to evaluate whether the SNR at the images with a b -value of 1300 s mm^{-2} was sufficient, SNR b_{1300} was calculated

Figure 1. Invasive ductal carcinoma in the right breast in a 55-year-old female with a lesion in the right breast: (a) the axial three-dimensional (3D) T_1 weighted fat-saturated image reveals an irregular lobulated and heterogeneous mass. (b) The axial 3D T_1 weighted fat-saturated image with gadolinium shows a centrally low signal mass, consistent with the necrotic part of the tumour with peripheral rim enhancement. (c) Subtracted image. (d) Maximum intensity projection image. Department of radiology, IASO Hospital.

by using the formula: $\text{SNR}_{\text{tumour}} = \text{SI}_{\text{tumour}} / \text{standard deviation of background air}$, where SI = signal intensity.

Statistical analysis

The K_{app} and D_{app} median values between benign and malignant lesions were compared by the Mann–Whitney U test (level of significance set at 0.05).

Receiver-operating characteristic (ROC) analysis was used to determine the most effective cut-off values for the differentiation between benign and malignant pathologies. All analyses were

performed by the use of MedCalc v. 15.0 software (Ostend, Belgium).

RESULTS

Histological analysis of breast lesions was used as gold standard in 51 cases from the total of 53 cases, and 2 cases were followed up for a time period exceeding 2 years and found to remain stable.

From the 53 breast lesions, malignancy was diagnosed in 34 cases through the course of surgery and histological verification.

Figure 2. Invasive ductal carcinoma in the right breast: (e) b_0 image of diffusion-weighted imaging sequence; (f) b_{1300} shows the lesion as a high signal mass; (g) corresponding K apparent (K_{app}) map and (h) D apparent (D_{app}) map. Department of radiology, IASO Hospital.

Figure 3. Fibroadenoma in the left breast in a 45-year-old female with a lesion in the left breast: (a) the axial three-dimensional (3D) T_1 weighted fat-saturated image reveals an isointense well-circumscribed ovoid mass. (b) The axial 3D T_1 weighted fat-saturated image with gadolinium shows a circumscribed mass with homogeneous enhancement. (c) Subtracted image. (d) Maximum intensity projection image. Department of radiology, IASO Hospital.

From the remaining 19 lesions, 17 cases were histologically proved to be benign, while 2 of them did not comprise tissue sampling, but instead were followed up for their stability for 2 years.

Malignant lesions were mainly invasive ductal carcinomas,¹⁹ invasive lobular carcinomas¹³ and ductal carcinoma *in situ*,² and benign lesions were mainly fibroadenomas,⁹ fibrocystic changes and sclerosis adenosis with no atypia⁶ and papillomas with no atypia.²

The mean size of benign lesions was 20.8 mm [(range 10.1–31.5 mm) and that of malignant lesions was 26.4 mm (range 10.5–42.3 mm)]. The minimum appropriate size for performing multislice histogram analysis is twice the image slice thickness of 4 mm. Lesions of smaller size were not included in this study.

Biopsy of all suspicious lesions was performed after the MRI in all cases included in this study in order to avoid subsequent tissue heterogeneity that could possibly alter the results. Images with susceptibility and distortion artefacts were also excluded.

The lowest and highest K_{app} values of benign lesions were significantly lower than those of malignant lesions (Figure 5). We found that a cut-off value of 0.71 provided specificity of 93.7% and sensitivity of 97.1% ($p < 0.0001$). The area under the curve (AUC) was 0.976.

The lowest and highest D_{app} values of the malignant lesions were lower than those of benign lesions (Figure 6). We found a cut-off of $1.57 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ provided specificity of 93.7% and sensitivity of 91.2% ($p < 0.0001$). The AUC is 0.949 (Tables 1 and 2).

Figure 4. Fibroadenoma in the left breast: (e) b_0 image of diffusion-weighted imaging sequence; (f) b_{1300} shows the lesion as a high signal mass; (g) corresponding K apparent (K_{app}) map and (h) D apparent (D_{app}) map. Department of radiology, IASO Hospital.

Figure 5. The graph shows that the lowest and the highest K apparent values of benign lesions (0.15–0.99) are significantly lower than those of malignant lesions (0.61–1.85).

