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Diffusion-weighted imaging compared to dynamic MRI in early response assessment of locoregional therapy (by trans-arterial chemoembolization & microwave ablation) of hepatocellular carcinoma

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Abstract

Background Purpose of this study is to compare between dynamic contrast-enhanced and diffusion-weighted MRI imaging techniques in early response assessment of hepatocellular carcinoma (HCC) after transcatheter chemoembolization and microwave ablation.

Methods Retrospective study was done over a period of 36 months (June 2015–June 2018). The study was conducted on 69 cases; 61 patients were males and 8 were females patients age ranged from 45 to 72 years (median 60). All patients suffered from liver cirrhosis secondary to chronic viral hepatitis. They underwent diffusion-weighted MR imaging and subtraction dynamic MR imaging techniques after trans-arterial chemoembolization (TACE) and microwave ablation (MWA). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall agreement were calculated for both the dynamic and the DWI images. Apparent diffusion coefficients (ADCs) were calculated searching for a cutoff value using the receiver operating characteristic curve (ROC).

Results Our study results revealed moderate accuracy of diffusion MRI in the diagnosis of complete ablation (no residue) less than that of dynamic and subtraction sequences with 71.43% sensitivity, 88.52% specificity, 83.3% PPV and 79.4% NPV. This is attributed to that diffusion MR study is not able to detect small enhancing tumor foci that appears clearly on dynamic and subtraction MR studies. Also, these results are attributed to false positive results on diffusion study corresponding to liquefactive necrosis with hemorrhagic component post-ablation.

Conclusions Our study concluded that subtraction and dynamic MRI had more accuracy than diffusion compared to our follow-up results. So combined subtraction dynamic MR study and diffusion is the main technique of early evaluation of post-interventional therapy of HCC to avoid pitfalls of diffusion study.

Keywords Hepatocellular carcinoma, Diffusion-weighted imaging, Dynamic contrast-enhanced imaging

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Background

Hepatocellular carcinoma is a major worldwide health concern; it is third leading cause of overall cancer-related mortality and the sixth most common cancer. Hepatocellular carcinoma frequently presents as a rapidly growing tumor and has historically been associated with poor prognosis and outcomes [1].

Locoregional therapies including trans-arterial chemoembolization (TACE) and microwave ablation (MVA) are an important part of the management of HCC because tumors are resectable or meet transplant criteria at the time of diagnosis in only 5–10% of patients [2]. In addition, locoregional therapy has the advantages of preservation of hepatic parenchyma and overall less morbidity and mortality compared with resection [3].

The sole changes lesion size after TACE, couldn't be utilized as a response marker and recent guidelines states take that the residual viable tumor tissue is what really counts. So, we recommend that diffusion-weighted imaging (DWI) and subtraction dynamic magnetic resonance imaging (MRI) should be fundamentally included in after TACE therapy follow-up [4].

Therefore, it has been recommended to modify the RECIST criteria to take into account only the diameters of the viable areas of the target lesions (i.e., the regions of tumors showing contrast enhancement during the arterial phase). In modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC, similar to conventional Response Evaluation Criteria In Solid Tumors (RECIST), overall patient response is a result of the combined assessment of target lesions, non-target lesions, and new lesions.

Computed tomography (CT) remains the most widely used examination following patients immediately after TACE interventional procedure to confirm lipiodol retention by the tumor [5]. However recent imaging as subtraction dynamic MRI study and DWI improves sensitivity in detection of focal lesions, helps differentiate benign from malignant focal hepatic lesions as well as permits evaluation of treatment response to systemic and loco-regional therapies in primary and secondary hepatic malignancies [6].

Methods

Patients population

This study was conducted on 69 cases of HCC with 100 focal lesions who underwent TACE and microwave ablation. Follow-up dynamic MR imaging is done within 1–3 months after treatment which was considered the gold standard imaging modality in detecting if there was residual tumor or not. The patients were referred from Department of tropical and internal medicine to the Department of diagnostic and interventional radiology over a period of 36 months (June 2015–June 2018). The age of patients' was between 45 and 72 years (median 60), regarding patients gender 61 were males while 8 were females. All patients suffered from liver cirrhosis secondary to chronic viral hepatitis. Patients who developed new lesions (remote from ablated lesions) or having a contraindication to MRI examination were excluded from our study.

