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**REVIEW**

- 1081** Diffusion weighted magnetic resonance imaging of liver: Principles, clinical applications and recent updates
Bhangle AS, Baliyan V, Kordbacheh H, Guimaraes AR, Kambadakone AR

MINIREVIEWS

- 1092** Risk of liver disease in methotrexate treated patients
Conway R, Carey JJ

ORIGINAL ARTICLE**Case Control Study**

- 1101** Regional differences in genetic susceptibility to non-alcoholic liver disease in two distinct Indian ethnicities
Bale G, Steffie AU, Ravi Kanth VV, Rao PN, Sharma M, Sasikala M, Reddy DN

Retrospective Study

- 1108** Conjugated hyperbilirubinemia presenting in first fourteen days in term neonates
Chiou FK, Ong C, Phua KB, Chedid F, Kader A

ABOUT COVER

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Diffusion weighted magnetic resonance imaging of liver: Principles, clinical applications and recent updates

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Abstract

Diffusion-weighted imaging (DWI), a functional imaging technique exploiting the Brownian motion of water molecules, is increasingly shown to have value in various oncological and non-oncological applications. Factors such as the ease of acquisition and ability to obtain functional information in the absence of intravenous contrast, especially in patients with abnormal renal function, have contributed to the growing interest in exploring clinical applications of DWI. In the liver, DWI demonstrates a gamut of clinical applications ranging from detecting focal liver lesions to monitoring response in patients undergoing serial follow-up after loco-regional and systemic therapies. DWI is also being applied in the evaluation of diffuse liver diseases such as non-alcoholic fatty liver disease, hepatic fibrosis and cirrhosis. In this review, we intend to review the basic principles, technique, current clinical applications and future trends of DW-MRI in the liver.

Key words: Liver imaging; Diffusion weighted imaging; Magnetic resonance imaging; Focal liver lesion; Diffuse liver disease; Response assessment

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Core tip: This article reviews the current role of diffusion weighted imaging for various oncological and non-oncological applications in the liver.

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INTRODUCTION

Diffusion-weighted imaging (DWI) is a functional imaging technique, allowing qualitative and quantitative assessment of the diffusion properties of various types of tissues^[1,2]. Numerous studies over the past decade have validated the role of DWI in oncologic and non-oncologic applications in the body^[1,3-6]. Multiphase contrast enhanced MRI is an established technique for evaluation of a wide spectrum of liver diseases including focal lesions and diffuse parenchymal abnormalities. DWI compliments routine MRI of the liver by providing both qualitative and quantitative assessment for both focal and diffuse hepatic parenchymal processes. Factors such as the ease of acquisition and ability to obtain functional information in the absence of intravenous contrast, especially in patients with abnormal renal function, have contributed to the growing interest in exploring clinical applications of DWI. DWI improves sensitivity in detection of focal lesions, helps differentiate benign from malignant focal hepatic lesions, and also permits evaluation of treatment response to systemic and loco-regional therapies in primary and secondary hepatic malignancies. This review article focused on the basic principles, technique, current clinical applications and recent updates in DWI of the liver.

DWI: BASIC PRINCIPLES AND TECHNIQUE

DWI exploits the regional differences in the motion of water molecules within the extracellular/extravascular compartment of tissues. In highly cellular tissues (*e.g.*, lymphoma, carcinoma and abscess), the compact nature of the extracellular space causes increased impediment to motion of water molecules and the resultant water diffusion in such tissues is said to be "restricted". On the contrary, in tissues that are necrotic or fluid filled (*e.g.*, cysts), there is unrestricted motion of water molecules and water diffusion in such tissues, which is said to be "free". Therefore, the diffusion properties in different tissues provide information on tissue cellularity and the integrity of cellular membranes^[1,2]. DWI is basically a modified T2 weighted sequence where the signal intensity depicts the tissue diffusion characteristics.

Single-shot spin-echo (SE) echo-planar technique is the most commonly utilized technique to acquire DW-MRI in combination with fat suppression^[7]. To obviate the effect of motion, it can be acquired either using breath-hold or free breathing sequences with multiple signal acquisitions (in combination with respiratory and/or cardiac triggering). Free breathing sequences provide improved signal to noise ratios (SNR), thinner image sections, and higher number of b-values obtainable compared to breath-hold sequences. However, these take longer time (3-6 min) to acquire than breath hold sequences to evaluate the liver compared to

free breathing EPI which takes (40-60 s)^[8]. The free breathing technique has been shown to have better reproducibility of ADC values than other acquisition techniques like breath-hold, respiratory-triggered (RT), and navigator-triggered DWI^[9,10]. Although cardiac motion also impacts quantitative ADC measurements, cardiac triggering is not routinely used in clinical practice^[11].

