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Role of MRI in Assessment of Hepatocellular Carcinoma (HCC) after TACE (Trans-arterial Chemoembolization) with Persistent High Alfa Fetoprotein (AFP)

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ABSTRACT

Background: evaluation of treatment success after TACE is essential for making therapeutic decisions, e.g., to repeat, interrupt or completely terminate TACE. An understanding of the various therapeutic strategies and their post therapy imaging appearance is essential for accurately assessing treatment response. Evaluation of tumor response should include not only tumor markers, but also imaging modalities. Evaluation of the therapeutic effect of HCC after TACE is primarily based on the findings of imaging studies. CT is the standard imaging technique for monitoring the effectiveness of TACE. MRI is complementary to CT in the evaluation of the therapeutic response. To know the advantages and limitations of each imaging technique in the evaluation of the therapeutic effect of HCC is important in determining if the treated tumor is completely necrotic or requires additional treatment. **Objective:** the purpose of this work was to study the MRI appearance of the HCC lesion after TACE in patients with high persistent AFP in cases when hyper-attenuating iodized oil impairs the assessment of residual tumor enhancement on contrast enhanced CT.

Patients and Methods: the age of patients ranged between 50 to 73 years with a mean age 58 years. All patients were diagnosed as HCC patients on a background of liver cirrhosis. Twelve patients were positive for HCV and three patients were positive for HBV infection.

Results: our study included 15 patients, 12 males and 3 females with age 51 and 73 years with a mean age of 58years. All patients included were diagnosed with HCC by a previous triphasic CT and alfa feto protein. The patients underwent TACE and the patient's response to embolization was assessed by AFP and CT or MRI within 1-3 months post chemoembolization. All the selected candidates showed persistent elevation of alfa feto protein after the procedure and within the 1-3 months post TACE. MRI was performed to these patients and their MRI results were either negative or positive explaining the persistent rise of AFP where 13 patients showed positive results and 2 patients showed negative MRI findings. The positive patients were further categorized into groups according to their post tace MRI findings. 4 patients had *de novo* new lesions, 6 patients had recurrence and 3 residual tumor patients.

Conclusion: diffusion-weighted MR imaging was found to be a reliable predictor along with contrast enhanced MR imaging when CT was not conclusive.

Keywords: hepatocellular carcinoma**,** hepatitis B virus (HBV) or hepatitis C virus**,** transarterial chemoembolization

INTRODUCTION

Most primary liver cancers are hepatocellular carcinoma (HCC), which is the third most common source of cancer fatalities worldwide. The main etiologies of HCC are infection of the liver by hepatitis B virus (HBV) or hepatitis C virus (HCV), and alcohol abuse [(1)]**.** Alpha-fetoprotein (AFP) is an oncofetal protein produced by fetal hepatocytes, yolk-sac cells and normal gastrointestinal cells immediately after birth. Serum AFP level decreased gradually after birth to <10 ng/mL within 300 days [(2)]. Normal adult serum AFP level is <20 ng/mL. Serum AFP level may be high in patients with drug or alcohol abuse or with chronic liver disease such as hepatitis or cirrhosis, but in these cases, the level is usually <100 ng/mL [(3)]**.**

The Barcelona Clinic Liver Cancer (BCLC) and the American Association for the Study of Liver Diseases guidelines consider serum of >400 ng/mL to be diagnostic for HCC [(4)] or a solid mass >2 cm in diameter with typical features of HCC on at least one imaging modality in a patient with liver cirrhosis [(2)]**.**

High serum AFP levels occur in 60–70% of HCC patients. However, Serum sFP levels remain in the normal range in 15–30% of HCC patients [(4)]**.** High serum AFP level correlates with more aggressive behaviour and poorer prognosis of HCC [(5)]. Transarterial chemoembolization (TACE) of hepatocellular carcinoma (HCC) is used as a bridge to liver transplantation. It is also used for patients with unrespectable HCC, and has been shown to improve survival [(6)]**.**

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According to the BCLC system, transarterial chemoembolization (TACE) is the treatment of choice for patients with intermediate-stage Hepatocellular carcinoma (HCC) BCLC stage B [(3)] or advanced (BCLC stage C) tumor stages, where only palliative treatment options can be offered resulting in a limited overall survival (OS) of 11–20 month.