Magnetic resonance imaging (MRI)

MRI was done using 1.5-T MRI scanner (Philips Inguinea) equipped with phased-array torso surface coil.

Examination includes pre-contrast axial T1- , T2- and SPAIR-weighted images in addition to dynamic contrast-enhanced and diffusion-weighted MRI imaging.

Dynamic study was done after injection of bolus of gadolinium contrast by the dose of 0.1 mmol/kg body weight injected at the rate of 2 ml/s, followed by manual injection of 20 ml of sterile saline solution through the antecubital vein.

Dynamic-weighted MRI imaging using T1 THRIVE (High Resolution Isotropic Volume Examination) technique. Pre-contrast series then followed by three consecutive post-contrast series, which are arterial and portal phases with 18–21 s intervals (including 17–20 s with breath-holding technique for image acquisition regarding to the size of the liver and 1 s delay for rebreathing at the start of each phase imaging of each phase) followed afterwards by 5-min delayed imaging phase. Acquisition of images starts 10 s after injection of contrast. Regarding the respiratory cycle, all patients were imaged at end expiration.

DWI was performed before the dynamic imaging using respiratory triggered fat suppressed single-shot echoplanar sequence by applying three different b factors of 0, 500, and 1000 s/mm^2.

Imaging analysis

The original data were transported to the workstation then the T1, T2 and fat saturated signal characteristics as well as pattern of enhancement at dynamic imaging, subtracted images, and color mapping were assessed by experienced radiologist with 10-year radiological training expertise.

Furthermore, all dynamic post-contrast images are subtracted from pre-contrast images to detect viable tumor tissue in case of post-interventional hemorrhage within ablated focal lesions especially after microwave ablation.

ADC measurement is done by drawing region of interest at areas of sustained hyperintensity on diffusion images.

Statistical analysis

Data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 23.0 to obtain statistical comparison between the different groups, the significance of difference was tested using one of the following tests:

- Student's t-test (Paired): Used to compare between mean of two related groups of numerical (parametric) data.
- Inter-group comparison of categorical data was performed by using Pearson's chi square test (X2-value) or fisher exact test or Monte-carlo.

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of dynamic MRI, diffusion MRI, ADC and subtraction MRI to differentiate between residue and residue groups were examined using receiver operating characteristic curve (ROC) analysis and for ADC to determine the best cutoff point as well as the diagnostic power of each test. *P* value < 0.05 was considered statistically significant.

Results

After evaluation of subtraction dynamic MR and diffusion studies done for 69 patients with HCC who underwent interventional therapy showed, six cases with no tumor residue diagnosed having residue by subtraction MRI (false positive diagnosis) while they diagnosed all the cases with no residue truly (by subtraction MRI). This means excellent accuracy of subtraction MRI in the diagnosis of complete ablation (no residue) with 90.2% sensitivity, 89.8% specificity, 88.5% PPV and 91.4% NPV (Table 1) (Fig. 1).

Seven cases with no tumor residue were diagnosed having residue by diffusion MRI (false positive diagnosis) while 7 cases with residue having no residue by diffusion MRI. This means that diffusion aids in evaluation of tumor residue with accuracy 80.9%, 71.4% sensitivity, 88.52% specificity, 83.3% PPV and 79.4% NPV (Table 2) (Fig. 2).

Six cases with no residue (by subtraction dynamic MRI) having residue by diffusion MRI (10.2%) while it shows that 23 cases diagnosed with residue (by dynamic MRI) having no residue by diffusion MRI (45.1%) (Table 3).

ADC value for non-residue group was about 1.35 and was about 0.99 for residue group, there was ADC statistically significance difference between residue and non-residue groups being higher in non-residue group than residue with cutoff value > 1.15. At this cutoff value, sensitivity was 81.6%, specificity 77.05%, PPV 74.1% and NPV 83.9% (Table 4) (Fig. 3).

