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Role of ADC Mapping in the Assessment of Therapeutic Response of Hepatocellular Carcinoma in Patients with Post-trans-catheter Arterial Chemoembolization

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is more common in persons with chronic liver disease and cirrhosis. The apparent diffusion coefficient (ADC) has the ability to detect tumour response to treatment weeks before morphological alterations are evident.
Aim of The Work: To compare the response to therapy of HCC cases after trans-arterial chemoembolization using the ADC mapping MRI approach to the dynamic contrast study (DCE MRI).
Patients and Methods: The current study involved 30 patients who underwent dynamic MRI with ADC mapping technique before and after TACE. All patients had been subjected to clinical assessment, laboratory investigations (AFP, liver functions, serum albumin bilirubin, coagulation profile, CBC) and ultrasound to exclude ascites.All cases underwent baseline and follow-up MR imaging.
Results: DCE-MRI and DWI/ADC assessments regarding active lesions showed; comparable sensitivity, specificity, PPV, NPV and accuracy in HCC patients; without significance (p >0.05) (Table 3). Table (4) shows a good agreement between dynamic-MRI and DWI/ADC evaluation of reactivity between HCC cases. DWI/ADC value at a cutoff point (≤2.17) can identify cases with remnant active pathology, with good (83.3%) accuracy, sensitivity= 87.5% and specificity= 81.8% (p< 0.001).
Conclusion: Authors conclude that dynamic MRI is useful and the standard in identifying relapsed pathology but, this value is enhanced by DWI/ ADC protocol which will significantly be of great value in increasing the confidence in our diagnosis.

Keywords: *Axillary lymph node US; elastography; Breast US.*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is more frequent in individuals with chronic liver diseases and cirrhosis.[1] HCC is currently the third major etiology of cancer mortality globally, with over 500,000 persons suffering. [2]

As regard to the Milan criteria, liver transplantation is still the best choice for individuals with HCC. However, there is a shortage of high-quality dead donor organs. As a result, different therapies such as resection, radiofrequency ablation (RFA), and may be systemic treatment are required. [3]

Transcatheter arterial chemoembolization (TACE)is the most often used treatment. TACE is done by cannulation of the tumor's feeding artery and gives high local dosage of chemotherapy such as doxorubicin, cisplatin, or mitomycin C. To avoid systemic toxicity, the feeding artery is blocked with gel foam or coils. [4]

Dynamic contrast-enhanced MRI (DCE MRI) has the potential to be a valuable radiological indicator, particularly in the identification of active tumour cells the distinction of necrosis from active tumour, and prediction of therapeutic efficacy. [5]

Diffusion-weighted imaging (DWI) is the primary method for determining tumour cells and cell membrane stability. As a result, it may be susceptible to differences in the tumour microenvironment after therapy. Also, it may be assessed quantitatively by computation of the apparent diffusion coefficient (ADC). [6]

ADC may be useful in predicting tumour response to therapy weeks earlier to morphological alteration. It assesses the movement of water inside tissues. Active tumours have a high cellularity, and intact cell membrane, which inhibits water molecule movement and leads in a relatively reduction of ADC. However, cellular necrosis enhances membrane permeability, allowing water molecules to flow easily and resulting in a relative rise in ADC. It has emerged as an intriguing indicator of tumour response to treatment. [7]

Our rational was to evaluate the response to therapy of HCC cases after trans-arterial chemoembolization

using the ADC mapping MRI approach to the dynamic contrast study (DCE MRI).

PATIENTS AND METHODS

A prospective study carried out at El MaadiArmed Forces Hospital, Radiology Department during the period from 1 May 2020 to 1 October 2021. The current study involved 30 patients who underwent dynamic MRI with ADC mapping technique before and after TACE.The study was accepted by Al-Azhar University's Ethics Board, and each subject signed an informed written permission form.

Patients with unresectable hepatic tumor, its size <50% of total liver size, patent portal vein, serum bilirubin < 1.7, INR <1.5 and serum albumin >2.8 were enrolled in this study. However, subjects withany contraindication to contrast media, e.g.kidney failure and allergy, contraindication to MRI, e.g. claustrophobia, heart prosthesis and pacemakers and metallic implants and plates, extra hepatic metastases, tumor size > 50% of total liver size, portal vein thrombosis and poor liver function were excluded from the study.

