Diagnostic accuracy of intermediate *b*-value diffusion-weighted imaging for detection of residual hepatocellular carcinoma following transarterial chemoembolization with drug-eluting beads

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Abstract

Purpose: To evaluate the role of diffusion-weighted magnetic resonance imaging (DW-MRI) in the detection of residual malignant tumor of hepatocellular carcinoma (HCC) after transcatheter arterial chemoembolization (TACE) with drug-eluting beads (DEBs). **Subjects and Methods:** Pre-contrast T1, T2, dynamic contrast–enhanced, and respiratory-triggered DW-MRI (*b* factor 0, 400, and 800 s/mm^2) were obtained in 60 patients with HCC who underwent tran-sarterial hepatic chemoembolization with DEBs. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the DW imaging images. Apparent diffusion coefficients (ADCs) were calculated searching for the optimal cut-off value using the receiver operating characteristic (ROC) curve. **Results:** DW-MRI had a sensitivity of 77.1%, a specificity of 60.7%, a PPV of 71.05%, and a NPV of 68%. The difference between the malignant and benign groups' ADC variables was statistically significant ($P < 0.003$). The ROC curve showed that the area under the curve is C = 0.718 with SE = 0.069 and 95% confidence interval from 0.548 to 0.852. **Conclusion:** In our study, we demonstrated that diffusion MRI has limited diagnostic value in the assessment of viable tumor tissue after TACE with DEBs in cases of HCC.

Key words: Drug-eluting beads; diffusion-weighted magnetic resonance imaging; hepatocellular carcinoma-transcatheter arterial chemoembolization; hepatic; malignant

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Introduction

Trans-arterial chemoembolization of the hepatocellular carcinoma (HCC) with drug-eluting beads (DEB) was recently introduced relative to the conventional lipiodol-based transcatheter arterial chemoembolization (TACE). This allows the use of higher doses of chemotherapeutic agents with higher rates of complete response and disease control.[1]

It is of critical importance to determine early response to the locoregional therapy for liver malignancy.[2] Magnetic resonance imaging (MRI) is more accurate than other radiological modalities to detect residual viable tumoral activity within the hepatic malignancies.[3]

The European Association for the Study of the Liver (EASL) disease recommended the tumoral enhancement pattern during the dynamic studies to determine treatment response. Diffusion-weighted (DW)-MRI could assess tumor cellularity. Thus, it may offer additional benefit to assess tumor response accurately for such therapies.[4]

Follow-up after TACE, evaluation with DW-MRI shows promising results in this aspect to detect treatment response, residual viable tumoral activity, and recurrent lesions, especially in combination with conventional dynamic contrast–enhanced (DCE) MRI.[5]

Kamel *et al.* compared between the conventional MRI and the diffusion-weighted imaging (DWI) for evaluation of HCC post TACE with DEBs, and they found that DWI could detect new or residual lesions and discriminate between the viable and necrotic tissue within the lesion.[6]

In view of an increasing use of MRI application after transarterial chemoembolization of HCC with DEBs (DEB-TACE), the purpose of our study was to assess the value of DW-MRI in the diagnosis of residual tumor, aiming to use DW-MRI as a reasonable modality especially when contrast administration is contraindicated.

Materials and Methods

This retrospective study was performed on 60 cases of HCC who underwent TACE with DEBs. The number of target lesions prior to DEB-TACE was 63 lesions (three patients had 2 lesions). The patients were referred from the outpatient clinic to the radiology department from November 2014 to June 2016.

The patients' age ranged from 40 to 73 years (mean 60 years); 45 patients were males and 15 were females. All patients had liver cirrhosis related to chronic viral hepatitis.

Exclusion criteria
- Contraindications to MRI, for example, claustrophobia, cardiac prosthesis, metallic coils

- Contraindications to contrast media, for example, patients with renal failure.

All cases had been subjected to the following:
- Imaging prior to DEB-TACE either triphasic CT or dynamic MRI
- DEB-TACE procedure: Transcatheter therapy through femoral artery access. The arteries supplying the lesion were catheterized super-selectively and treated using beads loaded with 50 mg of doxorubicin. The termination point for injection was administration of two vials of DEB or slow flow in the subsegmental branches to the region of the lesion
- Revision of the patient's laboratory investigations including renal function tests (blood urea and serum creatinine)
- Patients were scheduled to undergo dynamic MRI with DW-MRI after a mean duration of 1 month after one or more treatments of DEB-TACE.