Discussion

Hepatocellular carcinoma (HCC) is ranked as the most common primary hepatic malignancy and the third cause of cancer mortality worldwide. Locoregional therapies (LRTs) are considered the most widely used treatment modality for HCC nowadays and can be done either through thermal ablation or intra-arterial therapies [7].

Tantawy and Mohamed study included 36 patients 28 of them were males and 8 of them were females with male-to-female ratio about 3.4:1. Our study also concluded that HCC was commoner too in males than females, it included 50 patients that had HCCs, 44 of them about (88%) were male and 6 of them were females (12%) with male-to-female ratio about 4:1. Despite small sample size, it was too close to the world ratio 2.4:1[8].

Dynamic MRI is considered as an indicator for efficacy of treatment depending upon the criteria of enhancement and wash out so the European association for the study of liver disease (EASL) and the American association for the study of liver disease (AASLD) considered both the enhancement pattern of the tumor and its washout out as a biomarker for HCC viability [9].

Minami and Kudo stated that dynamic contrast-enhanced imaging is considered the main imaging modality in early detection of residual/recurrent tumors after interventional procedure of TACE and MWA [10]. Osama and colleagues also revealed that dynamic MRI had a sensitivity of 90.5%, a specificity of 96.6%, a positive predictive value of 95% and a negative predictive value of 93.3% [11]. That is why in our study we considered dynamic MR study as the main method of imaging.

Subtraction MRI study has fundamental role in evaluation of tumor necrosis after microwave or radiofrequency ablation. It is difficult to detect the pattern of enhancement at the ablated zone on the pre-contrast images due to the high signal intensity seen at T1-weighted image due to the coagulation necrosis. In order to get rid of this problem, dynamic contrast-enhanced subtraction technique is done in which through the use of MRI software; image-by-image the corresponding contrast-enhanced and non-enhanced

Table 1 Diagnostic accuracy of subtraction dynamic MRI

Count	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Accuracy
TP: 46 TN: 53 FP: 6 FN: 5	0.96 (0.90–1.00)	90.2%	89.8%	88.5%	91.4%	90%

TP True positive, *TN* True negative, *FP* False positive, *FN* False negative, *AUC* Area under the curve, *CI* Confidence interval, *PPV* Positive predictive value, *NPV* Negative predictive value