Intravoxel incoherent motion (IVIM) imaging is a technique that has been introduced to quantitatively study the effects of tissue perfusion on the signal acquired with DWI and it resolves DWI measurements into true molecular-based (*D*) and perfusion-related (*D**, *f*) diffusion^[12].

In patients with renal failure, gadolinium is contraindicated due to risk for developing nephrogenic systemic fibrosis (NSF)^[13]. These patients also have a risk of worsening renal failure with iodinated CT contrast. MRI without contrast is a reasonable option for these patients but non-contrast protocols do not have a diagnostic accuracy comparable to multi-phase contrast MRI. DWI does not require administration of intravenous contrast, and because of its performance in oncological applications in general, it has generated much interest recently. The diagnostic performance of DWI has been tested in metastatic liver disease and HCC, and the results were comparable to contrast MRI^[14-16].

CLINICAL APPLICATIONS IN LIVER

Imaging of focal liver lesions

Lesion detection: Multiphase contrast enhanced-MRI is currently the state-of-the-art imaging method for liver lesion detection and characterization. DWI at high b-values ($\geq b100$) provides a low background signal from normal liver parenchyma and thereby results in increased contrast between the background liver and lesions, enhancing the detection of focal liver lesions^[17]. DWI is especially useful in detection of small lesions around vessels and in the periphery of liver which can be challenging to detect on routine T2 weighted images^[18,19]. The DW-MRI can be particularly valuable in oncologic patients with compromised renal function who cannot get intravenous gadolinium based contrast agents^[14,16]. DWI adds value in oncologic patients (Table 1)^[15,20-22] by depicting more metastatic liver lesions when combined with multiphase contrast enhanced-MRI protocols, and improves reader confidence in lesion detection^[22-25]. DW-MRI alone is less sensitive than gadoxetic acid-enhanced MRI for detecting liver metastases, but increases the sensitivity of detection for liver metastases (90.6%-95.5%) when combined with multiphase contrast enhanced MRI^[25]. A major impact has been noted in the detection of metastases measuring ≤ 10 mm^[17,22,24-27] (Figure 1). DWI has been used in detection of metastatic liver lesions from colorectal, pancreatic and neuroendocrine primaries^[25,28,29].

DWI has also been found to be useful in detection

Table 1 Comparison of SSEPI diffusion-weighted magnetic resonance imaging *vs* conventional magnetic resonance sequences for detection of hepatic metastases^[15,20-22,27]

| Ref. | b value (s/mm ²) | Compared with (Seq) | Sensitivity of DWI <i>vs</i> other sequences | Accuracy of DWI <i>vs</i> other sequences | Advantages of DWI |
|--|------------------------------|--|---|---|--|
| Bruegel <i>et al</i> ^[27] | 50, 300, 600 | 5 different T2-TSE (Turbo Spin Echo) sequences | 0.88-0.91 compared to 0.45-0.62 | 0.91-0.92 compared to 0.47-0.67 | Better sensitivity and accuracy |
| Zech <i>et al</i> ^[21] | 50 | Fat suppressed T2WI | 83% <i>vs</i> 61% | - | Better image quality Fewer artifacts Better sensitivity |
| Hardie <i>et al</i> ^[15] | 0, 50, 500 | Gadolinium enhanced T1WI | 66.3% <i>vs</i> 73.5% | 88.2% and 88.2% for DW-MRI, 90.2% and 92.2% for CE MRI, respectively, for observers 1 and 2 | Not significantly different |
| Donati <i>et al</i> ^[20] | 0, 150, 500 | Combined (Gd-EOB-DTPA) enhanced MRI/DWI <i>vs</i> Gd-EOB-DTPA enhanced MRI and DWI alone | - | Gd- EOB-DTPA/DWI: 0.84 and 0.83 <i>vs</i> 0.73 and 0.72 for DWI alone | Increase in diagnostic confidence No significant increase in diagnostic accuracy |
| Colagranade <i>et al</i> ^[22] | 0-500 | Added value of DWI for lesion detection in unenhanced and Gd-EOB-DTPA enhanced MRI | -62.5% for unenhanced MRI w/o DWI -85.0% for unenhanced MRI+ DWI -95.6% for CE MRI -97.3% for CE MRI + DWI | -81.1% for unenhanced MRI w/o DWI -89% for unenhanced MRI + DWI -92.9% for CEMRI -95.5% for CE MRI + DWI | DWI improved all statistical parameters in the unenhanced examinations, as for nodules either smaller or greater than 1 cm. In EOB-enhanced examinations DWI increased specificity/negative predictive value |

DWI: Diffusion-weighted imaging; MRI: Magnetic resonance imaging.