MR protocol used
MRI was performed on high-field system (1.5 Tesla) magnet units (Philips Acheiva XR, Best, Netherlands) using a torso phased array coil.

Precontrast imaging included the following:
Transverse T2-weighted (T2W) images (single-shot free breathing): repetition time (TR) ≥445 ms, echo time (TE) =26–28 ms, matrix 180–200 × 240 with a field of view of 379 × 279, slice thickness 10 mm, and slice gap 1–2 mm.

Transverse in- and out-phase gradient echo sequence (dual/FFE): TR = 75–100 ms, TE = 4.6 ms for in-phase and 2.3 ms for out-phase, matrix 208 × 237 with a field of view of 379 × 279, slice thickness 10 mm, and slice gap 1–2 mm.

Transverse T2 spectral attenuated inversion recovery (SPAIR) fat suppression sequence: TR ≥400 ms, TE = 80 ms, matrix 204 × 384 with a field of view of 379 × 279, slice thickness 10 mm, and slice gap 1–2 mm.

Diffusion-weighted MRI
DW-MRI was performed before the dynamic imaging using respiratory triggered fat-suppressed single-shot echo planar sequence that combined the two diffusion (motion-probing) gradients before and after the 180° pulse along the three directions of section-select, phase-encoding, and frequency-encoding. We used three different b factors of 0, 400, and 800 s/mm^2 for data acquisition.

We applied parallel imaging with generalized autocalibrating partially parallel acquisition with an acceleration factor of 2 to reduce the acquisition time. These images were obtained in the axial plane. The other parameters were as follows: TR ≥1890 ms, TE = 70 m, number of excitations = 3,

matrix 124 × 120 with a field of view as small as possible, slice thickness 7–8 mm, slice gap 1–2 mm, and scan time 4–5 min.

Dynamic contrast–enhanced MRI
The DCE MRI study was obtained in the axial plane through bolus injection of the contrast agent "0.1 mmol/kg body weight of Gd-DTPA" through the antecubital vein. The injection rate was 2 mL/s, and then flushed with 20 mL of sterile 0.9% saline solution. The timing of the scan was performed using fixed bolus tracking technique and the patient was commanded to hold his or her breath. Dynamic imaging using THRIVE (T1 high resolution isotropic volume examination) technique was performed. A dynamic series consisted of one precontrast series followed by four successive postcontrast series including early arterial, late arterial, and portovenous phases imaging with 18–21 s intervals (17–20 s) for image acquisition according to liver size with breath-holding and 1 s for rebreathing for the start of each phase imaging followed by 3–5 min delayed phase imaging.

MR images were analyzed for the following:
- Pattern of enhancement in the DCE MRI
- Signal intensity on diffusion images with measurement of apparent diffusion coefficient (ADC) values.

Interpretation of the MR image
Dynamic study interpretation
Residual viable tumor tissue: nodular, mass-like, or thick irregular enhancement within the lesion or along its margin, which showed arterial phase enhancement and washout in the delayed phases.

Nonviable: lesions with no enhancement or with surrounding thin rim of enhancement that is expected after treatment.

DWI MRI
a) Qualitative analysis: restricted diffusion was recorded if the lesion has area of bright signal on DW-MRI that is not attenuated with increased b value and dark signal in the ADC map
b) Quantitative analysis (ADC measurement): the mean ADC of each lesion detected was measured by drawing a region of interest (ROI) over the lesion. The size of ROIs was estimated to include as much of the lesion, while as possible, leaving 1–2 mm of lesion periphery. In case of lesions with heterogeneous appearance in DWI, the ROI was drawn over the restricted part of the lesion. If no restricted part could be identified, the entire lesion was measured.

We categorize the patients into two groups:
- Resolved group (well ablated): no MRI signs of residual viable tumoral activity (regardless of the presence of other lesions)

- Unresolved group (residual): if there is evidence of residual viable tumoral activity at the ablated lesion.

