Malignant hepatic focal lesions: Improved detection and characterization by diffusion weighted MRI in comparison to T2W with the use of parallel imaging SENSE and different b values

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Abstract: Objective: to evaluate the utility of diffusion weighted MRI using different b values in the detection and characterization of hepatic focal lesions in comparison to conventional T2W MRI.. **Patients and Methods:** 45 patients with 83 malignant hepatic focal lesions (32 hepatocellular carcinomas, 4 cholangiocarcinomas and 47 metastases were included in this retrospective study). The MRI protocol for the upper abdomen included T2W, in and opposed phased T1 weighted images and post contrast T1W images. Respiratory triggered fat suppressed single shot echo planar DWMR images were performed for all patients. Two independent observers reviewed the T2W and DW images to detect and characterize the lesions. **Results**: The use of DWMR showed a significantly higher detection rate in the detection and characterization of malignant hepatic focal lesions than the use of T2W images ($p<0.05$) using B values of 500 and 1000. The detection rate was significantly higher for small lesions as well as in cirrhotic liver. DWMRI also showed improved detection of recurrent lesions following chemoembolization in patients. **Conclusion:** DW MRI can be used as a standard non contrast enhanced study in early detection and characterization of hepatic focal lesions.

[Reem H Basiouny, Nivine Chalabi, Nanees A. Adel, Hany Haroun, Eslam Safwat. **Malignant hepatic focal lesions: Improved detection and characterization by diffusion weighted MRI in comparison to T2W with the use of parallel imaging SENSE and different b values**. *J Am Sci* 2012;8(9):160-166]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 24

Key words: Malignant, Hepatic, Focal, MRI, SENSE.

1. Introduction

Malignant liver lesions include hepatocellular carcinoma, cholangiocarcinoma and metastasis.

Hepatocellular carcinoma is the most frequent primary tumor of the liver and the fifth more common malignancy worldwide. It represents the third cause of cancer-related death [23]. About 80% of HCCs appear in cirrhotic population. A liver mass in a cirrhotic patient should be considered a HCC until proved otherwise. Screening of HCC is recommended in these patients through the determination of AFP and a conventional ultrasound every 6 months. This makes possible a curative or palliative treatment in its early phases. HCC may be silent but is usually associated with weight loss, abdominal pain, hepatomegaly or ascites. Laboratory data include elevation of serum alkaline phosphatase, persistent leukocytosis and increased ratio of serum AST/ALT. For the diagnosis of HCC in cirrhotic patients, lesions over 2 cm in diameter need just one imaging technique showing typical findings or one imaging technique showing an AFP level over 400 µg. In nodules between 1 and 2 cm in diameter, two techniques showing typical imaging criteria are needed for the diagnosis. Follow-up every 3 mo is recommended for masses less than 1 cm in diameter [24].

Intrahepatic cholangiocarcinoma: It is generally a unique mass originated in small intrahepatic bile ducts. This tumor should be considered in patients with chronic primary sclerosing cholangitis, longstanding choledochocele, intrahepatic lithiasis, parasitic disease of the bile ducts, Caroli's disease, and in patients exposed to thorotrast for radiographic procedures[24]. Jaundice is the most common clinical presentation [25] and usually associated with a high serum bilirubin level. Up to 80% of the cholangiocarcinomas present elevated values of serum CA 19-9 and 50% present elevated CEA [26].

The liver is the most common site of metastasis from the gastrointestinal tract, pancreas, breast and lung. Colorectal cancer most commonly metastasizes to liver. Metastasis occurs in the most common malignant hepatic tumor. Generally, both hepatic lobes are involved [24]. Hypervascular metastases are associated to carcinoid tumors, melanomas, sarcomas, thyroid tumors and hypernephromas. They are completely enhanced in arterial phase with fast wash out and hypo enhanced in portal and late phases. Hepatic metastases can be classified into hypo and hypervascular [27].