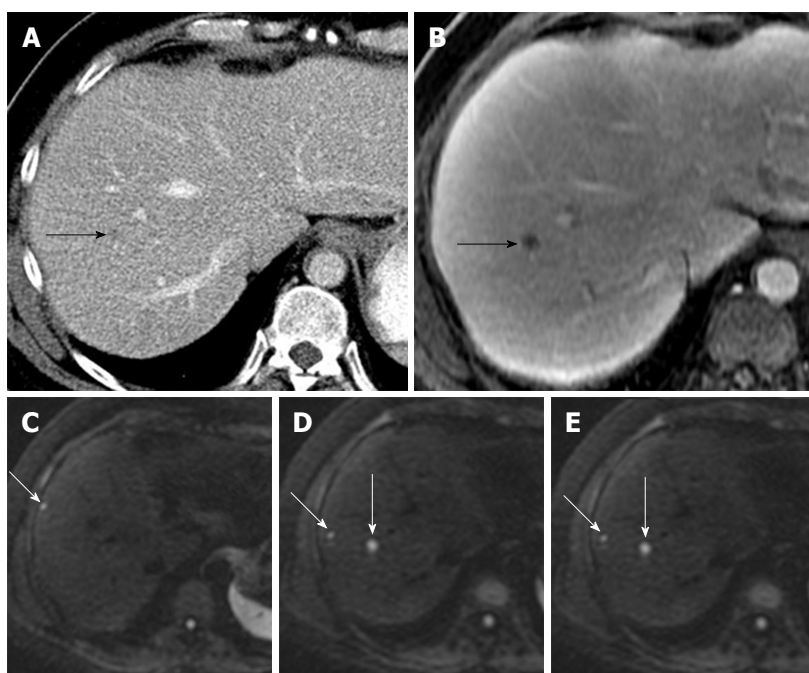


Figure 1 Value of diffusion-weighted magnetic resonance imaging in lesion detection in a 51-year-old male with metastatic leiomyosarcoma of the thigh. A: Axial contrast enhanced CT scan demonstrated a subtle hypodensity in the right lobe of liver (black arrow); B: Axial post gadolinium T1-weighted MR image demonstrates a single metastatic lesion (black arrow); C-E: DW-MR image at b=600 demonstrates additional lesions (white arrows). DW-MR: Diffusion-weighted magnetic resonance; CT: Computed tomography.

of primary hepatic malignancies such as hepatocellular carcinoma (HCC) and cholangiocarcinoma both in cirrhotic and non-cirrhotic livers (Figure 2). A combination of DW hyper-intensity and arterial hyper-enhancement results in increased sensitivity for diagnosis of HCC as compared to traditional criteria,

particularly for small HCC < 20 mm^[30,31].

A low cost abbreviated MRI (AMRI) protocol for HCC screening and surveillance has been proposed based on a simulation study using DWI and T1-weighted imaging obtained at the hepatobiliary phase (HBP) after gadoxetic acid injection^[32]. The AMRI