Standard of reference:
It was difficult to obtain pathologic confirmation in patients who underwent chemoembolization. This is related to the clinical practice where histology is not indicated. Up so, the standard of reference in this study was considered the pattern of enhancement on dynamic series.

Statistical methods
Statistical analysis and data interpretation were performed using computer software Statistical Package for the Social Sciences (SPSS) version 22. We used the means and standard deviations for summarizing the numerical data, while numbers and percentages were used for summarizing the categorical data. The standard diagnostic indices – sensitivity, positive predictive value (PPV), specificity, and negative predictive value (NPV) – and diagnostic efficacy were calculated.

The receiver operating characteristic (ROC) curve was used to determine the best cut-off point between residual tumor and no residual tumor.

Results

The study group consisted of 60 patients and 63 lesions. (The number of lesions prior to DEB-TACE was 63.) The lesions were assessed for residual viable tumor tissue. Assessment of disease recurrence or newly developed tumors other than the embolized lesions is beyond the scope of this study.

The results were analyzed as given below.

Demographic data
The patients' age ranged between 40 and 73 years (mean 60 years) [Table 1].

Overall, 45 (75%) patients were males and 15 (25%) patients were females.

Final diagnosis
The standard of reference in this study was considered the pattern of enhancement on dynamic series. According to dynamic MRI, lesions were categorized into the following:
a. Resolved group (no residual viable tumor): lesions with no enhancement or lesions with surrounding thin rim of enhancement that is expected after treatment

Table 1: Patients' age data

Age	Years
Minimum	40
Maximum	73
Mean	60
±SD	±7

SD: Standard deviation

b. Unresolved group (residual): nodular, mass-like, or thick irregular enhancement within the lesion or along its margin that showed arterial phase enhancement or washout in the delayed phases.

In dynamic MRI, 35 lesions displayed viable residual tumoral activity and the remaining 28 lesions appeared free of residual tumor tissue denoting good therapeutic response.

Qualitative analysis of DW-MRI
In DW-MRI, 38 lesions had restricted diffusion and 25 had facilitated diffusion [Table 2].

Seventeen of the remaining 28 lesions with no residual tumor tissue had facilitated diffusion, while 11 had restricted diffusion (false-positive) [Figures 1 and 2].
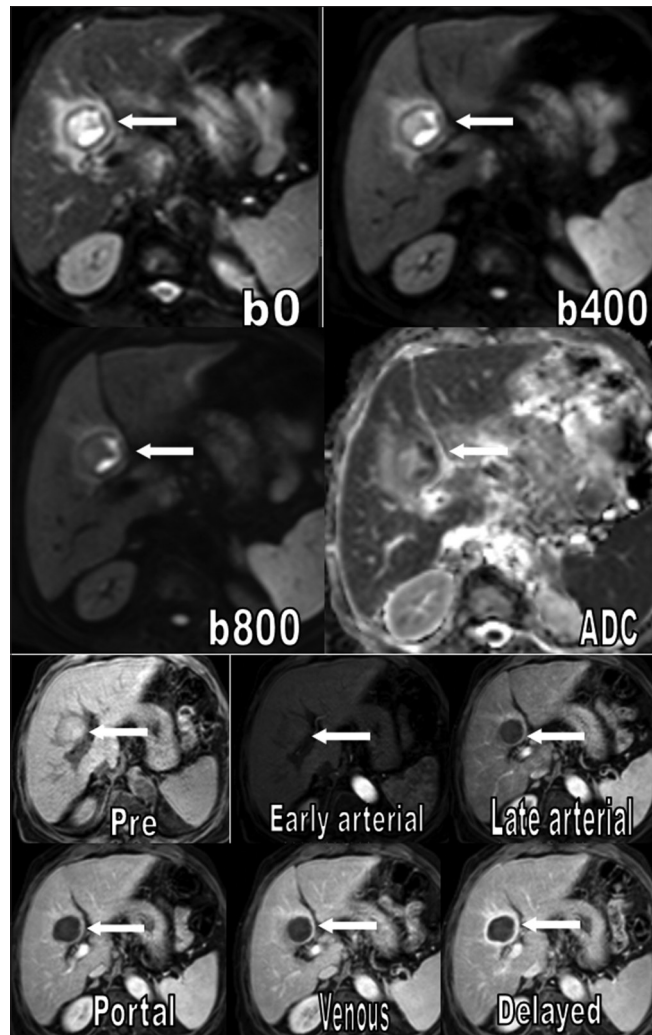
Twenty-seven of 35 lesions with viable residual tumor activity were detected with DW-MRI showing restricted diffusion (true-positive) [Figure 3]. The remaining eight lesions were missed (showing facilitated diffusion, false-negative).