Accurate detection and characterization of hepatic focal lesions is important for treatment planning in patients with hepatic tumors [1-2]. Ultrasonography (US) and/or computed tomography (CT) are generally employed for the detection of focal

hepatic masses and magnetic resonance imaging (MRI) is preferred when further characterization of these masses is needed [3]. MRI has many advantages (e.g., high contrast resolution, multiplanar capability, lack of ionizing radiation, and the safety of using particulate contrast media rather than those containing iodine). In hepatic MRI, artifacts due to cardiac activity, respiration, and intestinal peristalsis can negatively affect imaging quality, especially in T2-weighted sequences, which require a relatively long time to acquire, particularly in elderly patients [3].

Diffusion is the result of thermal fluctuations with a random pattern and this is often referred to as "Brownian motion" [4]. Diffusion-weighted magnetic resonance imaging (DWMRI) is a new technique at the level of molecular movements and can reflect the functions of human body without trauma [5-6].

Several studies have characterized focal hepatic lesions by measurement of the lesion apparent diffusion coefficient [10-11] However there is still controversy regarding the value of quantitative DW imaging for the characterization of focal hepatic lesions as the ADC values of different types of lesions overlap. A limited number of studies have been performed using DWI for the detection of hepatic lesions [12-13]. Even fewer number of studies over the last years has evaluated the use of DWI and ADC value measurement for the assessment of tumor response to chemotherapy, radiation therapy, and local ablation [7].

The value of this study was to evaluate the use of DWI for the detection and characterization of primary and secondary malignant hepatic masses in comparison to non contrast T2W and assessment of tumor response to chemoembolization in a limited number of lesions.

2. Patients and Methods

This retrospective study included 45 patients, 33 males and 12 females with age ranging from 21 to 78 years. All were referred from the hepatology clinics of Ain Shams University hospitals during the period between October 2008 and June 2010. They were all subject to detailed clinical history, examination by expert hepatologists of at least 3 years experience in the field of hepatic tumors, laboratory investigations (Alpha fetoprotein, liver profile, other related tumor markers e.g.: CA 19.9, CA125, CEA and PSA) and abdominal U.S. Abdominopelvic C.T was performed only in 15 patients) and abdominal MRI was done for all patients.

Inclusion criteria for the study included the presence of pathological, laboratory radiological and/or clinical confirmation of the nature of hepatic focal lesions, lesion size ≥ 2 mms and the availability of T2W and diffusion weighted images

MRI imaging technique:

MR imaging was performed on high field system (1.5 Tesla) magnet units (Philips Integra) using a phased array coil to cover the whole liver. All patients were examined initially with a routine MR protocol for the upper abdomen that included; T_1 weighted (T_1W) gradient echo sequence (GRE) with and without fat suppression (TR=100-200ms, TE ≤8ms, matrix 128-256x256, slice thickness 5mm and slice gap 0-2 mm), T_2 weighted fast spin echo sequence with and without fat suppression (repetition time (TR) ≥2000ms, echo time (TE) = 90-120 ms, number of excitations (NEX) 1-4, matrix 192-256x256 with a field of view as small as possible, slice thickness 5mm, slice gap 0-2mm) and dynamic contrast enhanced T1 weighted images. Dynamic study was performed after bolus injection of 0.1mmol/kg body weight of Gd-DTPA at a rate of 2ml/s, flushed with 20ml of sterile 0.9% saline solution from the antecubital vein using pump injector. Dynamic imaging using T1 weighted GRE without fat suppression was performed in triphasic sequence [arterial phase (16-20 sec.), portovenous phase (45-60 sec.) and delayed equilibrium phase (3-5 min).

