Research Article

The value of ADC calculations in assessment of early response of hepatocellular carcinoma (HCC) to trans arterial catheter chemoembolization (TACE).

Hosny S. Abd Elghany, Mostafa M. Mostafa and Kareem S. Said Megahed
Department of Radiology, Faculty of Medicine, Minia University, Egypt

Abstract
Transcatheter arterial chemoembolization (TACE) is a well-accepted method for Treatment of unresectable hepatocellular carcinoma (HCC). Determining the success of treatment by imaging studies would help to guide subsequent therapeutic planning. Diffusion-weighted imaging (DWI) with calculation of corresponding apparent diffusion coefficient (ADC) maps can give us an impression about the extent of the tumor necrosis after TACE. Also rapid image acquisition and dispensing of contrast are considered superior pros. ***Objective:*** To investigate changes in apparent diffusion coefficient (ADC) levels pre and post TACE to monitor early therapeutic response of hepatocellular carcinoma (HCC) to transcatheter arterial chemoembolization (TACE). ***Patients and methods*:** 20 patients with 22 lesions included in the study, underwent TACE for HCC lesions, All patients had MR-DWI pre TACE and 1 month after TACE with calculation of ADC values and comparing the percentage of change in ADC level pre and post TACE in 1 month after TACE with the results of contrast enhanced Dynamic MRI 3 or 6 month after TACE based on MRECIST criteria. ***Results*:** Of about 20 patients, 22 lesions was treated, ADC levels 1 month post-operative showed 75% sensitivity, 80% specificity and about 77.27% accuracy. It was found that the specificity of degree of ADC change is maximized by gaining at least 22% increase in ADC value, and the sensitivity is maximized by gaining less than 15% increase in ADC. At these points sensitivity increased to 91.67% and specificity up to 90%. ***Conclusion*:** the calculation of percentage of change in ADC levels 1 month after TACE with addition of specific Cut off values can improve the accuracy of assessment of early response to TACE and create proper planning for achievement of treatment goals. Although larger, more definitive and quantitative studies with clinical end points are needed.

Keywords: chemoembolization, hepatocellular carcinoma, therapeutic planning

Introduction
Early detection and treatment of residual viable HCC tissue will significantly have a positive impact on long term results and improvement of patient survival.[1] Different imaging modalities are used in the assessment of tumor response to TACE, typically contrast enhanced CT or MRI imaging, and functional response based on MRI-DWI.[2] DWI with corresponding ADC levels based on the free mobility of water molecules in tissues as intact necrotic cells with lost membrane integrity allow facilitation of water molecules mobility reflecting a realistic image about tumor internal changes after treatment in terms of tumor necrosis.[3]

Aim of the work
Assessment of early response of HCC to TACE by monitoring the percentage of change of ADC level pre TACE and after 1 month post TACE and correlation of its results with dynamic contrast images in the 3 or 6 month follow up period based on MRECIST (modified response evaluation criteria in solid tumors) to assess the validity of using the percentage of ADC change as a marker for assessment of early response of HCC to TACE.

Patients and methods.
Study participants
The current study was conducted during June 2018 through May 2019. After ethically approved

by our institution committee, twenty patients included in this study. All diagnosed with HCC by different dynamic imaging modalities. All patients are candidate for TACE based on Barcelona staging system performed in our department. All participants had pre-operative imaging, then follow up by triphasic CT or dynamic MRI with DWI of the liver within 1, 3 and 6 months post therapy to be recruited in the study.

Inclusion criteria

Patients with preserved liver function (Child-Pugh ≤ 7 points). HCC lesions should be either intermediate-stage (BCLC B) HCC and < 50% of hepatic volume or early-stage (BCLC A) HCC not candidates for other treatment options with PS 0.

Exclusion criteria

Patients having Contraindications to contrast media, e.g. patients with renal failure, or contraindications to MRI e.g. cardiac pacemakers. Contraindications to CT e.g. Pregnancy. And finally patients with decompensated cirrhosis (Child-Pugh > 8).

MRI imaging

The device used was a 1.5-T MR system (Philips achieva) with eight-channel phased-array coil used for acquisition of liver images. Synchronization with patients' breath was achieved by placing a "respiratory" belt around their abdomen.