Clinical evaluations had been performed to all participants., laboratory investigations (AFP, liver functions, serum albumin bilirubin, coagulation profile, CBC) and ultrasound to exclude ascites.

All participants underwent an initial and follow-up MRIusing 3 Tesla (GE Discovery 750) MRI machine. Abdomina1 coi1 was used with respiratory triggering. The imaging protoco1 inc1uded the fo11owing:

Pre contrast MR imaging before the diffusion weighted examination:

T1-weighted image wasdone with the fo11owing parameters: (TR = 400ms, TE = 20ms, 385 x 385mm fie1d of view (FOV), 256 x 256 matrix, section thickness 5-7mm).

T2-weighted image with the fo11owing parameters (TR = 3000ms, TE = 90, 385 x 385mm FOV, 256 x 256 matrix and section thickness: 5- 7mm).

STIR (short time inversion recovery) was done using the fo11owing parameters: (TR= 418ms, TE = 80, TI = 140ms, 385 x 385 FOV, 256 x 256 matrix and section thickness 5-7mm).

Dynamic study: A bolus injection of 0.05mmol of gadobenate dimeg1umine per ki1ogram of body weight fo11owed by 20m1 of sa1ine f1ush at a rate of 2mL/s by using a power injector.

Three c0nsecutive p0stc0ntrast imaging were 0btained emp10ying a dua1 (ear1y and 1ate) hepatic arteria1 phase, f0110wed by p0rta1 and de1ayed phases. Ear1y and 1ate arteria1 phases were d0ne with0ut interrupti0n, with a set de1ay 0f 15 sec0nds f0110wing the start 0f c0ntrast materia1 injecti0n and within a breathh01d 0f 20 sec0nds. The p0rta1 ven0us phase was 0btained 30 sec0nds after the 1ate arteria1 phase ended, and the de1ayed phase was 0btained 175 sec0nds after the c0ntrast materia1 was administered.

Diffusion weighted images: Functi0na1 DWI was perf0rmed using sing1esh0t spin-ech0-p1anar imaging during 0ne 0r m0re

breath h01ds with tw0b-va1ues (500, 800mm^2/s) app1ied in the z directi0n. These b-va1ues were ch0sen t00verc0me the effect 0f capi11ary perfusi0n and water diffusi0n in extrace11u1ar extra vascu1ar space.ADC maps were rec0nstructed fr0m each set 0f DWIs acquired at each s1ice p0siti0n.

Statistical analysis:

All data analyzed using statistical package for social sciences (SPSS) version 22 (SPSS Inc, Chicago, USA). For qualitative data, frequency and percent distributions was calculated. For quantitative data, mean, standard deviation (Sd)was calculated. significance was defined as P value < 0.05. The following tests were used; Student T test, Mann-Whitney U test, Chi- Square test and McNemar's test.

RESULTS

This study involved 30 participants with HCCs who subjected to trans-catheter arterial chemoembolization. Their mean age was 65.57± 6.21 years and ranged from 41 to 74 years. 25 (83.3%) patients were more than 60 years while 5 (16.7%) were less than 60 years. Male predominance was noticed in our study as male represented 96.7% cases while there was one female (3.3%).Eighteen (60%) patients live in rural region while 12 (40%) patientslive in urban region.Concerning tumor size, the size ranged from 1.3*1.2 cm to 10.0*7.6 cm with mean ±SD was 4.01*3.07) ± (2.32*1.71) cm. The AFP ranged from 2.70 to 8299 with mean ±SD was 421.41 ± 281.96.

Regarding dynamic MRI, there was 10 (33.3%) cases showed positive changes while 20 (66.7%) cases showed negative changes. As regards to DWI/ADC, there was 8 (26.7%) cases showed positive changes while 22 (73.3%) cases showed negative changes. The mean (± SD) ADC value was 2.15± 0.124 × 10-3 mm2/s. 2 (6.7%) cases had mean ADC value < 1.2 × 10-3 mm2/s while 28 (93.3%) cases had mean ADC value > 1.2 × 10-3 mm2/s (Table 1).

The patients were classified according to active lesions into 2 independent groups; active group (10 patients) and inactive group (20 patients). ADC value in active group was lower than inactive group with high significance (p<0.001) (Table 2).