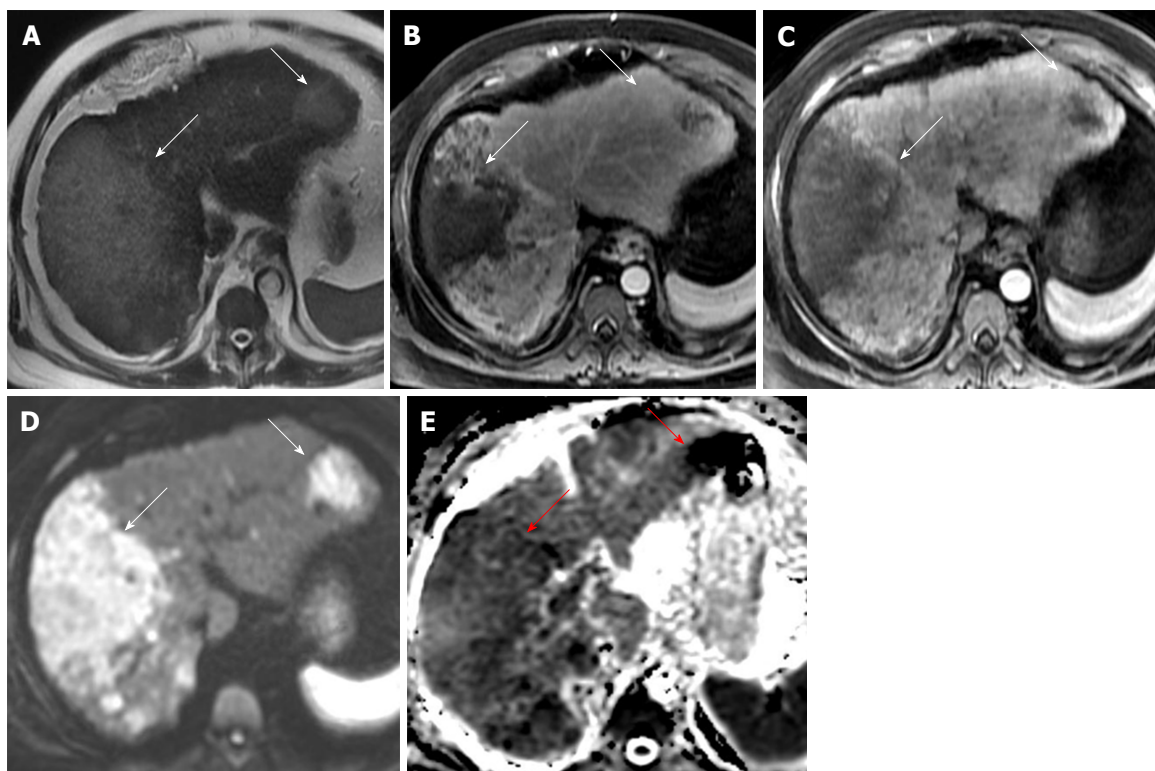


Figure 2 A 66-year-old lady with multifocal infiltrative hepatocellular carcinoma with improved detection on diffusion-weighted imaging. (A) Axial T2 weighted image demonstrates multifocal areas of T2 hyperintense masses (white arrows) which demonstrate heterogeneous arterial hyperenhancement on post gadolinium late arterial phase images (B) and washout appearance on portal venous phase images (C). (D) Axial DWI image at b-600 and (E) ADC image show that these masses demonstrate restricted diffusion and are better appreciated than the dynamic phase images. Serum Alpha feto-protein value of 1552. DWI: Diffusion-weighted imaging.

shows sensitivity and negative predictive values of 80.6% and 80% (for DWI + T1W HBP) compared to 90.3% and 94.9% for a full dynamic contrast enhanced data-set^[32].

Lesion characterization: Several studies have attempted characterization of liver lesions using DW-MRI^[33-38]. A general assumption is that ADC values are higher in benign lesions and lower in malignant liver lesions^[33-36]. In fact, studies have found statistically significant difference in ADC values between benign and malignant liver lesions^[3]. Different studies have reported variable success using various ADC cut-off values with high variability likely due to the difference in scanners and parameters used to obtain DW-MRI and ADC maps^[39-43]. Moreover, there is a high degree of overlap between solid benign and malignant lesions^[44,45]. Hence, the use of absolute ADC values or ADC value cut-off for characterization of focal hepatic lesions should be avoided and DWI should always be interpreted as a complimentary technique to conventional MR sequences^[42,46,47]. It is also important to note that solid benign lesions such as hemangioma, FNH and hepatocellular adenoma can also show diffusion restriction compared to normal liver parenchyma. ADC values for these lesions are intermediate, generally greater than solid malignant lesions but with a significant degree of overlap^[44,45]. Hepatic abscesses show lower ADC values than solid

malignant lesions, and restriction pattern may be different from malignant lesions^[42] (Table 2).