MRI protocol

a) Pre-contrast imaging included:

- T1 weighted (T1W) images: repetition time (TR)=10msec, echo time (TE)=4.58msec, matrix 179/320, slice thickness 7-8mm, slice gap 1-2 mm.
- T2 weighted (T2W) images: TR ≥445ms, TE=26-28 msec, matrix 180-200x240 with a field of view: 365, slice thickness 7-8mm, slice gap 1- 2mm.
- T2 SPAIR (Spectral Attenuated Inversion Recovery) fat suppression sequence: TR ≥400msec, TE=80msec, matrix 204x384 with a field of view: 365, slice thickness 7-8mm, slice gap 1- 2mm.
- Heavy T2 weighted images: TR=520msec, TE=200msec, matrix 235/384 with a field of view: 375, slice thickness 7-8mm, slice gap 1- 2mm.

b) Dynamic study:

Dynamic multiphase 3D FSPGR T1-weighted sequence, before and after a gadolinium contrast agent (Gd-DTPA 25 μmol/kg - 0.1 mL/kg). 3D FSPGR sequences. A dynamic multiphase study (arterial, portal and delayed phases) carried out using the smart prep system. A double injector used with 0.1 mmol/kg of Gadolinium injected IV at a rate of 4 mL/sec followed by a 20–30 ml saline flush. Imaging in the arterial phase (25-30 seconds post-injection), the portovenous phase (60-80 seconds post-injection) and the equilibrium phase (3-5 minutes post-injection) during breath-hold undertaken with a T1 2D.

c) Diffusion study:

Respiratory-triggered fat-suppressed single-shot echo planar DW imaging performed by using b values 0, 500 & 800 sec/mm2 followed by computer-generated ADC mapping of the lesion by placing ROI on different parts of the lesion repetition time (TR) ≥1880 msec, echo time (TE) = 70 msec, number of excitations (NEX)=3, matrix 256x256 with a field of view as small as possible.

Imaging analysis and assessment of treatment response

HCC Lesions assessed for their ADC values pre-TACE and within 1 month to measure the percentage of change in ADC, this was correlated with MRECIST results in 3 or 6 month follow up period.

In MRECST the Target Lesions Response includes:-

- Complete Response (CR):-
  - Disappearance of any intratumoral arterial enhancement in all TLs.
- Partial Response (PR):-
  - At least a 30% decrease in the sum of diameters of the viable TLs (arterial enhancement of the HCC lesions), taking as reference the baseline sum diameters of TLs.
- Progressive Disease (PD):-
  - At least a 20% increase in the sum of diameters of the viable TLs (arterial enhan-

cement of the HCC lesions), taking as reference the smallest sum of diameters of viable TLs on study provided that the absolute increase must be 5 mm at least.

- Stable Disease (SD):-
  - Neither PR nor PD, taking as reference the smallest sum of diameters on study.

Non-Target lesions (Non-TL) are all other lesions including:

- Small lesions <1cm.
- Lesions with ill-defined borders e.g. infiltrative HCC.
- Other lymph nodes shortest diameter ≥1 and <1.5 cm.

Results

20 HCC patients their ages ranged from 48 to 73 years old, 17 of them were males and 3 were females. In correlation of early response of HCC lesions by ADC values of treated lesions compared to contrast enhanced studies based on mRECIST, The following was obtained; CR patients had highest postoperative ADC levels and 80% of the lesions showed unequivocal increased ADC with average increase about 48% otherwise 20 % showed minimal increase in ADC value that was statistically not significant. This was also achieved by mRECIST in which 80% showed no enhancement and only 20% showed indeterminate enhancement. (table 1).

Table (1):- Summary of CR group results.

Patients		Pre TACE	Post TACE	
			1 month	6 month
Complete response (CR) group (10 patients	Enh.	100 % of lesions showed non-equivocal homogenous or heterogonous patchy Enh.	80 % showed –ve Enh. 20 % showed peripheral or indeterminate Enh.	100 % of lesions showed –ve enhancement.
	DWI	90% of lesions were restricted (mean ADC = 0.99±0.12) 10 % were equivocal (ADC = 1.21)	80% of lesions showed unequivocal increase ADC an average of 48% 20 % of lesions showed no significant increase. (Overall mean ADC= 1.4±0.18)	80% of lesions showed unequivocal similar ADC values to 1 month values (Overall mean ADC = 1.42±0.13)

The results obtained in PR group where about 50% of lesions showed increase of ADC value by about 22% and 50% showed no significant increase (table 2).