Imaging analysis:

Analysis of the MR images was performed with a picture archiving and communications systems (PACS) workstation monitor. Two experienced radiologists with at least 3 years experience in the interpretation of abdominal MRI evaluated all of the MR images independently. The morphological features of each lesion were recorded on a data sheet including lesion shape, margin, signal characteristics, pattern of enhancement in the dynamic imaging as well as number and site of the detected focal lesions. Images were reviewed to determine if differences in lesion detection were seen between the T2W images and DW images using a b value of 500 & 1000 sec/mm^2. Then images were reviewed with measurement of ADC values for final detection and characterization of focal lesions. The mean ADC of each focal lesion detected is measured by drawing a region of interest over the lesion. If the lesion was less than 3 cm, ADC was measured twice and the two measurements were averaged. To ensure that the same areas were measured, regions of interest were copied and pasted from DW images to ADC maps. For lesions not visualized on DW images, the location was determined by using post -contrast T1-weighted images,

Statistical analysis:

Statistical analysis was performed to compare the use of T2 weighted images and DW images for the detection and characterization of malignant hepatic focal lesions using the X^2 test. Probability values less

than 0.05 were considered statistically significant. Data were analyzed using a statistical software package. (SPSS, version 12, Chicago IL)

3. Results

The 45 patients included in this study had overall 83 lesions with an average diameter 2.8cm (range, 1.0-11 cm). 61 lesions were located in the right liver lobe and 22 in the left liver lobe. There were 36 primary hepatic focal lesions (32 HCCs and 4 cholangiocellular carcinoma), and 47 metastatic lesions. Twelve lesions were depicted in the 6 patients who were performing follow up studies after chemoembolization or radiofrequency. 38 lesions (45.8%) were found in non cirrhotic liver, two of which were accidentally discovered during MRCP (Magnetic Resonant Cholangio-Pancreatography), while 45(54.2%) were identified within cirrhotic liver (All cirrhotic patients were suffering of HCV.

For both observers the use of DWI was associated with a significantly higher detection rate of malignant lesions than the use of T2W images(p<0.05). Observer 1 detected 57 0f 83 (69%) on T2W and 73 of 83 (88%) lesions on DW. Observer 2 detected 55 of 83 (66%) on T2W images and 70 of 83 (84.3%) lesions on DW images. On T2W images 26 lesions (9 HCC, 1 cholangiocarcinoma & 16 metastases) were not detected by observer 1 and 28 lesions (11 HCC & 17 metastases) were not detected by observer 2. On DW images 10 lesions (4 HCC, 1 cholangiocarcinioma and 5 metastases) were not detected by observer 1 and 13 lesions (5 HCC, 1 cholangiocarcinoma and 7 metastases) were not detected by observer 2. The lesions that were missed in DWI were more located in left lobe, and, most probably were missed due to cardiac motion artifact.

17 out of 45 lesions (37.7%) found in cirrhotic liver were missed in T2WI compared to DWI where only 2 lesions (4%) were missed (statistically significant with P value <0.001), and were confirmed by dynamic contrast enhancement pattern.

Value of ADC values assessment

ADC values were obtained for all 83 lesions detected at consensus reading. It was obvious that ADC of malignant lesions is significantly lower than that of surrounding normal liver parenchyma. DWI was superior in differentiation between HCC and atypical regenerating nodules of cirrhotic liver, especially by detecting ADC values of the lesions, as ADC of HCC was found to be less than surrounding liver parenchyma, while that of regenerating nodules was almost the same in range to that of normal liver parenchyma. The ADC value in cirrhotic liver parenchyma was significantly lower than in non cirrhotic liver parenchyma as reported in ***table 4***.No statistically significant differences were detected between ADC values of different malignant lesions in cirrhotic and non cirrhotic liver

Table (1): Age and sex distribution according to diagnosis:

	Age	Gender	
	Mean (±SD)	Male: N (%)	Female: N (%)
HCC	57.2 (±7.2)	26 (81.8)	6 (18.2)
Lymphoma	25.5 (±6.4)	-	2 (100.0)
Pancreatic Cancer	57.0 (±9.8)	2 (66.7)	1 (33.3)
Breast Cancer	48.5 (±6.4)	-	2 (100.0)
Cancer Colon	63.0 (±2.3)	4 (80.0)	1 (20.0)
Ovarian Carcinoma	55.0 (±1.4)	-	2 (100.0)
Cholangiocarcinoma	52.0 (±2.8)	3 (100.0)	-
Unknown Origin	49	1 (100.0)	-