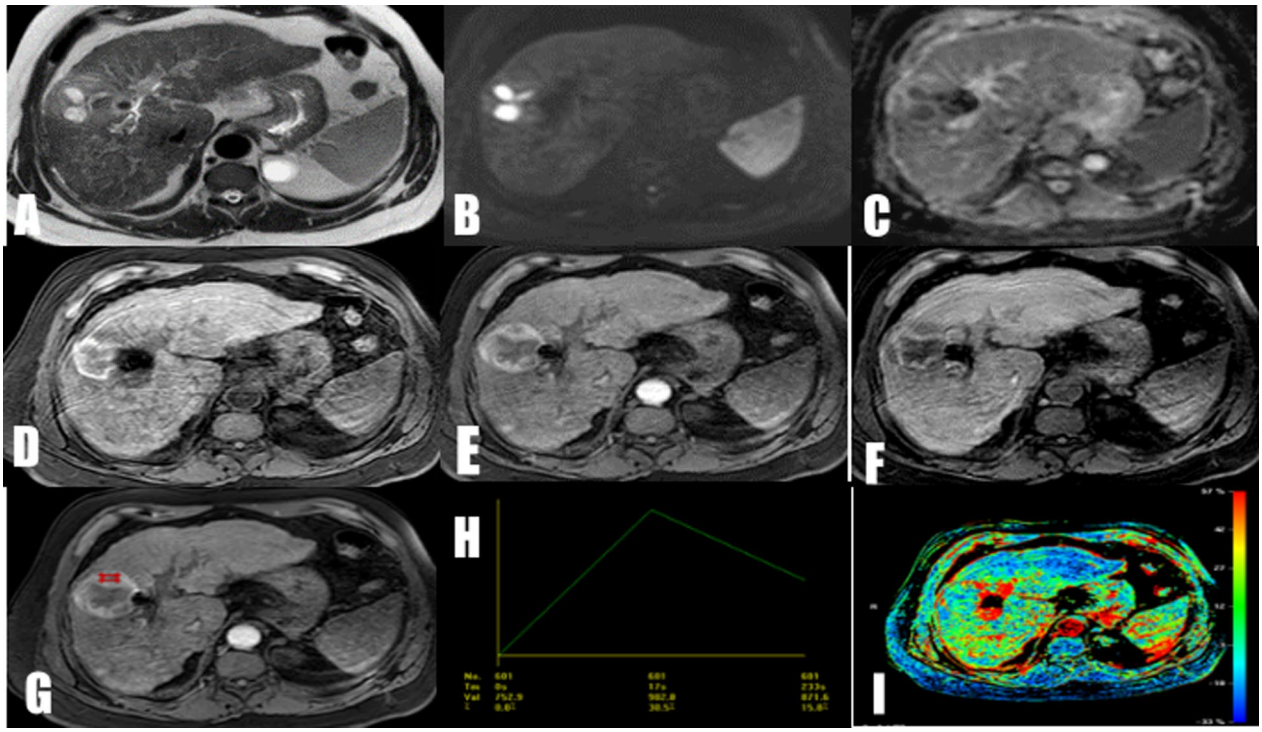

Fig. 1 MR imaging of male patient 1 m after microwave ablation. **A** Axial T2 seq. reveals central coagulative and liquefactive necrosis with hemorrhagic component as well as reveals peripheral hyperintensity at its lateral aspect and small foreign body at its medial aspect displaying signal void (suggesting broken needle). **B** & **C** Diffusion MR study and ADC map reveals central area of restricted diffusion within ablated lesion corresponding to liquefactive necrosis with hemorrhagic component. **D**, **E** & **F** Dynamic MR study reveals peripheral enhancement of ablated lesion at arterial phase with delayed washout. **G** & **H** Time insanity curve reveals type III curve of ROI placed at periphery of ablated lesion denoting viable tumor tissue. **I** color map also reveals enhancement at periphery of ablated lesion

Table 2 Diagnostic accuracy of diffusion MRI

Count	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV	Accuracy
TP: 35 TN: 54 FP: 14 FN: 7	0.81 (0.71–0.92)	71.43%	88.52%	83.3%	79.4%	80.9%

TP True positive, *TN* True negative, *FP* False positive, *FN* False negative, *AUC* Area under the curve, *CI* Confidence interval, *PPV* Positive predictive value, *NPV* Negative predictive value

T1-weighted sequences are subtracted digitally. The rational for this procedure was to get rid of the high signal intensity previously detected on pre-contrast T1-weighted image from the postprocessed images and by this the remaining high signal is because of enhancement alone. By subtraction, MRI imaging technique radiologists accuracy in noticing enhancement in previously ablated zone is tremendously improved and this helps in significant improvement of the overall detection of treatment response after locoregional therapy by MRI imaging modality In our study, we also add post-processing subtraction to dynamic MR imaging [12].

Our results revealed excellent accuracy of subtraction dynamic MRI in the diagnosis of complete ablation (no residue) with 100% sensitivity, 91.5% specificity, 89.3% PPV and 100% NPV exactly the same like dynamic MRI**.**

DWI is utilized to identify water molecules diffusion restriction in body tissues, as assessed by two or more imaging sequences on MRI. Restriction of water molecules movement appears as high signal on DWI sequences and low signal on apparent diffusion coefficient (ADC) sequences. After locoregional therapy, the high signal noted in ADC sequence is owing to tissue necrosis. Residual/recurrent disease during the first 90 days after locoregional therapy can be detected by