Upon correlating the DW-MRI findings to the dynamic MRI results, 8 cases were found to be false-negative (22.9%), 11 cases were false-positive (39.3%), 17 were true-negative (60), and 27 were true-positive (77.1%). The sensitivity for DW-MRI was 77.1%, specificity 60.7%, PPV 71.05%, and NPV 68%.

Table 2: Distribution of lesions in dynamic MRI and DW-MRI

		No.	%
Dynamic MRI	Positive	35	55.6
	Negative	28	44.4
DW-MRI	Positive	38	60.3
	Negative	25	39.7

MRI: Magnetic resonance imaging; DW-MRI: Diffusion-weighted magnetic resonance imaging

Figure 1: A 71-year-old male treated with DEB-TACE for HCC. DWIs of the lesion showed peripheral bright areas that became brighter with increasing the *b* value (0, 400, 800) in successive images from the top two rows with dark signal in the ADC map denoting restricted diffusion "arrows." Dynamic thrive images showed necrosis of the lesion with thin smooth rim of reactive enhancement "arrows." The bright T1 signal in the precontrast image represents coagulative necrosis
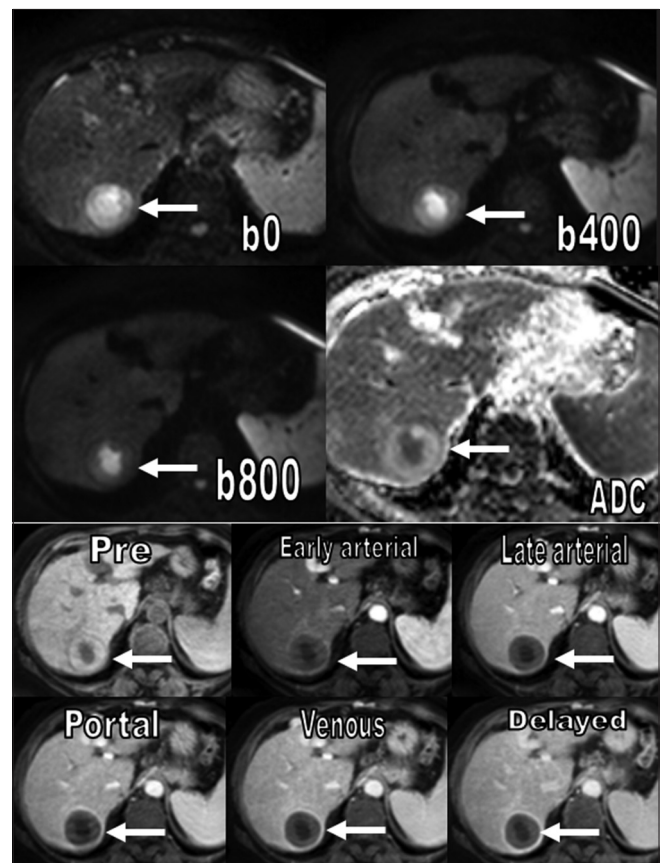