Table (2):- Summary of PR group results.

Patients		Pre TACE	Post TACE	
			1 month	3 month
Partial response (PR) group (4)	Enh.	100 % of lesions showed non-equivocal Enh.	100 % showed residual Enh.	
	DWI	100 % of lesions were restricted (Overall mean ADC = 1.08± 0.04)	50% of lesions showed increased ADC an average of 22% 50% showed no significant increase (Overall mean ADC = 1.32± 0.06)	

SD group, where all lesions showed residual enhancement, 66% of lesions ADC levels showed no significant changes whereas 33% showed mild increase (table 3).

Table (3):- Summary of SD group results.

Patients		Pre TACE	Post TACE	
			1 month	3 month
Stable disease group(SD) (2 patients) 3 lesions	Enh.	100% of lesions showed non equivocal homogenous or heterogonous patchy Enh.	100 % showed residual Enh.	
	DWI	100% of lesions were restricted (Overall mean ADC = 0.96±0.23)	33% of lesions showed increase ADC an average of 10% 66% showed decrease ADC by about 8%. (Overall mean ADC = 1.09)	

The ADC values of PD group was the least affected and 75 % lesions either showed no significant change or decrease in ADC levels. The same was obtained by application of MRECIST in 6 month follow up (table 4).

Table (4):- Summary of PD group results.

Patients		Pre TACE	Post TACE	
			1 month	3 month
Progressive disease(PD) (3 patients) 4 lesions	Enh.	100 % of lesions showed non-equivocal Enh.	25 % showed –ve Enh. 75 % showed residual Enh.	Multiple new lesions showed non-equivocal Enh.
	DWI	100 % of lesions were restricted (Overall mean ADC = 0.95±0.13	25% showed increase ADC by 20%. 25% showed no significant change 50% showed decrease ADC by 14%. (Overall mean ADC = 1.07±0.37)	Multiple new lesions showed overall decrease in ADC (Overall mean ADC = 0.86± 0.09)

Only 1 patient postoperative imaging showed advanced necrosis hindered measurement of an un-interrupted diameter of enhancement, MRECIST not adapted. However ADC level showed residual low values (1.18 x 10-3 mm2/sec) (table 5).

Table (5):- MRECIST not adapted lesions.

Patients		Pre TACE	Post TACE	
			1 month	3 month
Residual activity but not adapted to mRECIST (1 patient	Enh.	Showed patchy Enh.	Showed non-conclusive pattern of Enh.	Showed heterogeneous Enh.
	DWI	were restricted ADC = 1.02	Showed widely varied ADC levels ADC = 1.18 – 1.7	

Of about 20 patients, 22 lesions was treated, ADC levels 1 month post-operative showed 75% sensitivity, 80% specificity and about 77.27% accuracy. While Contrast based assessment achieved 83.33% sensitivity, 80% specificity and about 81.82% accuracy. It was found that the specificity of degree of ADC change is maximized by gaining at least 22% increase in ADC value, and the sensitivity is maximized by gaining less than 15% increase in ADC. At these points sensitivity increased to 91.67% and specificity up to 90%.

Cases presentation

Case 1

Sixty two years old male patient with HCC lesion seen at anterior-inferior segment of right hepatic lobe (segment V). Patient underwent TACE. 1 month and 6 months follow up by dynamic MRI and DW-MRI was done. (Figure 1)

Case 2

Fifty four years old male patient with HCC lesion seen at segment IVb of left hepatic lobe. Patient underwent TACE. 1 month and 6 months follow up by dynamic MRI and DW-MRI was done (Figure 2)

Figure (1):-
(A) MRI-T1WI Arterial phase
(B) MRI-T1WI portovenous phase
(C) DW-MRI images (b-value 800).
(D) Corresponding ADC map

Pre-operative images:-

(A) and (B) images show Segment V hepatic focal lesion with arterial enhancement measures about 4.35 cm and portovenous washout denoting active HCC lesion.