Transarterial chemoembolization (TACE) is the recommended treatment modality for asymptomatic, large or multifocal HCC without macrovascular invasion or extrahepatic metastasis (intermediate HCC, BCLC stage B) [(6)].

Assessment of tumour response after chemoembolization on CT is generally based on tumour enhancement. However, hyper attenuating Iodized oil impairs the assessment of residual tumour enhancement on contrast enhanced CT [(7)]. In contrast to CT, the high concentration of iodized oil after chemoembolization does not affect MR signal intensity.

The disadvantage of contrast-enhanced MRI is the incapability to distinguish viable cells from reactive granulation tissue. After TACE an enhancing rim can appear on contrast-enhanced MRI. This rim can correlate with either viable tumour as well as to reactive tissue [(7)].

AIM of the WORK

The purpose of this work was to study the MRI appearance of the HCC lesion after TACE in patients with high persistent AFP in cases when hyper-attenuating iodized oil impairs the assessment of residual tumor enhancement on contrast enhanced CT.

PATIENTS AND METHODS

They are ranging in age between 50 and 73 years with a mean age of 58 years. All patients were diagnosed as HCC patients on a background of liver cirrhosis. Twelve patients were positive for HCV and three patients were positive for HBV infection. Diagnosis of HCC was based on typical enhancement pattern on triphasic CT scan with enhancement of the focal lesion in the arterial phase and washout in the portovenous or delayed phases.

Type of Study: this was a cross sectional study.
Study Setting: MRI unit, El Demerdash Hospital, Ain Shams University.

Study Period: 1 year data collection.

Study Population: TACE was offered to BCLC-B HCC patients who fulfilled the following:

Inclusion criteria: HCC post Tace patients with persistent elevated AFP including: Patients with associated Child's A or B cirrhosis, normal main portal vein, less than 50% involvement of liver by HCC, some patients of BCLC A who were unsuitable for ablative therapy or surgery, HCC post Tace with persistent elevated AFP and no gender predilection.

Exclusion Criteria: patients known to have contraindications for MRI, e.g. an implanted magnetic device, pacemakers or claustrophobia, extrahepatic disease, coagulopathy, biliary obstruction, comorbid illness such as coronary artery disease, congestive heart failure chronic renal failure, metastatic chest or other extra hepatic tumour explaining high AFP and a previous history of encephalopathy/upper gastrointestinal bleed in the last 6 months.

Sampling Method: this was a convenience sample. **Sample Size:** this was a pilot study. A maximum of 15 patients could be recruited during the period of the study. No sample size has been calculated.

Study Tools: full history taking and full clinical examination. The selected hepatocellular carcinoma (HCC) patients after TACE with persistent high (AFP) alfa fetoprotein were imaged by MRI using the following sequences: T1 weighted (T1W) in phase gradient echo sequence (GRE). T1 weighted (T1W) out of phase gradient echo sequence (GRE). T1 weighted (T1W) gradient echo sequence (GRE) with fat suppression (FS). T2 weighted (T2W) images (fast spin echo sequence) (FS). Dynamic imaging using T1 weighted gradient echo sequence with fat suppression performed in a triphasic manner. Diffusion study respiratory triggered fat suppressed single shot echo-planar DW imaging.

The study was approved by the Ethics Board of Ain Shams University.