Figure 2: A 65-year-old female treated with DEB-TACE for HCC. DWIs showed central bright areas that became brighter with increasing the *b* value (0, 400, 800) in successive images from the top images with dark signal in the ADC map denoting restricted diffusion. Dynamic thrive images showed marginal reactive enhancement with no evidence of early pathological enhancement or washout of contrast "arrows" denoting good therapeutic response with no residual tumoral activity. The bright T1 signal in the precontrast image represents coagulative necrosis
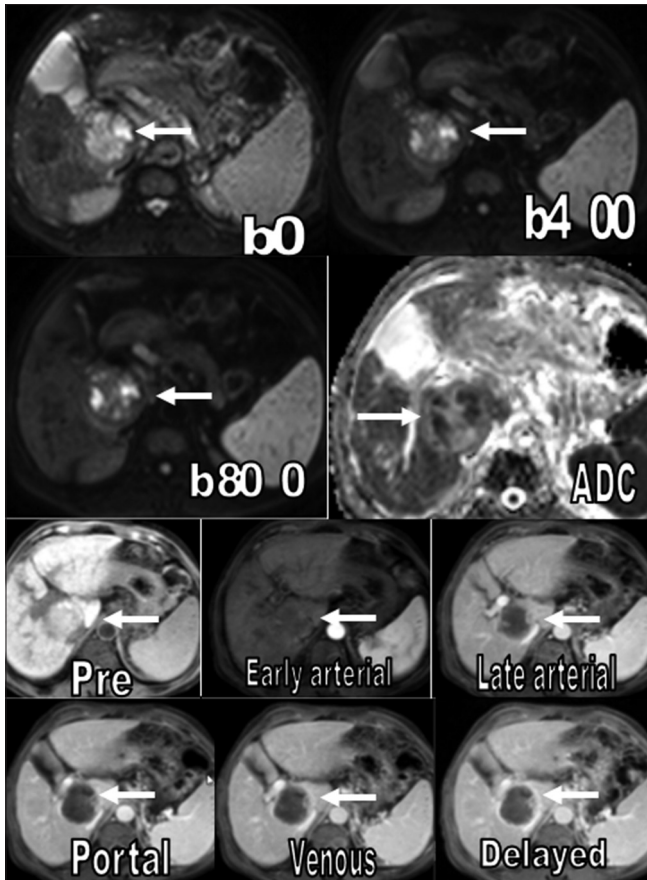
Figure 3: A 68-year-old male treated with DEB-TACE for HCC. DWIs of the lesion showed peripheral bright areas that became brighter with increasing the *b* value (0, 400, 800) in successive images from the top images with dark signal in the ADC map denoting restricted diffusion. Dynamic thrive images also showed heterogeneous enhancement with nodular vivid enhancement in the arterial and portal phases with delayed contrast washout matching the nodules of restricted diffusion pattern "arrows" denoting residual viable tumoral activity. The precontrast images show hyperintense T1 signal, suggestive of hemorrhagic foci

Qualitative analysis of the ADC value

The different ADC values elicited from the corresponding ADC maps were calculated. The difference between ADC variables among the malignant and benign groups was statistically significant ($P < 0.003$).

The ROC curve obtained by plot at different cut-off values is shown in Figure 4. The best cut-off that maximizes sensitivity and specificity is 1.375×10^{-3} mm^2/s. At this ADC value, the sensitivity is 80% and specificity is 60.7%. A statistical software showed that the area under the curve is C = 0.718 with SE = 0.069 and 95% confidence interval from 0.548 to 0.852. It seems from the ROC that ADC variable is a fair indicator to detect malignant residual of HCC after DEB-TACE (area under the curve: excellent 0.9–1, good 0.8–0.9, fair 0.7–0.8, poor 0.6–0.7, fail 0.5–0.6).
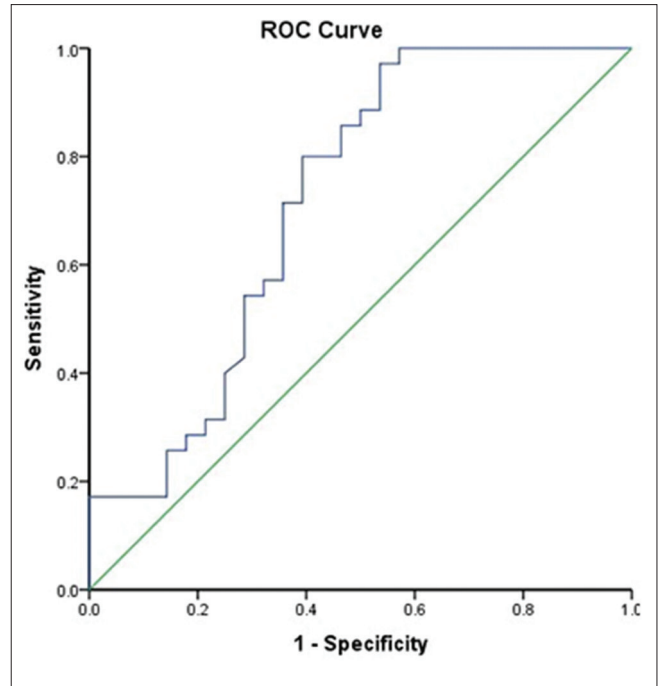

