# ASSESSMENT OF POST INTERVENTIONAL HEPATOCELLULAR CARCINOMA USING MORPHOLOGICAL AND FUNCTIONAL MRI DATA

**Ahmed M. Magdy[1], Mohamed A.E. Mahmoud[2], Mohamed A.M. Saad[3], Ashraf T. Youssef[4]**

*Department of Radiology, Faculty of Medicine, Fayoum University, **EGYPT***

E-mails: drmagdy1982@yahoo.com, mohamedsalem_1997@hotmail.com, saadams71@yahoo.com, ashraftalaat1@yahoo.com

## ABSTRACT

*The aim of this study is to evaluate the role of dynamic contrast enhanced and diffusion weighted (DW) MRI in the assessment of response to treatment and detection of residual tumour viability of hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). We utilize pre contrast T1, T2, T2 SPAIR, DWI and dynamic contrast enhanced MRI with post processing subtracted images and color mapping, applied for 50 patients with HCC (25 post-RFA and 25 post-TACE).The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for both the dynamic and DWIs in post-RFA & post-TACE patients were calculated. Apparent diffusion coefficients (ADCs) were also measured. Our results showed that dynamic contrast enhanced MRI are better than DWI in evaluating HCC response to locoregional therapy. Dynamic study with complementary DWI and ADC measurements provide better tissue characterization and help in effective monitoring of tumor response to locoregional therapy.*

***Keywords:*** *Hepatocellular carcinoma, MRI, ablation, chemoembolization, residual, dynamic, subtraction, diffusion, ADC*

## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and has a poor prognosis unless treated. Patients with cirrhosis are at highest risk of developing this malignant disease (1). Several minimally invasive locoregional therapies are increasingly used as a cornerstone for treating the disease. These include TACE and RFA (2).

In TACE, following selective catheterization; chemotherapeutic agents suspended in lipiodol (iodized oil), are injected into the feeding hepatic arteries of the neoplasm. This process is followed by embolizing the feeding arteries. The

purpose of embolization is to cause ischemia and to extend contact of the chemotherapeutic agent with the tumor cells (3).

RFA has been introduced as a promising therapeutic technique in the treatment of small HCC. It is designed to destroy tumors by heating tissue to temperatures exceeding 60 °C by converting radiofrequency waves into heat through ionic vibration. A radiofrequency current is emitted from an electrode that is inserted during either an open surgical or a percutaneous procedure with imaging guidance such as sonography or C.T (4).

Monitoring tumor response to loco-regional therapy with imaging is important in determining treatment success and in guiding future therapy (5). MRI is playing an increasingly important role in the evaluation of hepatic tumors after treatment, because of its high contrast resolution, lack of ionizing radiation and the possibility of performing functional imaging sequences. It provides anatomic parameters, as well as functional and molecular parameters, for the assessment of the response to treatment. Non-contrast T1 and T2 weighted images provide information on morphological changes, and dynamic contrast enhanced MRI and Diffusion- weighted MRI (DW MRI) can provide functional information about perfusion (6).

The European Association for the Study of Liver Disease (EASL) has recommended the use of lesion enhancement, rather than change in size, as the standard method to evaluate treatment response. 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) (7).

Dynamic contrast-enhanced MRI plays a significant role in the detection of viable active tumor foci, the differentiation between necrosis and viable tumor, and early prediction of tumor response (8). Recently, Subtraction and color mapping were developed to improve the evaluation of the ablated hepatic lesions. Removing any preexisting signal of T1 unenhanced images causes contrast enhancement within a mass to become more conspicuous on subtracted sequences. This is helpful when dealing with a lesion with high signal on unenhanced T1 WIs, where visual detection of the enhancement can be subjective and difficult on conventional MR bases (9).

DWI is a measure of the mobility of water in the tissues. After treatment, the viable tumor presented with hyperintense signals denoting restricted diffusion capacity, whereas a necrotic area exhibits hypointense signal indicating free diffusion (10). The apparent diffusion coefficient (ADC) has become a promising biomarker of tumor response to therapy. The viable tumors are highly cellular, and the cells have an intact cell membrane that restricts the mobility of water molecules and results in a relatively low ADC. Conversely, cellular necrosis increases membrane permeability, allowing water molecules to move freely and causing a relative increase in ADC (5).