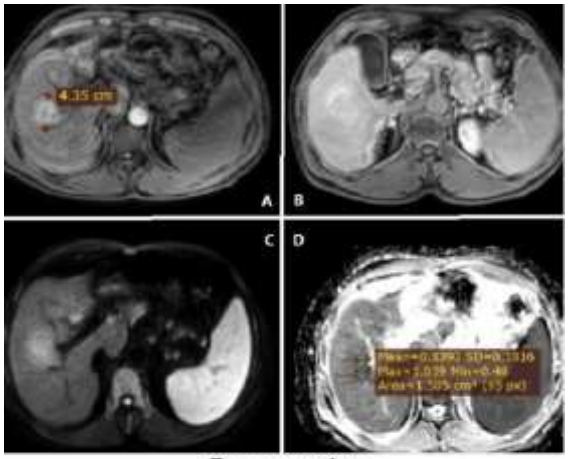
(C) and (D) images Show Diffusion restriction with show average ADC value (0.83 x 10-3 mm2/sec). Diffusion restriction was noted with hyper signal at DWI and corresponding low-signals at ADC.

1 & 6 month follow up images:-

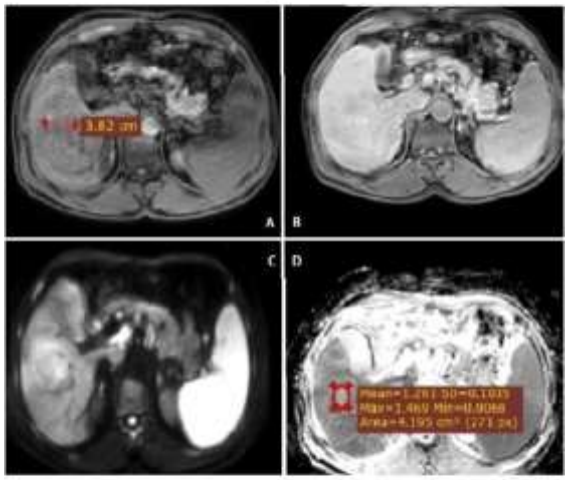
No arterial enhancement denoting inactive lesion in 1 and 6 months.

Early changes of ADC within the lesion at 1 month follow up, average ADC value of (1.26 x 10-3 mm2/sec) with percentage of ADC change pre-treatment and 1 month follow up about 50%...Denoting tumor necrosis.

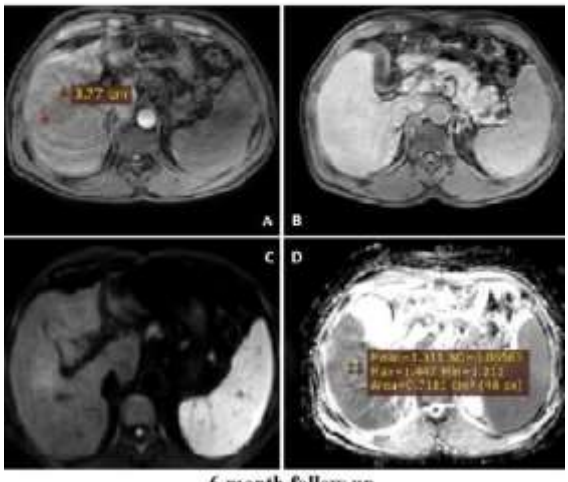
Diagnosis:- Complete response according to MRECIST criteria with early prediction in 1 month period by change of ADC level.