DWI has also been used to assist in differentiation of cirrhotic hepatocellular nodules^[48]. Lesion hyperintensity on DWI, especially in association with hypointensity on delayed hepatocellular phase images, and low lesion-to-liver ratios should raise the suspicion of HCC or high-grade dysplastic nodules^[49]. The HCCs have a tendency for angio-invasion and can present with filling defects in the portal or hepatic veins. Angio-invasion carries a high risk of distant metastasis and recurrence after transplantation. HCC invasion into the portal vein is considered as a contraindication for liver transplantation. It is important to distinguish tumor thrombus from a bland thrombus that is also common in chronic portal hypertension and has different clinical implications. In patients with locally advanced HCC, DW-MRI has been shown to be useful in characterization of the venous thrombus as bland vs tumor thrombus^[50]. The mean ADC ratio of tumor thrombus and HCC has been reported to be < 2 (0.998) as compared to bland thrombus (2.9)^[50].

Tumor grade and prognostication: Recently, there have been attempts to predict the histopathological grades of HCC using DWI. ADC values have been found to correlate with histopathological differentiation and microvascular invasion with poorly differentiated HCCs showing significantly lower ADC than well-differentiated

Table 2 Liver lesion characterization based on ADC values^[33,35,44,45,102]

| Ref. | Lesion type | Mean ADC (10 ⁻³ mm ² /s) | Sample size | b-values | Conclusion |
|---|-------------|--|-------------|--------------------|--|
| Parsai <i>et al</i> ^[44] | Cyst | 2.66 | 2 | 100, 200, 500, | ADC cutoff value threshold of 1.6 × 10 ⁻³ mm ² /s yielded higher accuracy for differentiating benign from malignant lesions. DWI is not reliable to differentiate malignant from benign solid lesions |
| | HCC | 1.07 | 26 | 750, and 1000 | |
| | Metastases | 1.04 | 39 | mm ² /s | |
| Taouli <i>et al</i> ^[98] | Cyst | 3.63 | 52 | 0, 500 | Threshold ADC value of 1.5 × 10 ⁻³ mm ² /s to differentiate between benign and malignant lesions, but with a significant overlap between benign hepatocellular lesions and HCCs |
| | HCC | 1.33 | | | |
| | Metastases | 0.94 | | | |
| Parikh <i>et al</i> ^[35] | Cyst | 2.54 | 211 | 0, 50, 500 | Accuracy of 75.3% for differentiating benign from malignant, by using a threshold ADC of less than 1.60 × 10 ⁻³ mm ² /s. Equivalent performance of DW imaging and T2- weighted imaging for lesion characterization |
| | HCC | 1.31 | | | |
| | Metastases | 1.5 | | | |
| Bruegel <i>et al</i> ^[33] | Cyst | 3.02 | 204 | 50, 300, 600 | 88% of lesions were correctly classified as benign or malignant using a threshold value of 1.63 × 10 ⁻³ mm ² /s. Measurements of the ADCs of focal liver lesions on the basis of a respiratory triggered DW-SS-EPI sequence may constitute a useful supplementary method for lesion characterization |
| | HCC | 1.05 | | | |
| | Metastases | 1.22 | | | |
| Gourtsoyianni <i>et al</i> ^[102] | Cyst | 2.55 | 37 | 0, 50, 500, 1000 | Sensitivity and specificity of 100% for differentiating benign from malignant lesions using a cutoff ADC value of 1.47 × 10 ⁻³ mm ² /s |
| | HCC | 1.38 | | | |
| | Metastases | 0.99 | | | |

HCC: Hepatocellular carcinoma; DWI: Diffusion-weighted imaging.

and moderately differentiated HCCs^[51-54]. A cut-off value of 1.175 × 10⁻³ mm²/s has been recommended as a predictor of microvascular invasion^[52]. Additionally, the recurrence-free survival has been found to be significantly shorter in low-ADC group than in high-ADC group^[52].

The association of ADC and histopathological grades has shown conflicting results in few other studies^[55,56]. This might be a result of tumor necrosis, as it can result in reduced cellularity and increased ADC in high-grade lesions. Higher signal intensity on DWI has been reported to be associated with higher pathological grades despite insignificant correlation with ADC values^[54,56].

Diffuse liver diseases

Evaluation of NAFLD: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in western industrialized countries with a prevalence of 6%-35% worldwide^[57]. The severe form of this disease is steatohepatitis which can progress to cirrhosis in 15% of the patients^[58]. Currently, the diagnosis of NAFLD is established based on histopathological evaluation of liver biopsy specimens. Liver biopsy is invasive and has risks of complications and sampling error, and cannot be frequently repeated.