## MATERIAL AND METHODS

### 1. Patients

This study included 50 cases with post interventional HCC (25 post-TACE and 25 post-RFA). The study was conducted in the Nile scan radiology center and National Cancer Institute (NCI) over a period of 16 months (June 2013– December 2014). The patients' age ranged from 42 to 75 years (median 60); 43patients were males and 7 were females. All patients had liver cirrhosis related to chronic viral hepatitis. The study was approved by the Faculty of Medicine, Fayoum University Research Ethical Committee.

### 2. MRI

MR imaging studies were performed using Philips 1.5 Tesla MRI scanner (Intera & Achieva) equipped with phased-array torso surface coil located at Nile Scan Diagnostic Center and National Cancer institute. The body coil was used for radio-frequency transmission and phased array surface coil for receiving signal.

- Examination included precontrast axial T1, in and out of phase, T2, T2 SPAIR, coronal T1 & T2 WIs, DWI and dynamic enhanced MRI.

- DWI was performed before the dynamic study using respiratory triggered fat-suppressed single-shot spin echo echoplanar sequence that combined the two diffusion (motion-probing) gradients before and after the 180° pulse. The acquisition parameters were: TR 1700 msec, TE 76 msec, matrix 120 x 95 with a field of view as small as possible, slice thickness 10 mm, slice gap 1-2 mm, scan time 3-4 min. We used b values of 0, 400 and 800 s/mm$^2$.

- Dynamic study was performed after bolus injection of 0.1 mmol/kg body weight of Gadolinium-DTPA at a rate of 2 ml/s, flushed with 20 ml of sterile saline solution via the antecubital vein. Dynamic imaging using 3D fat-suppressed T1-weighted gradient echo (THRIVE sequence i.e. T1 high resolution isotropic volume examination). A dynamic series consisted of one pre contrast series followed by five successive post contrast series including early arterial, late arterial, and porto-venous phases with 19-21 seconds intervals (17seconds for image acquisition with breath-holding and 2-4 seconds for re-breathing), this is followed by 3-minutes equilibrium and 5-min delayed phase imaging. All patients were imaged in end expiration to limit the risk of image misregistration. We perform arterial and portal phase subtraction which is automated process available on the workstation. Color coded perfusion mapping is then performed.

- ADC maps were generated on the workstation. The three b values (0, 400 and 800 s/mm2) were used for ADC calculation. The ROI included the entire ablation/embolization zone; another area of 2 cm diameter in the surrounding cirrhotic liver parenchyma was also measured in each case. In case of any sustained hyper intensity areas on diffusion images within or at the margins of the ablation zone; its ADC value was calculated. The ADC was measured three times and the three measurements were averaged.

**Interpretation of the MR images**

- MRI signal pattern at T1, T2 & SPAIR WIs.

- DWI, ADC map together with ADC measurement of the ablation zone, surrounding parenchymal changes and any focal hyperintensity.

- Pattern of enhancement in the dynamic imaging, subtracted images, and color mapping. For interpretation of the dynamic MRI, arterial hypervascularity and subsequent rapid washout were interpretated as suggestive findings of viable active lesions. Meanwhile; benign conditions were considered when progressive or persistent peri-lesional enhancement was detected on dynamic images.

**Standard of Reference**

It was difficult to obtain pathologic confirmation because most of these patients do not undergo surgery. In addition, biopsy may result in sampling error as residual/recurrent lesions are mostly small nodules.

So, the standard of reference was:-

- Benign findings (resolved lesions) are considered if there is no pathological enhancement detected along the dynamic post contrast study. For the benign conditions including the inflammatory or ischemic changes, or pseudolesions by abnormal vascular perfusion in the perilesional hepatic parenchyma, the perilesional abnormal signal intensity area should disappear or decrease in size on MRI in 2-3 months follow up.