Table (2): demonstrates the distribution of lesions according to their size:

Size of the lesions	Number of the lesions
1-2 cm	49
>2-5cm	24
>5-10cm	9
>10 cm	1

Table (3): Average size of FHLs in relation to better signals from T2WI compared to DWI modalities

	Average Size	
	Mean (±SD)	*Min – Max*
Better DWI	1.55 (±0.5)	1.0 – 3.0
Better T2WI	2.25 (±0.3)	2.0 – 2.5
Same	4.53 (±2.2)	2.0 – 11.0
P value	<0.001 (Statistically significant)	

Table (4): ADC of liver parenchyma according to presence or absence of cirrhosis

	Mean (±SD)	Min–Max
Cirrhosis +ve	0.73 x 10^{-3} (±0.24) mm^2 /sec.	0.40 – 1.17
Cirrhosis – ve	0.90 x 10^{-3} (±0.25) mm^2 /sec.	0.25 – 1.51
P value	<0.01(Statistically significant)	

No statistically significant differences in ADC values among different malignant lesions, either primary or secondary types. Mean ADC values of HCCs were 0.9 x 10^{-3} (± 0.3) mm^2 /sec and liver metastases were 0.73 x 10^{-3} (± 0.24). mm^2 /sec.

Table (5): Average ADC values according to diagnosis of malignant hepatic focal lesions.

	N	Mean (±SD)	Min – Max
HCC	32	0.90 x10^{-3} (±0.3) mm^2 /sec	0.25 – 1.51
Cholangiocarcinoma	4	0.95 x10^{-3} (±0.07) mm^2 /sec	0.90 – 1.0
Secondaries	47	0.73 x10^{-3} (±0.24) mm^2 /sec	0.40 – 1.17

Among the metastatic lesions, the lowest ADC value was for breast cancer metastasis, while colonic had the highest value as following

Table (6): The mean ADC values of different metastatic lesions

	Mean ADC value	±S.D
Metastases of cancer pancreas	0.75 x 10^{-3} mm^2 /sec.	±0.23
Metastases of cancer colon	0.91 x 10^{-3} mm^2 /sec.	±0.32
Metastases of cancer breast	0.7 x 10^{-3} mm^2 /sec.	±0.35
Metastases of ovarian carcinoma	0.72 x 10^{-3} mm^2 /sec.	±0.34
Metastases of unknown origin	0.78 x 10^{-3} mm^2 /sec.	±0.28

4. Discussion

A variety of primary and secondary malignant tumors may present in the liver. In clinical practice the most commonly encountered hepatic tumors are primary hepatocelluler carcinoma, metastatic carcinoma and primary cholangiocarcinoma, each with its separate prognostic and management implications. When these tumors are poorly differentiated and the biopsy size is limited to a needle core, the distinction can be extremely difficult [28].

The importance of liver imaging lies in the accurate detection and exact differentiation between malignant and frequent benign lesions [14]. Although dynamic contrast enhanced examinations have become a routine component of abdominal imaging, the high cost/benefit ratio and risk of contrast media side effects remain an issue [15].

DWI is a widely accepted technique in neuroradiology. The use of DWI in other parts of the body e.g. liver, is relatively new, but very promising for the detection and differentiation of benign and malignant lesions as well as in pretreatment planning and for post-therapeutic follow up and assessment of tumor response to therapy of malignant tumors (especially chemotherapy) [16]**.**

Our results showed significantly improved detection rates of malignant hepatic focal lesions when using DW imaging (86%) compared with standard breath-hold T2-weighted imaging (67.5%) , particularly for small malignant lesions measuring 1–2 cm, while there was no statistical significance in detection of lesions larger than 2 cm in diameter. These results agreed with those of ***Bachir and Dew*** [8] who reported significantly improved detection of small malignant lesions (< 2 cm) by DWI when compared with breath-hold T2-weighted imaging (78.5% versus 45.8%, **P** < .001) in a study performed on 24 patients. ***Parikh et al.,*** [17] also showed significantly improved detection rates of both malignant and benign FLLs compared with standard breath-hold T2-weighted imaging, particularly for small malignant lesions measuring 1–3 cm.