The corresponding ROC curves of K_{app} and D_{app} are illustrated in Figure 7.

DISCUSSION

An accurate diagnosis of breast cancer is essential for patient treatment, and it has always been a challenge for radiologists using conventional breast imaging, especially in dense fibroglandular breast tissues.²³

Breast MRI has been increasingly used in the evaluation of patients with suspicious breast lesions owing to its non-invasive

nature and excellent soft-tissue contrast as compared with other diagnostic imaging modalities.^{24–27}

Diffusion MRI is a non-invasive MRI technique that allows *in vivo* characterization and quantification of the molecular water diffusion in tissues by measuring a series of functional parameters that reveal the water diffusion in a microscopic environment, which can serve to characterize the pathological conditions of breast lesions.^{21,28,29} The measurement of the water diffusivity has been shown to help distinguish between normal fibroglandular breast tissues and benign or malignant lesions.^{30–36}

Figure 6. The graph shows that the lowest and the highest D apparent (D_{app}) values of malignant lesions ($0.81\text{--}2.14 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) are lower than those of benign lesions ($1.40\text{--}2.44 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$).

Table 1. K apparent (K_{app}) and D apparent (D_{app}) parameters

Lesion type	K_{app}	D_{app}
Benign lesions ($n = 19$)	0.6 (0.15–0.99)	1.87 (1.40–2.44) ^a
Malignant lesions ($n = 34$)	1.13 (0.61–1.85)	1.32 (0.81–2.14) ^a
p -value (Mann–Whitney U -test)	<0.0001	<0.0001

^a $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

However, benign and malignant lesions cannot always be distinguished from each other based only on their diffusion rate values, because of a wide overlap between them; so, advanced diffusion MRI techniques are needed for better characterization and differentiation of the breast lesions.

Conventional diffusion MRI follows a monoexponential Gaussian diffusion of water protons. However, in fact, the complex biological tissues with several barriers and compartmentalization restrict the free displacement of water molecules resulting in a non-Gaussian biexponential distribution of the water molecules.^{20,37–40}

It has been shown that the behaviour of DW signal with higher b -values, whether in benign or malignant lesions, is better characterized by the DKI model rather than the monoexponential Gaussian model (Figure 8).

It has also been suggested that as tumour cells proliferate and cellularity increases, water molecule motion becomes more restricted mainly owing to a decrease of the extracellular space. This may reflect microstructural differences between benign and malignant tissues.^{18,19}

Moreover, a moderate correlation between water diffusivity and tumour cellularity has been previously illustrated. Changes in DKI parameters may reflect physiologic and morphologic alterations associated with breast tumour tissues.¹⁹

Kurtosis is zero for a perfect Gaussian diffusion, and a large kurtosis value indicates that diffusion considerably deviates from a perfect Gaussian behaviour. Diffusivity is a corrected apparent diffusion coefficient that removes this non-Gaussian bias.

Table 2. Comparison of the K apparent (K_{app}) and D apparent (D_{app}) receiver-operating characteristic (ROC) curves in differentiation of benign and malignant breast lesions

ROC analysis parameters	K_{app}	D_{app}
Cut-off value	0.71	1.57×10^{-3a}
Sensitivity	0.971	0.912
Specificity	0.937	0.937
AUC	0.976	0.949

AUC, area under the curve.

^a $\ln \text{ mm}^2 \text{ s}^{-1}$.

Figure 7. Corresponding receiver-operating characteristic curves for K apparent (K_{app}) and D apparent (D_{app}).

In our study, both K_{app} and D_{app} showed their ability to characterize and differentiate benign from malignant tumours with excellent specificity and sensitivity. The benign lesions in our population displayed a tendency of significantly lower K_{app} values and significantly higher D_{app} values than the malignant tumours. According to the ROC analysis, a cut-off value of 0.71 for the K_{app} provided specificity of 93.7% and sensitivity of 97.1% with AUC of 0.976, and for the D_{app} a cut-off of $1.57 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ provided specificity of 93.7% and sensitivity of 91.2% with AUC of 0.949.