- Unresolved group (malignant, residual/recurrent) is considered if a focal area at the margin of the treated zone that shows:

1- Early or late arterial phase enhancement that must be proved by the subtraction and color map images.
2- Contrast wash out: the lesion becomes hypo intense relative to the liver parenchyma in the delayed phase.
3- Follow-up image findings of further tumor growth.

**STATISTICAL ANALYSIS**

SPSS computer program (version 16 windows) was used for data analysis. For quantitative variables, mean (as a measure of central tendency), standard deviation (as a measure of variability) were presented. Frequency and percentages were presented for qualitative variables. Comparison between categorical data was performed using Chi square test. Standard diagnostic indices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated as described by Galen (1980). Comparison between mean ADC values in the studied groups was performed using unpaired t test. P-values less than 0.05 were considered as statistically significant.

**RESULTS**

In our study, 29 patients (58%) have resolved lesions and 21 patients (42 %) have unresolved lesions with MR evidence of residual or recurrent viable tumor tissue (Table 1).

***Table 1.*** *Size of resolved and unresolved lesions. Data are expressed in cms as mean ± SD.*

| | Resolved | Unresolved |
|---|---|---|
| Post RFA | 3.16 ± 0.63 | 3.95 ± 0.91 |
| Post TACE | 3.25 ± 0.41 | 4.85 ± 1.16 |

Among the 50 patients included in our study, about 50% of lesions showed heterogeneous MR signal intensity. 70% of the residual/recurrent viable lesions exhibited high T2 signal intensity and 10% of the benign group lesions exhibited high T2 signal intensity.

There is no significant difference in the signal intensity of the entire ablated/embolized zone between the resolved and unresolved lesions at the early follow up imaging.

In post-TACE lesions, dynamic MRI had a sensitivity of 90%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 93.8% and an accuracy of 96% compared to 100%, 66.66%, 66.66%, 100% and 80%, respectively of DWI. In post-RFA lesions, dynamic MRI had a sensitivity of 100%, a specificity of 92.9%, a positive predictive value of 91.7%, a negative predictive value of 100% and an accuracy of 96% compared to 100%, 71.4%, 73.3%, 100% and 84% respectively of DWI (Fig. 1, 2, 3).