The feasibility of DWI and IVIM was first tested in animal models with early results showing that the IVIM diffusion parameters, in particular the "f" values, might be potential biomarkers of NAFLD^[59]. The correlation between histologic features of NAFLD and quantitative measures derived from IVIM-DWI was later tested in humans which showed that the true molecular diffusion was significantly decreased with steatosis^[60,61]. ADC was not found to be associated with any histological feature^[60]. Although these early results are promising, standardization of acquisition and post-processing

techniques of IVIM DW-MRI is needed.

Evaluation of liver fibrosis and cirrhosis: Aubé *et al*^[62] reported early benefits of DWI in the evaluation of diffuse liver diseases, particularly in the detection and quantification of hepatic fibrosis. Several authors thereafter have tried to find a simple, reliable and non-invasive method to detect and monitor hepatic fibrosis, thereby avoiding the existing gold standard involving liver biopsy and its complications^[63,64]. A recent meta-analysis suggests that DWI and IVIM parameters can reliably stage hepatic fibrosis^[65,66]. However, IVIM measurements and ADC values have been reported to be influenced by presence of fat or iron within the liver that can impact their accuracy for staging of fibrosis^[67-69] and ascites^[70]. Recent studies comparing MR elastography (MRE) and DWI in characterizing hepatic fibrosis demonstrate higher predictive ability of MRE in distinguishing stages of fibrosis compared to DWI^[71,72]. Gadoteric acid enhanced liver MRI is also more strongly correlated with fibrosis stage as compared to DWI^[73,74]. Considering the conflicting evidence, it can be concluded that at present, DWI cannot replace liver biopsy in liver fibrosis. Further investigations and analysis are needed to increase the reliability of the technique.

Monitoring treatment response

There has been a lot of interest in using DWI as an imaging biomarker for monitoring treatment response to various locoregional and systemic therapies in hepatic malignancies (Table 3)^[75-79]. In comparison to conventional morphological methods of monitoring response such as RECIST and WHO which rely on changes in tumor dimensions for quantitating tumor response, DW-MRI allows evaluation of treatment response to novel targeted therapies which cause

Table 3 Role of diffusion-weighted magnetic resonance in assessment of treatment response^[75-79]

| Ref. | Treatment modality | Tumor type | DW-MR parameter evaluated | Study results/teaching point |
|---------------------------------------|-------------------------|--|--|---|
| Chapiro <i>et al</i> ^[79] | TACE | HCC | (3D) quantitative enhancement-based and DW volumetric MR | High accuracy and intermethod agreement of 3D quantitative techniques in the assessment of tumor necrosis after TACE is clinically relevant High diagnostic performance of qEASL criteria and qADC may help in triaging patients for repeat treatment after a TACE session |
| Mannelli <i>et al</i> ^[87] | TACE | HCC | ADC measured with DWI in treatment response | Pre TACE ADC obtained at 0, 50, 500 s/mm ² b values before and after treatment may be used to predict HCC response to TACE |
| Park <i>et al</i> ^[42] | Radiotherapy | HCC | DW MR <i>vs</i> conventional MR for treatment response | Improved detection of viable tumor when DW MR is added to conventional sequences |
| Yu <i>et al</i> ^[76] | Radiation therapy | HCC | DW MR | Change in ADC value before and after RT is related to local progression free survival. Hence ADC value and RECIST may substitute for mRECIST in patients who cannot receive contrast agents |
| Schraml <i>et al</i> ^[77] | Radiofrequency Ablation | <i>n</i> = 16 HCC, 1 = cholangiocarcinoma, and 37 = metastases (28 colorectal cancer, 3 melanoma, 3 breast cancer, 1 pancreatic cancer, 1 gastric cancer, esophageal cancer) | DW MR and mean ADC values | ADC-based evaluation of signal alterations adjacent to the ablation zone may contribute to the identification of local tumor progression and nontumoral post-treatment tissue changes |

HCC: Hepatocellular carcinoma; DW MR: Diffusion-weighted magnetic resonance; TACE: Trans-arterial chemoembolization.

early changes in tumor physiology prior to change in tumor size. The increase in post-treatment ADC values precedes a decrease in size of tumor which has been the traditional method of measurement for post-treatment response, especially in systemic therapy^[80-82].