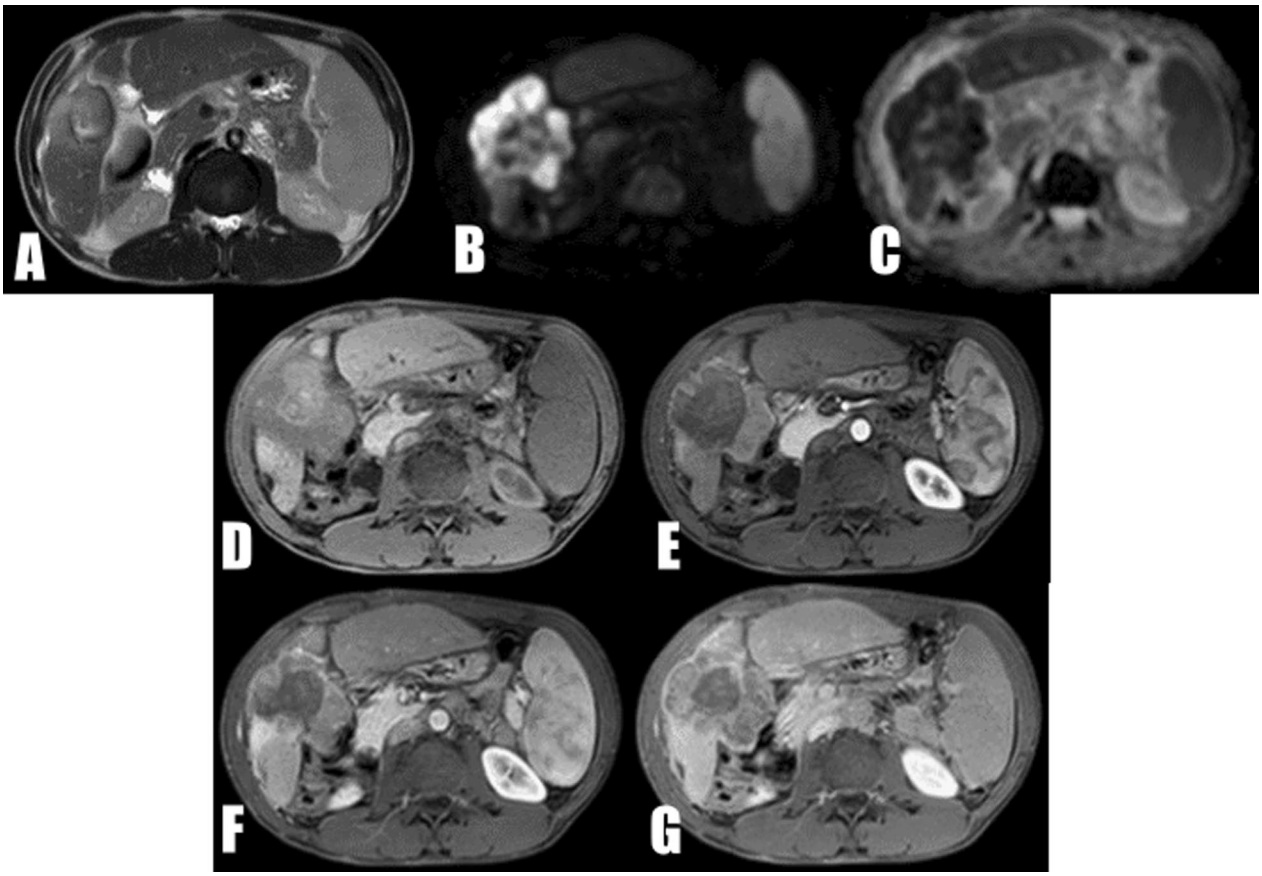

Fig. 2 MR imaging of female patient with elevated AFP 2 m after TACE of right liver lobe HCC. **A** Axial T2 seq. reveals central coagulative and liquefactive necrosis at ablated lesion with peripheral hyperintensity. **B** & **C** Diffusion MR study and ADC map reveals restricted diffusion at periphery of ablated lesion denoting malignant viable tumor tissue **D**–**G** Dynamic MR study shows no contrast enhancement at periphery of ablated lesion in arterial or portal phases

Table 3 Association between subtraction dynamic MRI & diffusion

	Subtraction dynamic MR				*P*
	No residue group *n* = 59		Residue group *n* = 51		
	Count	Column *N* %	Count	Column *N* %	
Diffusion					
Free diffusion	53	89.8%	23	45.1%	< 0.001*
Restricted diffusion	6	10.2%	28	54.9%	

Data expressed as frequency (Number-percent)

P: Probability

*significance < 0.05

Test used: Chi-square

DWI imaging technique. Some authors have stated that DWI can be used in tumor response prediction as early as 1 month [7].