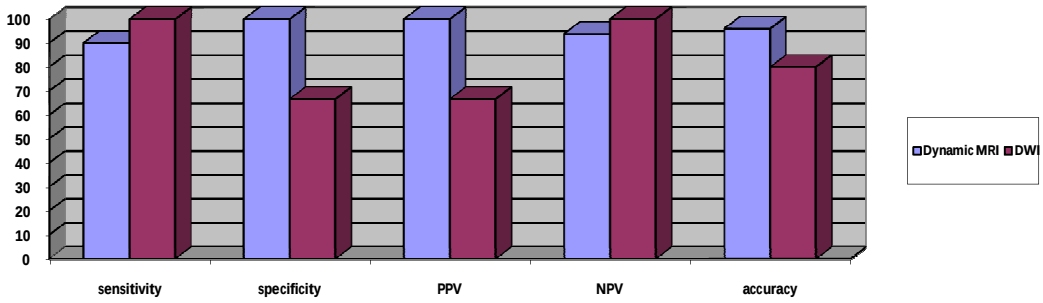


***Figure 1.*** *The different indices of the Dynamic MRI and DWI in post-TACE lesions.*

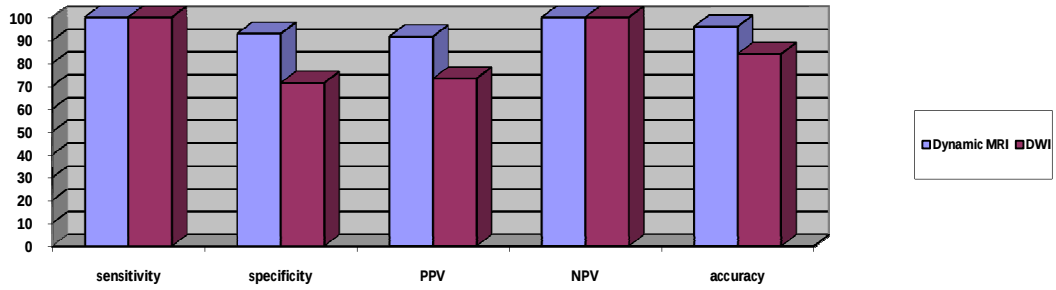


***Figure 2.*** *The different indices of the Dynamic MRI and DWI in post-RFA lesions.*

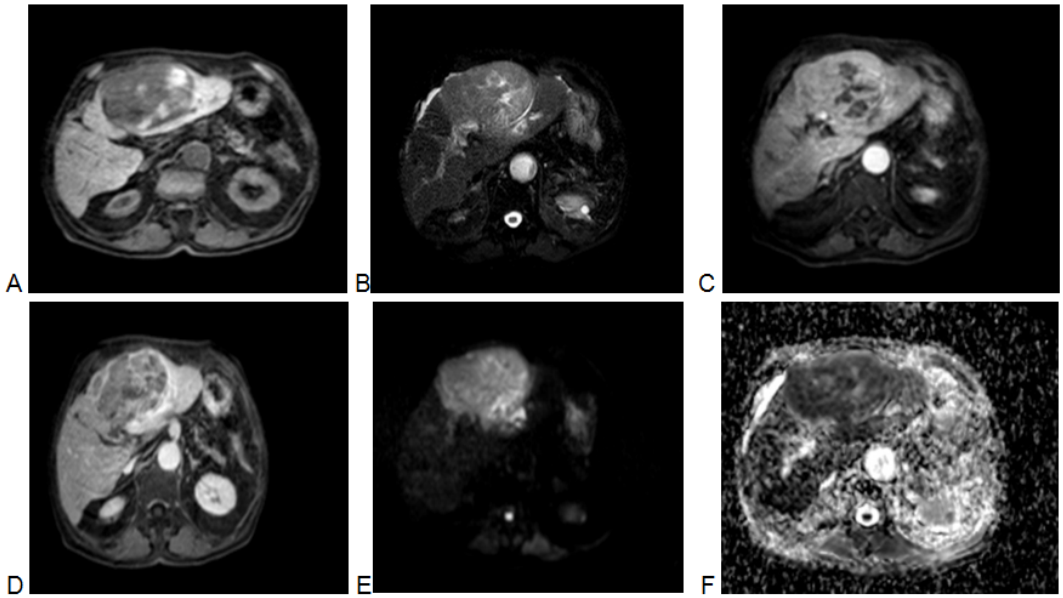


***Figure 3.*** *Residual active viable tumoral tissue following TACE. (A, B) axial T1 & T2 SPAIR WIs obtained 1 month after TACE. The embolized zone in the left hepatic lobe elicits low T1 and elevated T2 SPAIR signal (C). axial arterial phase image, (D) axial equilibrium phase image, the ablation zone shows gross heterogeous pathological lesional contrast enhancement with rapid washout denoting active viable tumoral tissue.(E,F) Diffuse lesional hyperintensity is noted on DWI with corresponding low signal noted on ADC map denoting diffusion restriction.*

The types of tumor residue/recurrence were studied and we found that nodular type was the most common and detected in 57.1% of cases followed by the halo type 28.6% and the gross heterogeneous type 14.3%. For exclusion of tumor residue/recurrence; subtracted images and color mapping were also studies (Fig. 4).