Figure 8. Comparison of diffusion-weighted imaging (DWI) and diffusion kurtosis imaging (DKI) fitting models: for the DWI (black line), the logarithm of diffusion-weighted signal intensity as a function of the b -value is fit, for small b -values, to a straight line. For the DKI (black line with measured data [circles]), the logarithm deviates from the linear diffusion function and is well fit for higher b -values (>1000). Image taken from the article Diffusion Kurtosis Imaging: An Emerging Technique for Evaluating the Microstructural Environment of the Brain.⁴⁰

It is, however, important to point out the parameter of lesion size. All lesions we studied—both benign and malignant—were at least 8 mm thick (*i.e.* twice the image slice thickness of 4 mm), which is the minimum appropriate size to perform multislice processing, as it is likely that for small lesions (*e.g.* <8 mm diameter), there were too few pixels/DKI values to get meaningful histogram (statistical) metrics from when our voxel size is $1.7 \times 1.7 \times 4$ mm.

We applied multiple *b*-values with a maximum of 1300 s mm^{-2} , coupled with the use of a parallel imaging factor of 2 and 5 averages, resulting in images with acceptable SNR at 1.5 T. In malignant and benign regions of interest, mean SNR values at the image series with a *b*-value of 1300 s mm^{-2} were 13 and 9, respectively.

Recent studies have shown that DKI offers a method to evaluate the non-Gaussian diffusion behaviour in complex biological tissues in various brain diseases⁴⁰ and in breast cancer.⁴¹ It has also been shown that in patients with invasive breast cancer, kurtosis was positively correlated with the tumour histological grade.⁴¹

The results of our study support the previously reported studies showing the potential utility of DKI technique in differentiation of breast lesions, increasing the overall sensitivity and mainly the specificity of breast MRI technique. It is also important to point out that DKI does not require contrast administration, and thus it potentially could play an important role in patients with kidney failure.

The limitations of this study pertain mainly to the limited number of cases (53 breast lesions) and the lack of histological verification in a small portion of benign lesions (2 cases). Another limitation is the selection bias deriving from lesion size. As explained earlier, all the lesions we analyzed were >10 mm.

In conclusion, DKI is an alternative diffusion technique based on the non-Gaussian biexponential diffusion model providing valuable information of the breast lesion behaviour resulting in accurate characterization and differentiation between the benign and the malignant tumours, increasing the diagnostic efficacy of the conventional breast MRI technique. Further studies on a larger scale are required to investigate more meticulously the diagnostic value of this method.