Bruegel et al., [11]compared respiratory-triggered DW MR imaging to T2-weighted sequence for the diagnosis of hepatic metastases in 52 patients with 118 lesions at 1.5T. DW MR was far superior to T2-weighted fast SE techniques in lesion detection especially for small metastatic lesions (≤ 1 cm). ***Vandecaveye et al.,*** [18] concluded that DWI provided higher sensitivity and positive predictive value for the detection of HCC < 20 mm compared to conventional contrast enhanced MRI (*P*< .002). While DWI did not show significantly better results than conventional MRI in detecting HCC > 20 mm.

These findings can be explained by the better contrast-to-noise ratio and background suppression of normal liver parenchyma and vascular or bile structures in DWI, which make small lesions more visible, especially when they are in close vicinity to vessels or bile ducts. Furthermore the solid tumors tended to appear larger on DWI than on T2W images.. Although the use of T2W images is helpful for the detection of focal hepatic lesions , lesion delectability is suppressed by low lesion-to-liver contrast and the interfering high signal intensity from intra hepatic vessels . Intra hepatic vessels may be seen as false positive lesions on T2W images [9-17]

Also the use of *b* value played a rule in those results as this study was conducted with high *b* value (500&1000 sec/mm^2) to overcome the effect of capillary perfusion and water diffusion in extracellular

extravascular space, as high **b** value will result in the reduction of signal from moving protons in the bile ducts, cysts, vessels, and fluid in the bowel. This will result in an increased contrast between the lesion and liver. Furthermore, the differences in the relative contrast ratio between malignant and benign lesions were shown to increase with a high **b** value in previous studies [3-15]. ***Parikh et al.,*** [17] used small *b* values (50 sec/mm^2) and the high detection rates were attributed to suppression of background vessels, equivalent to that achieved with black-blood images, with better contrast-to-noise ratio and better lesion conspicuity.

Our study had limited numbers of treated lesions on follow up. However, it showed better and early detection of recurrence (3 months post-therapy). ***Goshima et al.,*** [19] reported significant increase in ADC values after chemoembolization, but they varied widely and did not contribute to the accurate diagnosis of tumor necrosis by any cut-off points. ***Yu et al.,*** [20] found that DWI added to conventional MRI could increase the sensitivity for determining earlier tumor response especially in the case of atypical lesions. However, they also noticed an increase in the number of false positive findings by adding DWI which affected the overall accuracy of MRI. ***Kamel et al.,*** [21] reported a significant increase in ADC value of HCC 1-2 weeks after chemoembolization and ***Cui et al.,*** [22] found an early increase in ADC value at 3-7 days after chemotherapy of colorectal secondaries among responders, but not in non responders.

We found that DWI had better detection rate of malignant lesions in cirrhotic liver than T2WI that went in line with a study conducted by ***Qayyum*** [7] on 30 patients and found that much higher contrast between HCC and cirrhotic liver on DWI than on T2WI. One potential explanation is possible association between iron deposition in Kupffer cells and hepatocytes in cirrhotic liver that causes T2 shortening resulting in increase lesion-to-liver contrast in echo-planar images, and that the heterogeneity and increased signal intensity of cirrhotic liver parenchyma resulting from nodular regeneration, fibrosis and scarring can obscure the mildly hyper intense HCC nodules on T2WI.

Our study had many limitations:

First, the DW data set included only respiratory-triggered images that have superiority over breath-hold DW imaging for lesion detection. However, respiratory triggered technique has several limitations like cardiac motion artifacts and noise contamination that may distort ADC values to a certain degree. Additional pulse triggering may overcome cardiac motion related artifacts. **Second**, ADCs were measured using only high *b* values (500&1000) to improve sensitivity to cellular packing. Theoretically, ADC measurement with DW images obtained with multiple *b* values might reduce the measurement error, thus potentially improving reproducibility. However, that increases study time and results in patient incompliance. Therefore, further studies regarding the effect of multiple *b* values on the reproducibility may be worthwhile. **Third**, pathologic diagnosis was not available for some patients. **Fourth**, lack of lesions <1 cm in diameter, as most of Egyptian patients present late to hepatology clinics with well established lesions. **Fifth**, difficulty in follow up of lesions after therapy, owing to financial and psychological causes. So, recommendations have been elicited to use this technique as a standard one in early detection and characterization of hepatic focal lesions.