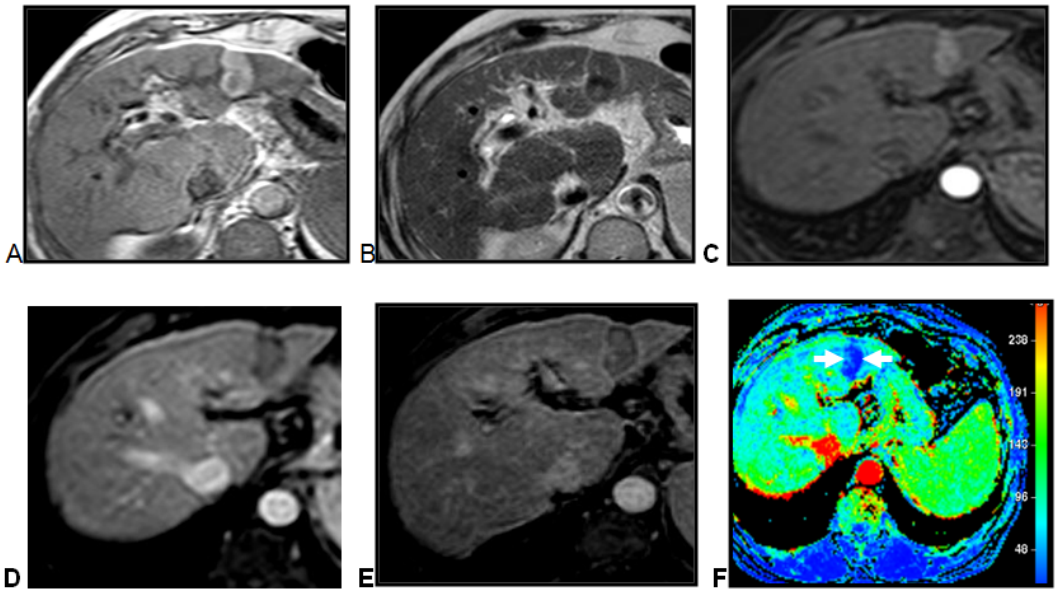


***Figure 4.*** *Well ablated hepatic focal lesion. A & B axial T1 and T2 WIs obtained 1 month after ablation. The ablated zone in the left hepatic lobe exhibits high T1 and low T2 signal with peripheral thin rim of low T1 and high T2 signal (C). axial arterial phase image, (D) axial portal phase image and (E). axial delayed phase image, the ablation zone appears of hyperintense signal in the arterial phase and low signal in the portal and delayed phases, however this is not due to arterial enhancement and rapid wash out, but this is due to drop of the signal of the non enhancing ablation zone relative to the progressively enhancing liver parenchyma. This is proved by the color map image (F) where the lesion appears blue (in the lowest part of the color scale) which confirms the non enhancing pattern of the lesion.*

Well-defined thin rim of marginal enhancement was present in 50% of patients. Ill-defined perilesional enhancement that represents reactive inflammatory and vascular changes of the liver parenchyma adjacent to the treated zone was present in 20% of patients (with more prevalence in post RFA patients).

**Regarding the measured ADC values:**

- The mean ADC value of the recurrent or residual malignant lesions in the 21 patients of the unresolved group was significantly lower than the mean ADC value of the entire ablation/embolization zone in all the 50 patients in the study (p value 0.001**).

- The mean ADC value of the recurrent or residual malignant lesions was significantly lower than the mean ADC value of the post treatment perilesional parenchymal changes (p value 0.001**).

- The measured cut off value between the benign and malignant group is $1.07x10^{-3}$ $mm^2/s$.

- There was no statistical difference in the mean ADC value between the entire lesion post RFA and post TACE.

- Also there was no statistical difference in the mean ADC value between the entire lesion of the resolved and unresolved groups.

**p<0.01 = highly significant.

**DISCUSSION**

MRI provides anatomic and functional as well as molecular parameters, for the assessment of response of HCC to locoregional treatment (6).

Among the 50 patients included in our study, about 50% of lesions showed heterogenous MR signal intensity making post interventional assessment of HCC necrosis based on signal intensity on precontrast sequences a major conflict issue. The heterogeneity of the treated lesion in the early post interventional imaging could be explained by the different local tissue changes (edema, hemorrhage and inflammatory reaction).

We found that nodular type of tumor recurrence was the most common and detected in 57.1% of cases. This agreed with Chopra et al. (2001) (11) who found that 47.5 % of the recurrent lesions were of nodular type.