REFERENCES

- Bloom S, Morrow M. A clinical oncologic perspective on breast magnetic resonance imaging. *Magn Reson Imaging Clin N Am* 2010; **18**: 277–94.
- DeMartini W, Lehman C. A review of current evidence-based clinical applications for breast magnetic resonance imaging. *Top Magn Reson Imaging* 2008; **19**: 143–50.
- Berg WA, Gutierrez L, Ness-Aiver MS, Carter WB, Bhargavan M, Lewis RS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in pre-operative assessment of breast cancer. *Radiology* 2004; **233**: 830–49. doi: <https://doi.org/10.1148/radiol.2333031484>
- Morakkabati N, Leutner CC, Schmiedel A, Schild HH, Kuhl CK. Breast MR imaging during or soon after radiation therapy. *Radiology* 2003; **229**: 893–901. doi: <https://doi.org/10.1148/radiol.2293020167>
- Ikeda DM, Baker DR, Daniel BL. Magnetic resonance imaging of breast cancer: clinical indications and breast MRI reporting system. *J Magn Reson Imaging* 2000; **12**: 975–83.
- Pereira FP, Martins G, Carvalhaes de Oliveira RV. Diffusion magnetic resonance imaging of the breast. *Magn Reson Imaging Clin N Am* 2011; **19**: 95–110. doi: <https://doi.org/10.1016/j.mric.2010.09.001>
- Medeiros LR, Duarte CS, Rosa DD, Edelweiss MI, Edelweiss M, Silva FR, et al. Accuracy of magnetic resonance in suspicious breast lesions: a systematic quantitative review and meta-analysis. *Breast Cancer Res Treat* 2011; **126**: 273–85. doi: <https://doi.org/10.1007/s10549-010-1326-9>
- Kul S, Eyuboglu I, Cansu A, Alhan E. Diagnostic efficacy of the diffusion weighted imaging in the characterization of different types of breast lesions. *J Magn Reson Imaging* 2014; **40**: 1158–64. doi: <https://doi.org/10.1002/jmri.24491>
- Peters NH, Borel Rinkes IH, Zuithoff NP, Mali WP, Moons KG, Peeters PH. Meta-analysis of MR imaging in the diagnosis of breast lesions. *Radiology* 2008; **246**: 116–24. doi: <https://doi.org/10.1148/radiol.2461061298>
- Brinck U, Fischer U, Korabiowska M, Jutrowski M, Schauer A. The variability of fibroadenoma in contrast-enhanced dynamic MR mammography. *AJR Am J Roentgenol* 1997; **168**: 1331–4. doi: <https://doi.org/10.2214/ajr.168.5.9129437>
- Hochman MG, Orel SG, Powell CM, Schnall MD, Reynolds CA, White LN. Fibroadenomas: MR imaging appearances with radiologic-histopathologic correlation. *Radiology* 1997; **204**: 123–9. doi: <https://doi.org/10.1148/radiology.204.1.9205233>
- Bone B, Wiberg MK, Parrado C, Falkmer U, Aspelin P, Gad A. Mechanism of contrast enhancement in breast lesions at MR imaging. *Acta Radiol* 1998; **39**: 494–500. doi: <https://doi.org/10.1080/02841859809172214>
- Stomper PC, Winston JS, Herman S, Klippenstein DL, Arredondo MA. Angiogenesis and dynamic MR imaging gadolinium enhancement of malignant and benign breast lesions. *Breast Cancer Res Treat* 1997; **45**: 39–46.
- Martincich L, Deantoni V, Bertotto I, Redana S, Kubatzki F, Sarotto I, et al. Correlations between diffusion-weighted imaging and breast cancer biomarkers. *Eur Radiol* 2012; **22**: 1519–28. doi: <https://doi.org/10.1007/s00330-012-2403-8>
- Rahbar H, Partridge SC, Eby PR. Characterization of ductal carcinoma in situ on diffusion weighted breast MRI. *Eur Radiol* 2011; **21**: 2011–19. doi: <https://doi.org/10.1007/s00330-011-2140-4>
- Marini C, Iacconi C, Giannelli M, Cilotti A, Moretti M, Bartolozzi C. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. *Eur Radiol* 2007; **17**: 2646–55. doi: <https://doi.org/10.1007/s00330-007-0621-2>
- Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. *J Magn Reson Imaging* 2002; **16**: 172–8. doi: <https://doi.org/10.1002/jmri.10140>
- Rubesova E, Grell AS, De Maertelaer V, Metens T, Chao SL, Lemort M, et al. Quantitative diffusion imaging in breast cancer: a clinical prospective study. *J Magn*