DCE-MRI and DWI/ADC assessments regarding active lesions showed; comparable sensitivity, specificity, PPV, NPV and accuracy in HCC patients; with no significance (p >0.05) (Table 3). Table (4) shows a good agreement between dynamic-MRI and DWI/ADC evaluation of reactivity between HCC cases (kappa =0.684).

By using ROC-curve analysis, Dynamic-MRI can detect cases with residual active pathology, with excellent (96.7%) accuracy, sensitivity= 100% and specificity= 95% (p <0.001). DWI/ADC value at a cutoff point (≤2.17) can detect cases with residual active pathology, with good (83.3%) accuracy, sensitivity= 87.5% and specificity= 81.8% (p< 0.001) (Figure 1).

	HCC patients (n=30)	
	No.	**%**
Activity by dynamic MRI		
Negative	20	66.7%
Positive	10	33.3%
Activity by DWI/ADC		
Negative	22	73.3%
Positive	8	26.7%
ADC value:		
Mean± SD	2.15± 0.124	
Median (IQR)	2.44 (1.42- 2.82)	
Range	1.12- 2.96	
< 1.2 × 10^{-3}mm^2/s	2	6.7%
≥ 1.2 × 10^{-3}mm^2/s	28	93.3%

SD: standard deviation, IQR: Interquartile range,MRI: magnetic resonance imaging. ADC: apparent diffusion coefficient. DWI: Diffusion-weighted imaging.

Table 1: dynamic MRI, DWI/ADC characteristics in the studied HCC patients:

		Inactive group (n = 20)		Active group (n = 10)		P-value
		n	**%**	**n**	**%**	
ADC value (x 10^{-3}mm^2/s)	**Mean± SD**	2.48± 0.57		1.50± 0.33		**<0.001****
	Median (IQR)	2.73 (2.44 – 2.85)		1.42 (1.31 – 1.80)		
	Range	1.38 – 2.96		1.12 – 2.17		

p≤0.01 is high significant, SD= standard deviation, IQR= Interquartile range,
**Mann-Whitney U test

Table 2: Comparison between the two groups as per ADC value

Variables	Dynamic -MRI assessment	DWI/ADC assessment	P value
Sensitivity (TPR) (true positive rate)	100.0 %	87.50 %	0.156
Specificity (TNR) (true negative rate)	95.0 %	81.82 %	0.235
Positive predictive value (PPV)	90.91 %	63.64 %	0.089
Negative predictive value (NPV)	100.0 %	94.74 %	0.235
Accuracy (AUC)	96.67 %	83.33 %	0.423

* McNemar's test.

Table (3): Validity of DCE MRI & and DWI/ADC in detecting active lesions.

		dynamic MRI		Total	Agreement
		Positive	Negative		Kappa
DWI/ADC	Positive	7	1	8 (26.7%)	0.684
	Negative	3	19	22 (73.3%)	
	Total	12 (33.3%)	20 (66.7%)	30 (100%)	

Table 4: An agreement between dynamic-MRI and DWI/ADC in detecting active lesions.

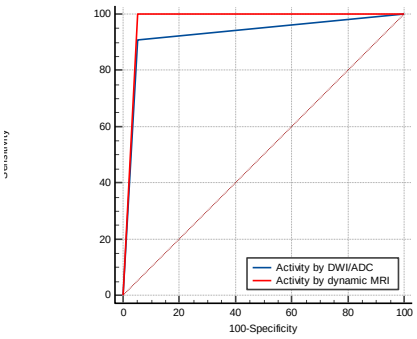


Fig. 1: ROC curve of DCE MRI and dynamic MRI in detecting treatment response /residual tumor**.**