Pre operative



1 month follow up



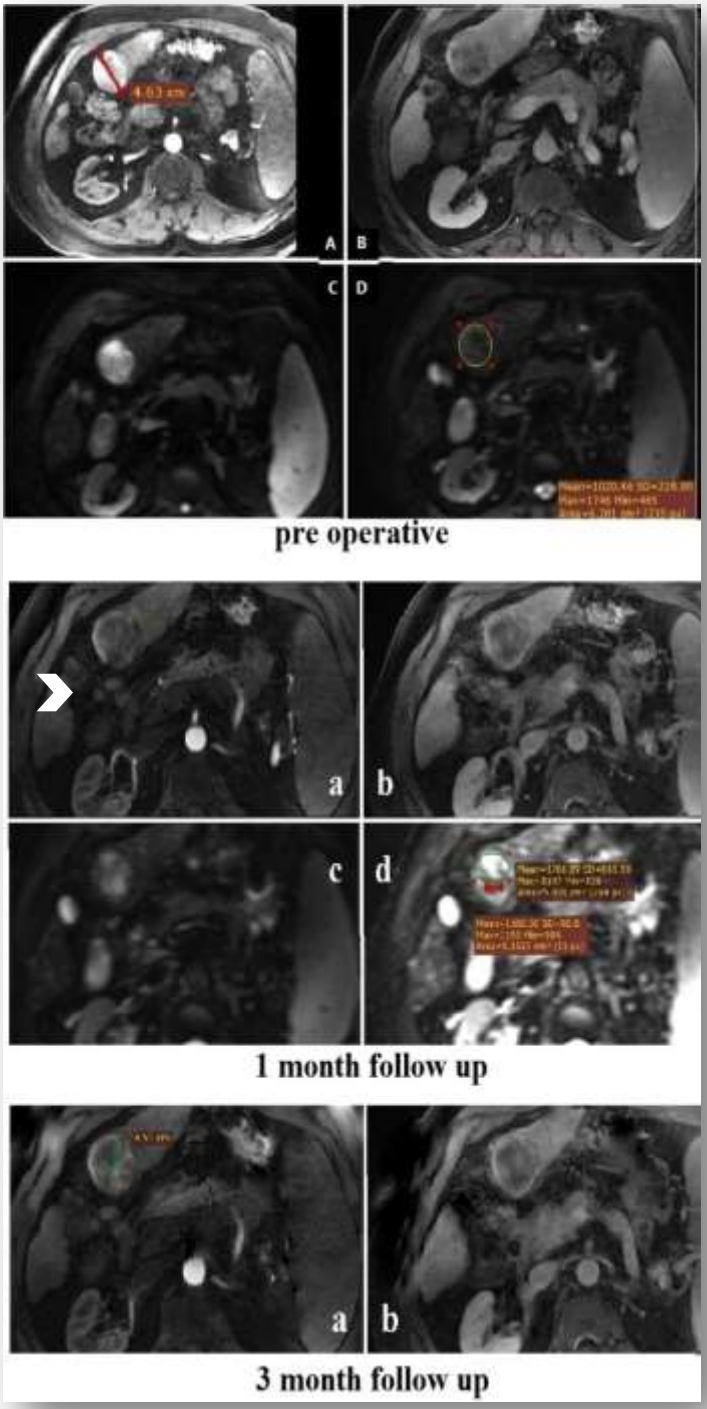
6 month follow up

Figure (2):-
(A) MRI-T1WI Arterial phase
(B) MRI-T1WI portovenous phase
(C) DW-MRI images (b-value 800).
(D) Corresponding ADC map

Pre-operative images:-
(A) and (B) images show segment IVb hepatic focal lesion measures about 4.6 cm with arterial enhancement and portovenous washout denoting active HCC lesion.
(C) and (D) images Show diffusion restriction with average ADC value (1.02 x 10-3 mm2/sec). Diffusion restriction was noted with hyper signal at DWI and corresponding low-signals at ADC.

1 & 3 month follow up images:-
In 1 month follow up, contrast images were not conclusive, there was persistent smooth enhancing periphery consistent with hyperemia, whereas the lesion show heterogeneous appearance with no evident enhancement. The enhanced portion became more evident at the 3 month images (arrow head). The ADC map in 1 month follow up detected a peripheral area of low ADC value at the posterior aspect of the lesion (arrow) which showed no significant change compared to pretreatment value. This was confirmed by contrast study in 3 month follow up. However the pattern of enhance-ment was patchy heterogeneous that hinders application of MRECIST as the measurement of un-interrupted line of enhancement was not possible.

Diagnosis: - MRECIST not adapted due to heterogeneous enhancement. Early prediction of residual active tumor tissue by unchanged ADC value pre and post TACE.