Braga et al. (2005) (12) states that dynamic MRI for unsuccessful locoregional treatment shows focal arterial hypervascularity after contrast administration. However, the perilesional hypervascularity detected by dynamic MRI is not specific only for the residual/recurrent lesions but can also occur in benign conditions as a result of nearby inflammation or other nontumorous arterio-portal shunts or compromised portal venous flow related to iatrogenically injured portal tracts. Yu et al. (2009) (13) stated that benign perilesional parenchymal changes appear as a rind-like contour with progressive or persistent enhancement in delayed phase post contrast images and could be distinguished from the more focal irregular nodular contour with rapid washout of contrast material in the delayed phase of dynamic imaging in residual/recurrent lesions.

In our study we found the ill-defined perilesional enhancement that represents reactive inflammatory and vascular changes of the liver parenchyma adjacent to the treated zone in 20% of patients (with more prevalence in post RFA patients). These areas may exhibit mild hyper intensity in the diffusion imaging. This agreed with Schraml et al. (2009) (14) who reported perilesional ill-defined area of enhancement and diffusion hyper intensity in 22.5% of the patients imaged within the first 6 months after locoregional therapy.

Kim et al. (2010) (15) reported that image subtraction was helpful for the evaluation of post interventional HCC as the high T1 signal makes the assessment of tumor enhancement difficult on post-contrast T1-weighted images. To accurately assess tumor enhancement, we used the image subtraction techniques and colour mapping.

In our study we found that dynamic contrast enhanced MRI to be superior to diffusion weighted MRI in evaluating HCC response to locoregional therapy.

Regarding the false negative case by dynamic MRI in our study, it was attributed to inappropriate breath holding leading to motion artifact with resultant false interpretation by the viewer. We had also one false positive case due to misinterpretation of a perilesional perfusional abnormality secondary to arterioportal shunt.

9 false positive cases out of 50 patients were misdiagnosed on diffusion MRI in our study. We considered that the increase in false positive findings in our study could be attributed to intra-lesional hemorrhage or coagulative necrosis that caused diffusion restriction. Another cause is the perilesional benign parenchymal insults that showed sustained hyper intensity on DWI with increasing b values due to perilesional reactive inflammation, which is more frequently depicted after radiofrequency ablation and may result from TACE.

Our study agreed with those of yu et al. (2009) (13), Goshima et al. (2008) (16) & Reham et al. (2013) (17) in showing that dynamic contrast enhanced MRI to be superior to diffusion weighted MRI in evaluating HCC response to locoregional treatment.

Our study also agreed with Yu et al. (2009) (13) in that diffusion MRI helps to improve the sensitivity, but decreased the specificity and PPV as it increases the false positives due to intra-lesional hemorrhage and perilesional post interventional parenchymal changes causing diffusion restriction.

We found that ADC measurement helps in differentiation between the active viable malignant lesions and the post treatment perilesional benign reactive and vascular changes as there is significant difference between mean ADC values of residual/recurrent malignant lesions and post treatment perilesional benign changes reflecting the fact that therapeutically induced non tumoral perilesional changes usually show decreased cellularity and therefore exhibit less signal in DWI and high ADC value.

In the study performed by Yu et al. (2009) (13), ADC was calculated to distinguish the marginal recurrence of HCC from perilesional benign changes. The results of this study did not demonstrate statistically significant differences.

Thoeny et al. (2005) (18) stated that DWI has some advantages compared to dynamic MRI as there is no contrast material required; and the examination time is relatively short compared to dynamic MRI.

In our study, we had some diagnostic limitations. First, lack of pathologic proof in most cases, related to clinical practice where biopsy is not always indicated. Second, few lesions included in our study were located at the hepatic dome, that may cause selection bias and challenge to diffusion weighted MRI; being more sensitive to motion artifacts. For the ROI placement, despite our efforts for precise placement and three repeated measurements to minimize any possible errors, there could be unavoidable errors including the partial volume effect for the small and irregular lesions.

In conclusion, we found that dynamic contrast enhanced MRI is better than DWI in evaluating HCC response to locoregional therapy. Dynamic study with complementary diffusion imaging and ADC measurements allow better tissue characterization and help in effective monitoring of tumor response to locoregional therapy.

**CONFLICT OF INTEREST STATEMENT**

None to declare.

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