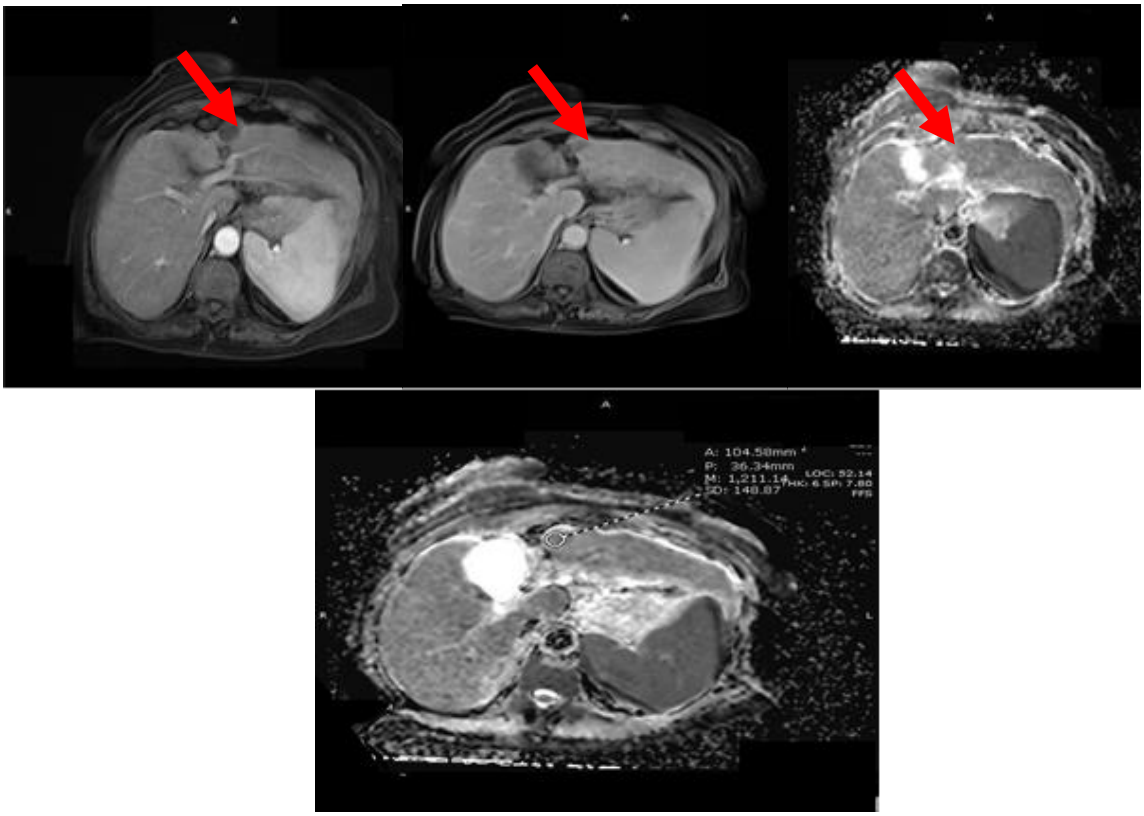
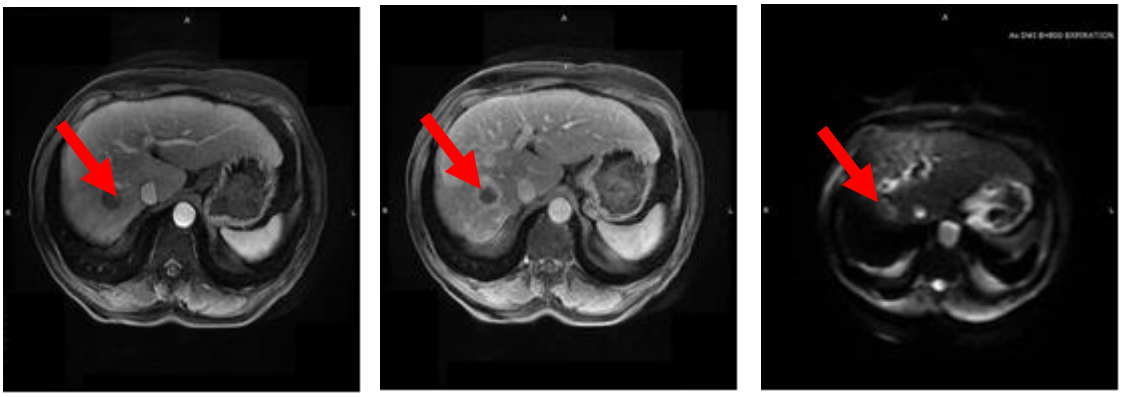
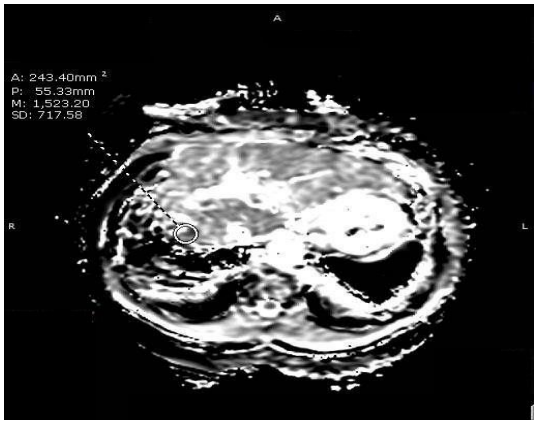