Also, Kamel and colleagues concluded that diffusion of water is better with tumor necrosis, by that ADC value aids in differentiating viable from non-viable tumor tissue [13].

Contrast media injection affects diffusion and ADC value in ways that it may decrease ADC value by decreasing intra vascular signal intensity so decreasing

Table 4 Diagnostic accuracy of ADC

Count	AUC (95%CI)	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
TP: 40 TN: 47 FP: 14 FN: 9	0.89 (0.76–0.98)	1.15	81.6%	77.05%	74.1%	83.9%	79.0%

TP True positive, *TN* True negative, *FP* False positive, *FN* False negative, *AUC* Area under the curve, *CI* Confidence interval, *PPV* Positive predictive value, *NPV* Negative predictive value

the perfusion effect on calculated ADC. Also, it may decrease DWI signal intensity especially on b0 and b500 images by T2 shortening effect [14].

In our study, we also performed DWIs before dynamic study to avoid the effect of contrast media on ADC values, this is correlated with studies done by Chiue and colleagues [14].

Osama and coworkers revealed 100% sensitivity, 65.5% specificity 70% PPV, 100% and 80% overall accuracy for diffusion-weighted imaging. Our study results disagreed to the one done by Osama and colleagues and revealed moderate accuracy of diffusion MRI in the diagnosis of complete ablation (no residue) less than that of dynamic and subtraction sequences with 71.4% sensitivity, 88.5% specificity, 83.3% PPV and 79.4% NPV. This is attributed to that diffusion MR study not able to detect small enhancing tumor foci that appears clearly on dynamic and subtraction MR studies. Also, these results are attributed to false positive results on diffusion study corresponding to liquefactive necrosis with hemorrhagic component post-ablation.

Comparing dynamic to diffusion MRI our study showed that six cases with no residue (by dynamic MRI) have residue by diffusion MRI (10.2% false positive results) while showed 23 cases with residue (by dynamic MRI) having no residue by diffusion MRI (45.1% false negative results).

This showed an agreement with a previous study done by Elsaid and colleagues who had in their study many diffusion pitfalls compared to dynamic study with sensitivity 70% specificity 75% PPV 82% and NPV 60% for reader 1 and was 76% sensitivity, 90% specificity, 92% PPV and 69% NPV for reader 2 [8].

When measuring ADC value, we tried to put the ROI within the area in the lesion corresponding to the most enhancing area in dynamic study, our results concluded that mean ADC value for non-residue/recurrence group was about 1.35 and was about 0.9 for residue/recurrence group, there was ADC statistically significance difference between malignant and non-malignant being higher in no residue/recurrence group with cutoff value > 1.15. At this cutoff value sensitivity was 81.6%, specificity 77.05%, PPV 74.1% and NPV 83.9%.

Bonekamp and co-workers also observed increased ADC values in ablated lesions compared to non-ablated by mRECIST criteria for cTACE [15]. However, Yuan and colleagues reported ADC cutoff value for ablation 1.84×10^{-3} mm^2/s with 92.3% sensitivity and 100% specificity which is far from ADC cutoff value in our study [16].

Osama and colleagues also concluded significance of ADC value in differentiation between benign and malignant with cutoff value 1.26. It is near to our results in which cutoff was 1.15.

Tantawy and Mohamed also concluded that ADC values were significantly higher in lesions that responded to TACE or RFA than in non-responding lesions. The mean ADC of the lesions before treatment was 1.27 ± 0.25 10×3 mm^2/s and increased after treatment in responding lesions to reach 1.57 ± 0.22 10×3 mm^2/s with a statistically significant difference ($P=0.002$).

Our results agreed with the previous studies however dis-agreed with a study done by Elsaid and colleagues who stated that ADC value is variable and can't determine cutoff value for ablation at the area under the curve. (AUC) explaining that by many diffusion pitfalls.