Figure 4: Results of receiver operating curves for ADC values in distinguishing benign and malignant groups

Discussion

MRI is used to differentiate completely treated zones in HCC treated with TACE from those containing residual tumor. The American Association for the Study of Liver Diseases as well as the EASL recommended the use of tumor enhancement as a biomarker of disease response.[4]

Functional MRI techniques such as DW-MRI detect early MR signal changes in tissues within several weeks of treatment, based on the degree of cell membrane integrity.[7] So viable tumor cells with intact membranes will show restricted water diffusion, while the necrotic tumor cells will demonstrate facilitated water diffusion owing to disruption of their cell membranes.[8]

The application of DW-MRI in the abdomen requires a compromise to choose the optimal *b* value. Low *b* values may result in increased ADC values due to contamination of other forms of intravoxel incoherent motion like perfusion in the capillary bed. In contrast, high *b* values require long acquisition times and decrease in signal-to-noise ratio.[9]

In our DW-MRI study, *b* values were 0, 400, and 800 s/mm^2; we applied parallel imaging with breath triggering technique and got a satisfying image quality on a 1.5-T scanner within an acceptable acquisition time.

The major aim of this study was to determine the usefulness of DWI in detection of residual viable tumor tissue in HCC after TACE with DEBs.

In our work, the sensitivity of DW-MRI qualitative analysis was 77.1%, specificity 60.7%, PPV 71.05%, and NPV was 68%. Quantitative analysis of the ADC value showed best cut-off value that maximizes sensitivity and specificity was 1.375. At this ADC value, the sensitivity was 80% and specificity 60.7%.

The results of our study match with that of a study by Mohamed *et al.*,[10] in which the sensitivity and specificity of DWI were 83.9% and 64.3%, respectively. The best ADC cut-off value in this study was 1.395×10^{-3} mm²/s.[10]

Our results differ from Osama *et al.*,[11] who observed higher sensitivity of DWI (100%) with a similar specificity of 65.5%. The best ADC cut-off value in this study was 1.26×10^{-3} mm²/s.[11]

Goshima *et al.* found that detection of local tumor recurrence after TACE was greater by DCE MRI than DW-MRI. They could not determine ADC cut-off value owing to a wide range in the calculated ADC values. They recommended use of DW-MRI as a supplementary sequence.[12]

Data on DW-MRI for tumoral response evaluation are still highly heterogeneous owing to difference in study protocols used as well as the variable MR hardware and software.[13]

Combining DW-MRI and Gd-MRI, Yu *et al.*[14] stated that DW-MRI increased the sensitivity compared with Gd-MRI alone (92% vs. 85%; $P = 0.125$) only to a nonsignificant degree while specificity decreased from 65% to 50%. Therefore, according to literature, DW-MRI is only of little or no value to detect residual viable tumoral activity within the hepatic focal lesion which underwent locoregional therapy.[14]

False-positive cases in DW-MRI of posttherapeutic necrosis of malignant lesions could originate from coagulative necrosis that shows restricted diffusion or fibrotic component in the inflammatory granulation tissue associated with hypercellularity that could restrict water diffusion and show persistent hyperintensity on DW-MRI.[14]

The limitations of the study were the lack of histopathologic evaluation and follow-up imaging as the gold standard for the viable tumor portion. Instead, we considered dynamic postcontrast MRI as the golden standard in this study.

Conclusion

DW-MRI has poor specificity and fair sensitivity in assessment of viable tumor tissue after DEB-TACE for cases of HCC. Its poor specificity limits its diagnostic value in assessment of residual viable tumor tissue after DEB-TACE.

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