- Reson Imaging* 2006; **24**: 319–24. doi: <https://doi.org/10.1002/jmri.20643>
19. Kul S, Cansu A, Alhan E, Dinc H, Gunes G, Reis A. Contribution of diffusion-weighted imaging to dynamic contrast-enhanced MRI in the characterization of breast tumors. *AJR Am J Roentgenol* 2011; **196**: 210–17. doi: <https://doi.org/10.2214/AJR.10.4258>
 20. Jensen JH, Helpert JA, Ramani A, Lu H, Kaczynski K. Diffusional kurtosis imaging: the quantification of non-Gaussian water diffusion by means of magnetic resonance imaging. *Magn Reson Med* 2005; **53**: 1432–40. doi: <https://doi.org/10.1002/mrm.20508>
 21. Sinha S, Sinha U. Functional magnetic resonance of human breast tumors: diffusion and perfusion imaging. *Ann N Y Acad Sci* 2002; **980**: 95–115.
 22. Wu D, Li G, Zhang J, Chang S, Hu J, Dai Y. Characterization of breast tumors using diffusion kurtosis imaging (DKI). *PLoS One* 2014; **9**: e113240. doi: <https://doi.org/10.1371/journal.pone.0113240>
 23. Kacel GM, Liu P, Debatin JF, Garzoli E, Caduff RF, Krestin GP. Detection of breast cancer with conventional mammography and contrast-enhanced MR imaging. *Eur Radiol* 1998; **8**: 194–200. doi: <https://doi.org/10.1007/s003300050362>
 24. Rankin SC. MRI of the breast. *Br J Radiol* 2000; **73**: 806–18. doi: <https://doi.org/10.1259/bjr.73.872.11026854>
 25. Kneeshaw PJ, Turnbull LW, Drew PJ. Current applications and future direction of MR mammography. *Br J Cancer* 2003; **88**: 4–10. doi: <https://doi.org/10.1038/sj.bjc.6600713>
 26. Sinha S, Sinha U. Recent advances in breast MRI and MRS. *NMR Biomed* 2009; **22**: 3–16. doi: <https://doi.org/10.1002/nbm.1270>
 27. Petralia G, Bonello L, Priolo F, Summers P, Bellomi M. Breast MR with special focus on DW-MRI and DCE-MRI. *Cancer Imaging* 2011; **11**: 76–90. doi: <https://doi.org/10.1102/1470-7330.2011.0014>
 28. Wesbey GE, Moseley ME, Ehman RL. Translational molecular self-diffusion in magnetic resonance imaging. II. Measurement of the self-diffusion coefficient. *Invest Radiol* 1984; **19**: 491–8.
 29. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; **161**: 401–7. doi: <https://doi.org/10.1148/radiology.161.2.3763909>
 30. Sinha S, Lucas-Quesada FA, Sinha U, DeBruhl N, Bassett LW. *In vivo* diffusion-weighted MRI of the breast: potential for lesion characterization. *J Magn Reson Imaging* 2002; **15**: 693–704. doi: <https://doi.org/10.1002/jmri.10116>
 31. 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**: 644–9.
 32. Lo GG, Ai V, Chan JK, Li KW, Cheung PS, Wong TT, et al. Diffusion-weighted magnetic resonance imaging of breast lesions: first experiences at 3 T. *J Comput Assist Tomogr* 2009; **33**: 63–9.
 33. 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 tumour aggressiveness. *Clin Radiol* 2010; **65**: 1005–12.
 34. El Khouli RH, Jacobs MA, Mezban SD, Huang P, Kamel IR. Diffusion-weighted imaging improves the diagnostic accuracy of conventional 3.0-T breast MR imaging. *Radiology* 2010; **256**: 64–73. doi: <https://doi.org/10.1148/radiol.10091367>
 35. Partridge SC, Demartini WB, Kurland BF, Eby PR, White SW. Differential diagnosis of mammographically and clinically occult breast lesions on diffusion-weighted MRI. *J Magn Reson Imaging* 2010; **31**: 562–70. doi: <https://doi.org/10.1002/jmri.22078>
 36. Le Bihan D. Molecular diffusion, tissue microdynamics and microstructure. *NMR Biomed* 1995; **8**: 375–86. doi: <https://doi.org/10.1002/nbm.1940080711>
 37. Alexander DC, Barker GJ, Arridge SR. Detection and modeling of non-Gaussian apparent diffusion coefficient profiles in human brain data. *Magn Reson Med* 2002; **48**: 331–40. doi: <https://doi.org/10.1002/mrm.10209>
 38. Liu C, Bammer R, Acar B, Moseley ME. Characterizing non-Gaussian diffusion by using generalized diffusion tensors. *Magn Reson Med* 2004; **51**: 924–37. doi: <https://doi.org/10.1002/mrm.20071>
 39. Assaf Y, Freidlin RZ, Rohde GK, Basser PJ. New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. *Magn Reson Med* 2004; **52**: 965–78. doi: <https://doi.org/10.1002/mrm.20274>
 40. Steven AJ, Zhuo J, Melhem ER. Diffusion kurtosis imaging an emerging technique for evaluating the microstructural environment of the brain. *AJR Am J Roentgenol* 2014; **202**: W26–33.
 41. Sun K, Chen X, Chai W, Fei X, Fu C, Yan X, et al. Breast cancer: diffusion kurtosis MR imaging-diagnostic accuracy and correlation with clinical-pathologic factors. *Radiology* 2015; **277**: 46–55. doi: <https://doi.org/10.1148/radiol.15141625>