RESULTS

Table 1: demography and MRI findings

Patient	AFP (ng/mL)	Post TACE AFP (ng/mL)	Post TACE MRI
Patient 1	1000	1300	Positive (Recurrent lesion)
Patient 2	400	629	Positive (Recurrent lesion)
Patient 3	250	243	Negative
Patient 4	870	1050	Positive (De novo lesion)
Patient 5	930	910	Positive (Recurrent lesion)
Patient 6	550	500	Negative
Patient 7	670	945	Positive (Residual lesion)
Patient 8	1150	1400	Positive (De novo lesion)
Patient 9	350	560	Positive (Residual lesion)
Patient 10	330	600	Positive (Recurrent lesion)
Patient 11	2000	2500	Positive (De novo lesion)
Patient 12	430	615	Positive (Residual lesion)
Patient 13	645	810	Positive (Recurrent lesion)
Patient 14	760	1110	Positive (De novo lesion)
Patient 15	500	829	Positive (Recurrent lesion)

Table 2: post TACE MRI distribution of the studied group

Post TACE MRI	No.	%
Negative	2	13.33%
Positive	13	86.67%
De novo lesion	4/13	30.77%
Recurrent lesion	6/13	46.15%
Residual lesion	3/13	23.08%
Total	15	100.00%

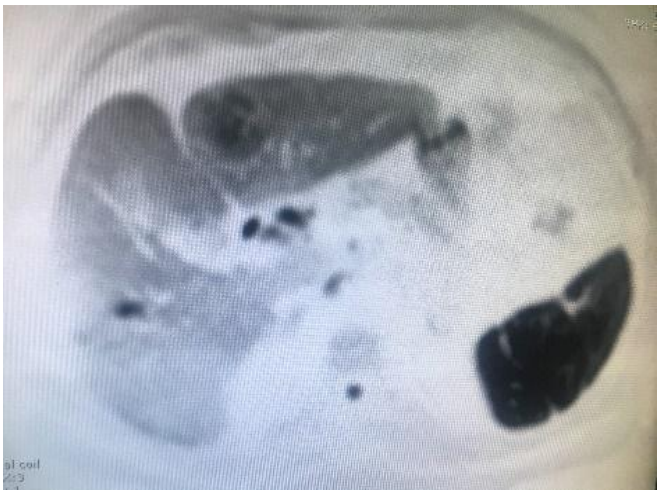
Table 3: comparison between pre and post AFP (ng/mL) of the studied group.

AFP (ng/mL)	AFP (ng/mL)		Paired Sample t-test	
	Range	Mean	t	p-value
Pre	250-2000	722.33±443.34	-5.521	<0.001**
Post	243-2500	933.40±533.66		

CASE 1

A 57 years old male patient with well ablated lesion at segment VI underwent TACE for HCC lesion at segment III. Follow up was done using 4 slice CT 1 month post TACE and the results were not convenient.

Dynamic MRI shows:



On DWI, the lesion exhibits relative diffusion restriction compared to the rest of hepatic parenchyma.

ARTERIAL PHASE

-Axial post-contrast T1WI in the arterial phase showing heterogeneous enhancement of the embolized focal lesion.

DELAYED PHASE

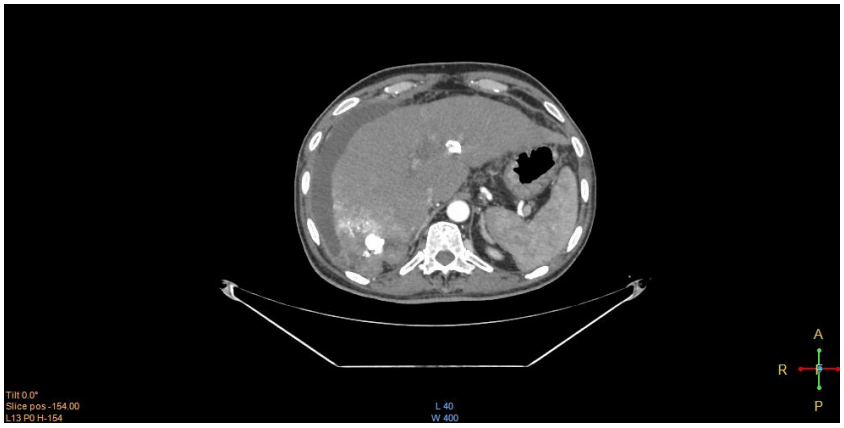
-Axial post-contrast T1WI in the arterial phase showing early washout of contrast in the delayed phase.