False positive results in our study (ablated lesions which show restricted diffusion although they have no tumor residue on dynamic MRI) may be attributed to post-treatment sequelae which creates heterogenous signal of tumor as liquefactive necrosis and hemorrhage as well as intralesional lipidol uptake which show restricted diffusion. This also was discussed by many studies conducted by Elsaid, Yuan and Osama & their colleagues.

Our study showed false negative lesions (ablated lesions which had residue on dynamic MRI and showed free diffusion on DWIs), this may be attributed to primary high ADC value of well-differentiated tumors, which remains high even after treatment and may be due to small lesions (< 1.5 cm) not appeared on DWI.

This was correlated with the study of Gue and coworkers who included 27 patients and found that those 27 HCC patients could be classified into 6 well, 10 moderately, and 11 poorly differentiated HCCs. The overall ADC value for all HCC cases was $(1.28\pm0.19)\times10^{-3}$ mm^2/s. The ADC value for poorly differentiated HCCs was

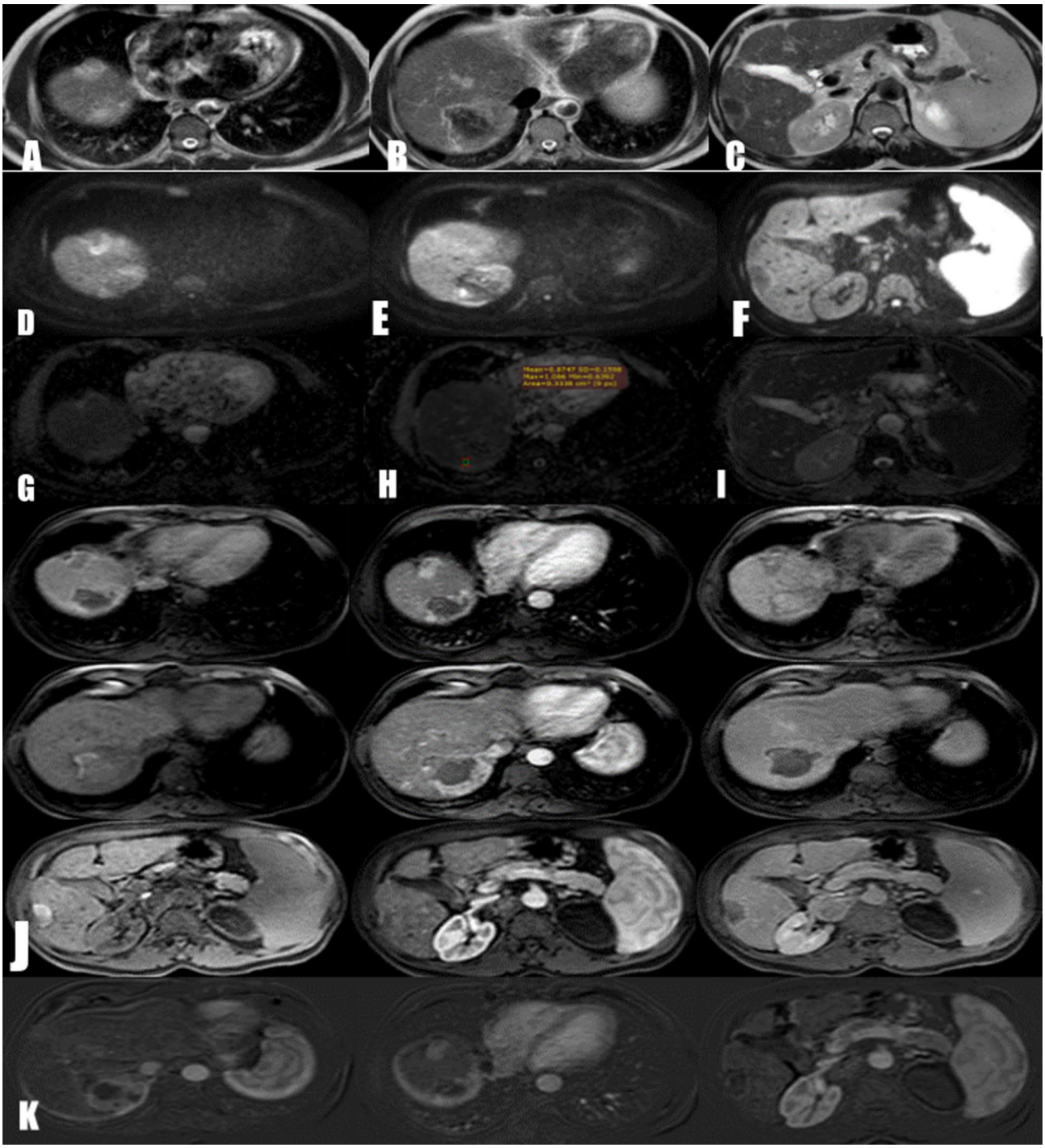

Fig. 3 MR imaging of male patient 2 m after combined microwave and TACE for multifocal right lobe HCC. **A**–**C** Axial T2 seq. reveals coagulative necrosis within central portion of ablated lesion and peripheral hyperinensity at segments VIII and VII focal lesions. **D**–**I** Diffusion MR study and ADC map reveals areas of restricted diffusion at periphery of segments VIII and VII (ADC value = 0.8) as well as free diffusion of segment V/VI focal lesion. **J** & **K** Dynamic contrast-enhanced MR study and subtraction reveal no contrast enhancement of segment V/VI focal lesion at arterial or portal phases as well as areas of arterial and portal enhancement at periphery of segments VIII and VII focal lesions with delayed washout denoting viable tumor tissue

$(1.16 \pm 0.16) \times 10^{-3}$ mm^2/s, significantly lower than well differentiated $[(1.43 \pm 0.09) \times 10^{-3}$ $mm^2/s]$ and moderately differentiated $[(1.34 \pm 0.19) \times 10^{-3}$ $mm^2/s]$ [17]. And from that we concluded that the histological grade of 1ry tumor affects ADC value significantly. So, well differentiated tumors may have high ADC value which may still remain high even after treatment and make an obstacle in diagnosis by giving false negative results.

This misinterpretation may be also due to complication of treatment which is better understood by dynamic combined subtraction which have greater specificity than diffusion which may give high false positive and negative results, this is correlated with studies of Elsaid & Osama and their colleagues.