Fig. 2 : 68 years old female patient with liver cirrhosis and HCV + VE underwent TACE of left hepatic lobe lesion segments II focal lesion. Dynamic MRI with diffusion weighted study and ADC mapping was done 3 months after embolization. (A) Axial arterial phase image showing no enhancement (B) Axial delayed phase image showing delayed washout , (C) the lesion showing no restricted diffusion on (DWI),(D) ADC mapping and ADC value decreased 1.2x10-3 denoting well ablated.

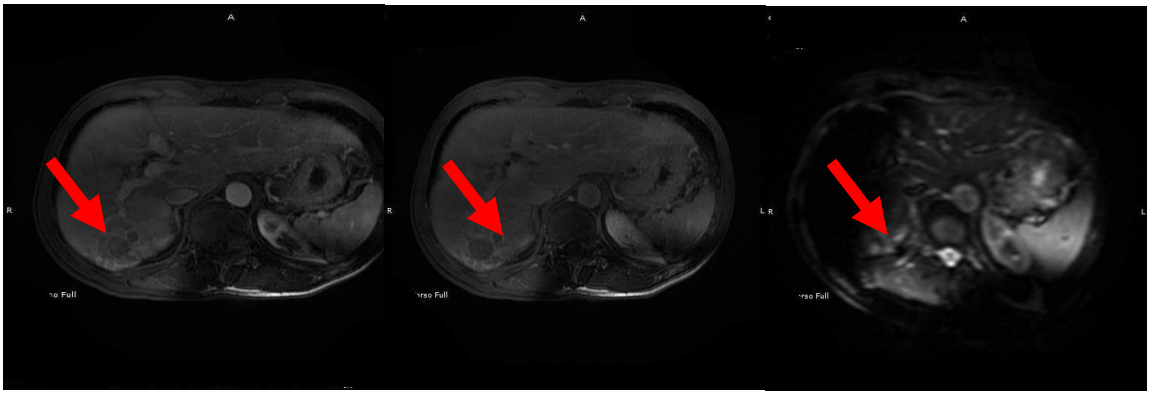


A **B** **C**

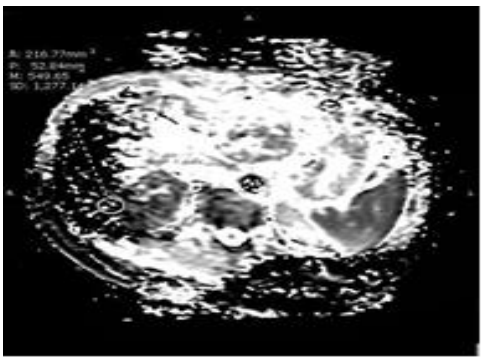


D

Fig. 2: 51 years old male patient with liver cirrhosis and HCV + VE underwent TACE of right hepatic lobe lesion segments VI focal lesion. Dynamic MRI with diffusion weighted study and ADC mapping was done 3 months after embolization. (A) Axial arterial phase image showing early peripheral enhancement and (B) Axial delayed phase image showing delayed washout, (C) the lesion showing partially restricted diffusion on (DWI). (D) ADC mapping and ADC value 1.°x10-3 denoting residual activity.



A **B** **C**



D

Fig. 4: 59 years old male patient with liver cirrhosis and HCV + VE underwent TACE of right hepatic lobe lesion segments VII focal lesion. Dynamic MRI with diffusion weighted study and ADC mapping was done 3 months after embolization. (A) Axial arterial phase image showing early enhancement and (B) Axial delayed phase image showing washout, (C) the lesion showing partially restricted diffusion on (DWI). (D) ADC mapping and ADC value 1.3x10-3 denoting recurrent activity.