Discussion

Prediction and assessment of early HCC response after TACE is essential for making therapeutic decisions. This is based on cross sectional imaging (CT and MRI) including evaluation of tumor enhancement with contrast studies and necrosis by DWI and calculation of ADC values.[4]

The usual method for imaging is multiphasic contrast-enhanced CT or MRI, the main limiting factor to CT is the beam hardening induced by dense lipiodol hindering visualization of nearby tumor tissue. While MRI signal in not affected by lipiodol, hypovascular lesions are another limiting factor for both CT and MRI studies. In addition, CT and MRI conventional contrast imaging may not depict therapy-induced inflammation and granulation tissue from viable tumor.[5]

(DWI) has widened its role in lesion detection and assessment of treatment response to chemotherapeutic agents. DWI has some advantages compared to contrast study. Not only no need for contrast. But also less time consuming post processing with easily generated ADC maps.[6]

From June 2018 to May 2019, our study included 20 patients with 22 HCC lesions as diagnosed by triphasic CT or MRI study & MR-DWI with ADC calculations. All patients underwent TACE and then were evaluated by triphasic CT or dynamic MRI with DWI imaging of the liver within 1, 3 or 6 moths post therapy.

Several studies recommend using ADC as a functional marker of early tumor response to treatment where an increase in the ADC value can occur prior to any measurable change in tumor size.[6,7]

Yaghmai et al., 2013 reported that role of ADC in assessment of HCC response to TACE and before that was Chiao-Yun Chen et al., 2006, they told that ADC may allow monitoring of therapeutic responses of HCC. This was observed in our study where the mean ADC values at 1 month after TACE was 1.37 x 10^{-3} mm^2/s compared to 0.99 x 10^{-3} mm^2/s in pre TACE denoting the predominance of intra tumoral water molecules mobility and hence diffusion facilitation due to TACE induced necrosis. The minimum post TACE ADC value for non-enhanced portions was 1.18 x 10^{-3} mm^2/s which was noted in partial response lesion and also being relatively low may be attributed to post TACE induced hemorrhagic or coagulative necrosis and/or and the minimum value for enhanced tumor portion was 0.76 x 10^{-3} mm^2/s which was noted progressive disease lesion.

In Susanne Bonekamp et al., 2011 study to investigate volumetric analysis of ADC in assessment of early response of HCC after TACE, that showed that the increase in ADC was significantly different between different response groups (CR, PR,SD and PD) in 1 month follow up which is in agreeing with our study. By comparing the mean ADCs of different response groups after 1 month we found that responder group (CR, PR) show much higher mean ADC (1.4±0.18) and (1.32±0.06) respectively than non-responder group (SD, PD) (1.09) and (1.07±0.37) respectively. so the true indicator of response in not the level of ADC reached after TACE but the degree of change of ADC level of each lesion which was found highly different reaching up to 0.41 x 10^{-3} mm^2/s in CR group, 0.24 x 10^{-3} mm^2/s in PR group, 0.13 x 10^{-3} mm^2/s in SD and 0.12 x 10^{-3} mm^2/s in PD.

Other authors reported that Diffusion weighted MR imaging has lower specificity compared to dynamic studies with increased false positives. This was in many studies like Osama et al., 2013, Juliane et al., 2014 and Mannelli et al., 2009. In addition, Goshima et al. 2008 stated that DWI was not a reliable predictor of local HCC recurrence following TACE when compared with gadolinium-enhanced MRI. Other authors report the reverse, In Omar Hussein et al., 2018 study, diffusion-weighted MR imaging was found to be a reliable predictor along with gadolinium-enhanced MR imaging as regards the positive patients with persistently elevated alfa feto protein. In addition, Mannelli et al., 2013 demonstrated excellent performance of ADC for prediction of complete tumor necrosis after chemoembolization with Lipiodol with an area

under the curve (AUC) of 0.85, sensitivity of 75%, and specificity of 88% with ADC, and no significant difference between ADC and contrast-enhanced imaging. This was in agreeing with Hazim I. Tantawy et al., 2016 who concluded that ADC is reliable in assessing the efficacy of TACE in treating HCC and even more can replace contrast studies and so, DWI and ADC value correlation should be added in the protocol of HCC imaging in pre and post locoregional therapy as initial ADC is a predictor for therapeutic response.

Conclusion

The percentage of ADC change is highly impressive of early treatment response and furthermore by confining specific cut off values for ADC change, gaining at least 22% increase in ADC value to predict complete response, and less than 15% increase in ADC to predict residual tumor viability. Sensitivity increases to 91.67% and specificity to 90% thus we postulate that, the use of percentage of change of ADC pre and post-therapy is much more beneficial than subjective determining the facilitation and restriction to exclude the conflict of cut off values and also to exclude the fallacies resulting from high initial ADC level of well differentiated tumors.

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