A B C D

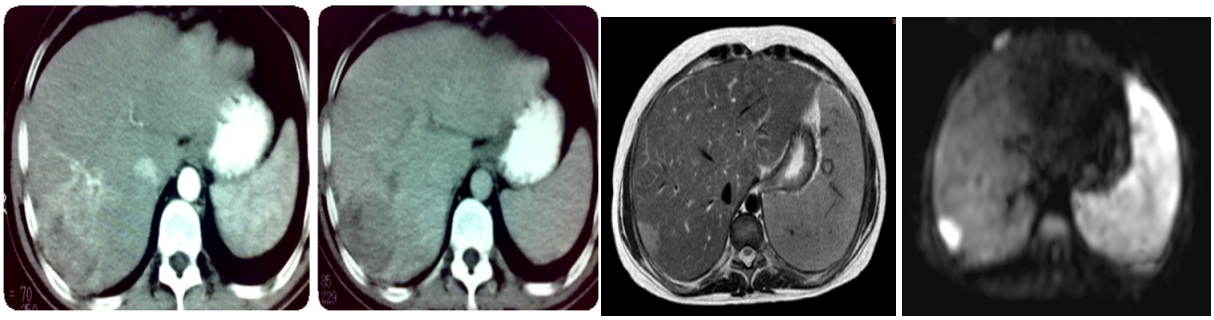

Fig 1:A 21 year-old female presenting with abdominal pain**,** HCV +ve , elevated CA125 (510 IU/ml) normal, CA 19.9&alpha fetoprotein**. (A)** And **(B)** CT showed a sub segment VII lesion with early arterial enhancement and subsequent washout**.(C)** T2W revealed a hyper intense mass **(D) . On DWMRI** the lesion is more obvious with ADC value of 0.85X 10^{-3} mm^2 /sec. Note is made of splenic focal lesion. Histopathological diagnosis was lymphoma

A B C D

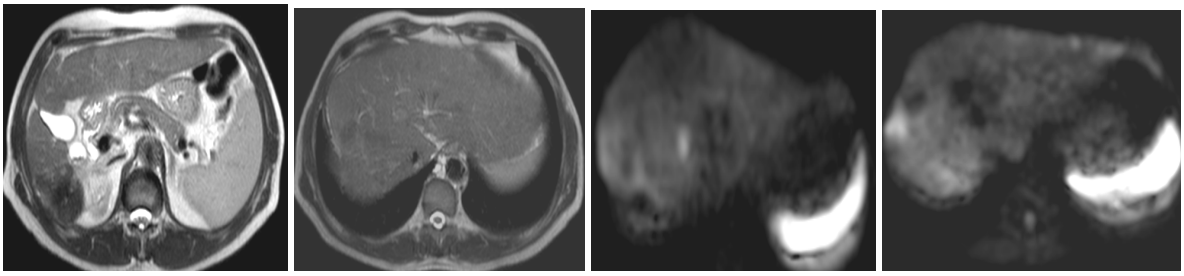

Fig 2:A 58 year-old male patient underwent chemoembolization for HCC 1 month prior to the current study. Alphafetoprotein was 586 IU/m and US showed a small well defined right lobe focal lesion. The chemoembolized lesion appeared as hypo intense lesion at sub segment VI on T2WI **(A)** . Another small is to faint hyper intense lesion is seen at sub segment V on T2W **(B)**. On DWI **(C)** and **(D)** At least two hyper intense focal lesions at sub segments V&VII, were better detected with ADC values 0.8&1.02X 10–3 mm2 /sec.

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7/28/2012