Conclusions

Our study concluded that subtraction and dynamic MRI had more accuracy than diffusion compared to our follow-up results. So combined subtraction dynamic MR study and diffusion are the main technique of early evaluation of post-interventional therapy of HCC to avoid pitfalls of diffusion study alone especially in initially small sized lesion (smaller than 1.5 cm).

Limitations

The retrospective nature of the study. Some desired clinical data would have been available if the study had been prospective.

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Trans-arterial chemoembolization
MWA	Microwave ablation
PPV	Positive predictive value
NPV	Negative predictive value
ADCs	Apparent diffusion coefficients
ROC	Receiver operating characteristic
LRTs	Locoregional therapies.
mRECIST	Modified response evaluation criteria in solid tumors
RECIST	Response evaluation criteria in solid tumors
DWI	Diffusion-weighted imaging
MRI	Magnetic resonance imaging
CT	Computed tomography
THRIVE	T1-weighted high-resolution isotropic volume examination
TP	True positive
TN	True negative
FP	False positive
FN	False negative
AUC	Area under the curve
CI	Confidence interval
P	Probability
AASLD	American association for the study of liver disease.
EASL	European association for the study of liver disease

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Author contributions

All authors have read & approved the manuscript. The study concept and design were proposed by AE, SS, & MZ. Statistical analysis of data; SS & MZ. Writing the original manuscript; AE. Revision of the manuscript for important intellectual content; AE& MZ.

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Availability of data and materials

All the scientific data are available and presented in the manuscript. The source data are available on request.

Declarations

Ethics approval and consent to participate

Written informed consent was waived by the Institutional Review Board (IRB), Institutional Review Board (IRB) was obtained, IRB approval: R.23.05.2180.

Consent for publication

All the patients were consented and informed of possible research publication. All authors hereby confirm all the copyrights if such work will be accepted in the Egyptian Journal of Radiology and Nuclear Medicine (EJRNM).

Competing interests

The authors declare that they have no competing interests.

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