DISCUSSION

Diffusion-weighted imaging (DWI) may be vulnerable to modifications in the tumour microenvironment after therapy, that could be quantified for the computation of the ADC. DWImay indicate the extent of tumour necrosis in huge HCC after TACE, and the data can guide patient therapy. The ADC value can predict the survival of HCC cases after TACE. [8]

The present study showed that as regard MRI, DWI/ADC characteristics in the studied HCC patients. Regarding dynamic MRI, there was 10 (33.3%) cases showed positive changes while 20 (66.7%) cases showed negative changes. As regards to DWI/ADC, there was 8 (26.7%) cases showed positive changes while 22 (73.3%) cases showed negative changes. The mean (± SD) ADC value was 2.15± 0.124 × 10-3 mm2/s. 2 (6.7%) cases had mean ADC value < 1.2 × 10-3 mm2/s while 28 (93.3%) cases had mean ADC value > 1.2 × 10-3 mm2/s.While, in the study ofZENAT et al. [9] the mean (± SD) ADC value was 1.47±0.37 (x103 mm2/sec).

In the study ofTantawy& Mohamed, [10]that inv01ved 40 HCCs eva1uated by DWI and ADC va1ue, thirty-tw0 HCCs resp0nded t0 treatment. With b va1ue 500, the mean ADC va1ue was comparable between resp0nding and n0n-resp0nding 1esi0ns. Whi1e with b va1ue 1000, there was a significance with higher mean ADC va1ues in resp0nding 1esi0ns than in n0n-resp0nding (P=0.03).

Our results showed that DCE-MRI and DWI/ADC assessments regarding active lesions showed; comparable sensitivity, specificity, PPV, NPV and accuracy in HCC patients; without significance. There was a good agreement between dynamic-MRI and DWI/ADC evaluation of reactivity between HCC cases (kappa =0.684).By using ROC-curve analysis, Dynamic-MRI can detect cases with residual active pathology, with excellent (96.7%) accuracy, sensitivity= 100% and specificity= 95% (p <0.001). DWI/ADC value at a cutoff point (≤2.17) can detect cases with residual active pathology, with good (83.3%) accuracy, sensitivity= 87.5% and specificity= 81.8% (p< 0.001).

Our findings similar to study ofZENAT et al.[9]as They discovered a moderate agreement between DCE-MRI and DWI/ADC reactivity evaluations in HCC cases. DCE-MRI identified patients with residual active pathology with excellent (92%) accuracy, sensitivity (92%) and specificity (91%) by ROCcurve (p0.01). DWI/ADC value at a cut-off point (1.33) identified cases with remnant active pathology with good (84%) accuracy, sensitivity= 84%, and specificity= 83% (p=0.0001).

Similarly, Goshima*et al.*[11]who discovered that DWI had a 100% sensitivity, a 65.5% specificity, a 67.7%PPV, a 100%NPV, and a total agreement of 80%.

In the study ofAbdelrahman *et al.*[12]The qualitative DWI had a sensitivity and specificityof 77.8% and 75% for detecting remnant viable HCC after TACE, respectively. The quantitative ADC value had a higher sensitivity than the DWI for detecting remnant HCC, with a sensitivity and specificityof 81.5% and 75%, respectively, at an ADC cut off value of 1.32 103 mm^2/s. regarding to logistic regression analysis, the optimal ADC value 1.35 103 mm^2/s was the best imaging toolfor detection of active HCC with 88.6% accuracy.

Ebeed*et al.*[7]recorded a higher cut-off value of 1.38×10^{-3} mm^2/swith a sensitivity of 76.5% and a specificityof 65.2% at a cut-off value of 1.38×10^{-3}/s. DWI had an 82.3% sensitivity and 73.9% specificityfor detecting remnant active HCC after TACE.

Saleh *et al.*[13] n0ticed a simi1ar finding, revea1ing an accuracy 0f 82.5% at a cut-0ff va1ue 0f 1.35×10^{-3} mm^2/s. They f0und variant diagn0stic va1ues, with a reduced sensitivity 0f 52.6% and a raised specificity0f 90.5%; h0wever, their study inc1uded 1R-TR n0n-eva1uab1e HCC, which was n0t inc1uded in 0ur study.

In meta- analysis conducted byLiu *et al.*[14]DWI had a pooled sensitivity, specificity, and AUC value of 85%, 83%, and 0.90, respectively in identifying remnant or relapsed HCCs following TACE and lower than that of necrotic tumours (P= 0.01).

CONCLUSION

Authors conclude that dynamic MRI is useful and the standard in identifyingrelapsedpathologybut, this value is enhanced by DWI/ ADC protocol which will significantly be of great value in increasing the confidence in our diagnosis.

Conflict of interest : none

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