Percutaneous ablation: ADC-based evaluation of signal alterations adjacent to the ablation zone may contribute to the identification of local tumor progression and non-tumoral post-treatment tissue changes after radiofrequency ablation of hepatic primary tumors and metastases^[77]. Early post-ablation zone may show heterogeneous signal on non-enhanced T1 and T2 weighted images due to edema, hemorrhage and inflammatory reaction. These changes resolve within 4-6 mo after ablation leaving behind a characteristic homogenous high T1 signal and low T2 signal (coagulation necrosis). Nodular enhancing foci within the ablation zone are considered as a sign of local recurrence. Low ADC values at 1 mo ($< 1.145 \times 10^{-3} \text{ mm}^2/\text{s}$) after RFA have been shown to be associated with an early local recurrence of HCC^[83].

Intra-arterial therapies: The utility of DWI has been assessed in treatment response after trans-arterial chemoembolization (TACE) of HCC^[84-87]. DWI has been shown to perform equally^[78] or better than gadolinium-enhanced MRI in quantifying the area of tumor necrosis after chemoembolization^[78,86,88]. Increased ADC values in non-enhancing tumors show a high correlation to the degree of tumor necrosis at pathology^[86,88]. Mannelli *et al*^[78] showed excellent performance of ADC for prediction of complete tumor

necrosis after TACE (sensitivity of 75% and specificity of 88%) which was comparable to 100% sensitivity, and 58%-79% specificity for contrast-enhanced MRI.

Transarterial radioembolization (TARE) using yttrium-90 (⁹⁰Y)-loaded resin microspheres is a treatment option for various liver malignancies (including liver-dominant breast metastases). Early arterial blood flow stasis with consecutive incomplete dose administration may occur in 12%-25% of resin-based radioembolization procedures. The perfusion-sensitive IVIM parameter "*f*" may predict early blood flow stasis in patients undergoing TARE for liver-dominant breast metastases^[89].

Image-guided radiation therapy: Image-guided targeted external beam radiation therapy is emerging as an alternative option in the treatment of advanced unresectable HCC. Accurate post-radiation response assessment can be challenging due to the concomitant changes occurring in the radiation zone. MRI is the preferred modality for response assessment. Inclusion of DWI in the imaging protocol has been shown to significantly enhance the diagnostic accuracy (91%-97% vs 72%) for detection of viable tumors after radiation treatment with improved sensitivity, specificity, and negative predictive value as compared to routine MR sequences (90%-97%, 91%-97% and 91%-97% vs 41%-55%, 86%-97% and 67%-70%, respectively)^[75]. ADC values have also been shown to correlate with local progression-free survival^[76]. Another group demonstrated that ADC values correlate with local progression-free survival and proposed that ADC and RECIST criteria could be substituted for mRECIST in

post-radiation evaluation of patients not amenable to receiving contrast agents^[76].

Systemic chemotherapy: DWI can detect the effects of chemotherapy combined with antiangiogenetic treatment on liver metastases in patients with advanced colorectal cancer^[90]. An increase in ADC values following systemic chemotherapy can be a sign of tumor response with non-responders showing lower ADC values than responders^[91]. In addition to monitoring therapeutic response, DWI has also been found to be useful in prediction of response to chemotherapeutic agents^[92,93].

Limitations of DWI

Diffusion imaging has several limitations, mostly attributable to the EPI based nature of the sequence^[94,95]. SS EPI provides a limited image quality with low spatial resolution and poor SNR and is susceptible to several artifacts, including blurring, ghosting and distortions. Although modern scanners with multichannel coils, strong gradients, high magnetic fields and advanced software have been successful in reducing such effects to a great extent^[96]. In addition, parallel imaging techniques improve SNR by allowing a decrease in acquisition time (TE)^[97,98]. 3T MRI offers an advantage due to an inherent high SNR, but suffers from several limitations. Uniform fat suppression for liver DWI has always been a challenge with 3 Tesla magnets and susceptibility artifacts are also more pronounced at 3 Tesla scanners^[99].

The reproducibility of quantitative ADC values has also been questioned. ADC values have been reported to vary significantly depending on the hardware, human or biologic factors^[100]. There has been considerable effort, however, to "industrialize" this important biomarker across vendor platforms^[101].

CONCLUSION

DWI is useful for focal liver lesion detection and is a desirable tool in patients who cannot receive intravenous contrast. In patients receiving systemic and local therapies for hepatic malignancies, DWI acts as a clinical tool for monitoring treatment response and predicting prognosis. Its utility in the assessment of diffuse hepatic parenchymal diseases is still at a research level. Further investigation and analysis are needed to increase the reliability of the technique for these indications. DWI has certain limitations and remains an adjunct and not a replacement to conventional sequences.

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