Diagnosis: residual tumor tissue at segment III.

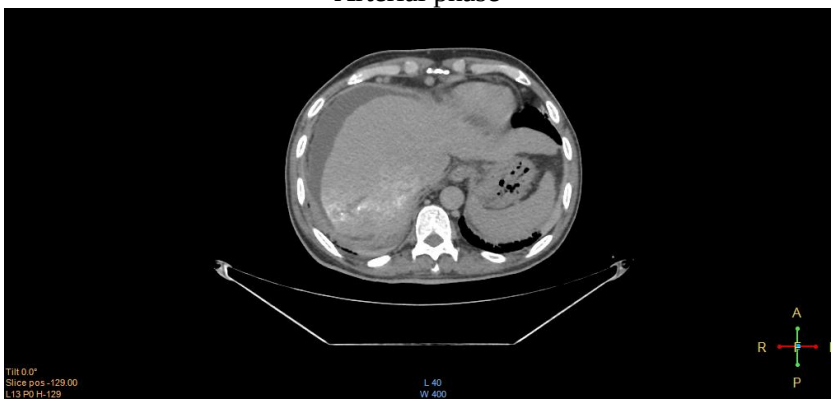
CASE 2

A 55 year old male patient with well ablated lesion at segment VIII underwent TACE for HCC lesion at segment VI.

-Triphasic CT after one month showed dense lipidol impairing the assessment of the embolized lesion



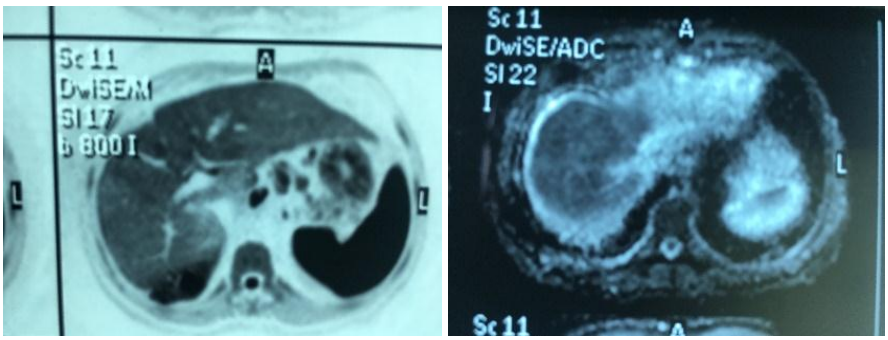
Arterial phase



Delayed phase

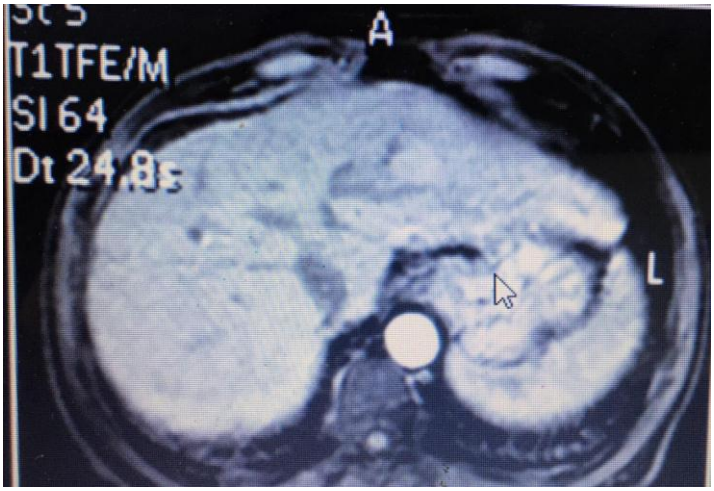
Dynamic MRI shows:

On DWI, the lesion exhibited relative diffusion restriction compared to the rest of hepatic parenchyma

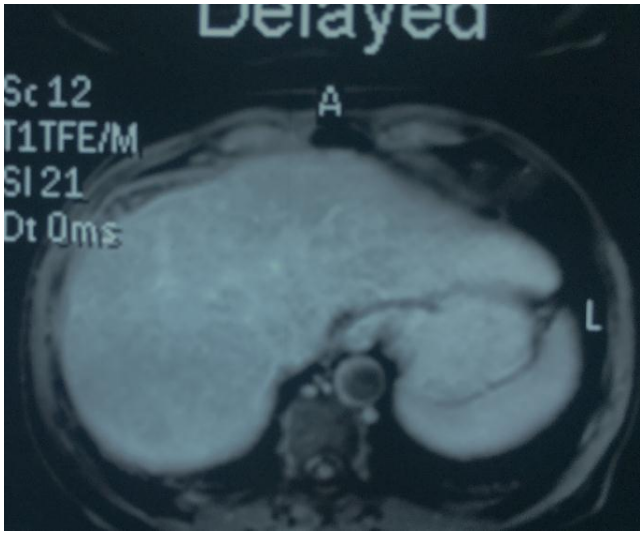


DWI and ADC map

Axial post-contrast T1WI in the arterial phase showed heterogeneous enhancement of the focal lesion with washout of contrast in the delayed phase (B).



Arterial phase



Delayed phase

Diagnosis: residual tumor tissue at segment VI.

DISCUSSION

The administration of TACE mixed with iodized oil and anticancer agents followed by the application of gelatin sponge particles because ischemic damage to HCCs, and results in hemorrhage or coagulation induced tumor necrosis. Although contrast-enhanced CT is able to reveal residual or recurrent tumors as areas of hyper vascularity, it is often difficult to assess correctly contrast enhancement in such tumors adjacent to retained iodized oil on CT, because of beam-hardening artifacts caused by iodized oil [(8)].Moreover, because MR imaging is barely influenced by the presence of iodized oil, viable tumors were better depicted by gadolinium-enhanced MR imaging where gadolinium-enhanced MR imaging well revealed tumor hemodynamics and that it is helpful for evaluating the therapeutic efficacy of TACE with iodized oil for the treatment of HCC. Our study showed that diffusion-weighted imaging and gadolinium-enhanced MR imaging after TACE are complementary to each other in detectability of any residual viable tumor.Although diffusion-weighted MR imaging was straighter forward because of no need for breath holding or contrast material administration, we would recommend gadolinium-enhanced MR imaging as a baseline tool for the evaluation of HCC after TACE.

Regarding the current role of diffusion-weighted imaging in hepatic MR imaging, diffusion-weighted imaging may have additional values in the diagnosis of hepatic diseases especially in patients gadolinium-enhanced MR imaging is contraindicated due to renal dysfunction, allergic tendency, and difficulty in breath holding, etc. Diffusion-weighted MR imaging visualizes water-

molecule diffusion or the Brownian motion of water protons in biologic tissues ***which*** provided an insight on water composition within malignant tumors and tumor viability [(9)]. Viable tumor cells have intact membranes that restrict water-molecule diffusion, whereas in necrotic tumors disrupted membranes allow higher levels of diffusion. ADC values are useful for assessing the early therapeutic responses of large HCCs after TACE; tumor necrosis was determined by ADC increased and by signal intensity changes on diffusion-weighted MR images accompanied by ADC maps [(9)].

In our 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.

CONCLUSION

In conclusion, diffusion-weighted MR imaging was found to be a reliable predictor along with contrast enhanced MR imaging when CT is not conclusive.

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