

Magnetization Transfer Magnetic Resonance Imaging of Hepatic Tumors

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ABSTRACT

Magnetization transfer (MT) technique provides a new type of MR imaging contrast based on biochemical properties due to magnetization interaction between bulk water protons and macromolecular protons. The aim of this study is to evaluate the significance of MT as a new technique in assessment of focal hepatic tumors. This work included 6 volunteers as a control group for determination of MT values and 25 patients with pathologically proven focal hepatic tumors. Qualitative and quantitative analysis of the signal intensities of the liver parenchyma as well as the liver tumors were done both before and after gadolinium enhancement. MT Gradient Recalled Echo (GRE) combined with gadolinium enhancement has significantly increased the lesion to liver contrast ratio in cases of hepatic haemangioma and metastatic adenocarcinomas whereas in cases of hepatocellular carcinoma enhanced MR (GRE) imaging showed equivocal results and has no significant superiority over conventional imaging sequences.

Key Words: *Magnetization transfer (MT) - Hepatic tumors.*

INTRODUCTION

Over the last few years a variety of new MRI techniques have been used with better results. The more recent development of phased array coils, fast spin echo multi-slice breath held imaging and echo planar imaging (EPI) give a number of new exciting approaches that place MRI at the forefront of liver imaging [3].

Conventional magnetic resonance (MR) imaging contrast is basically generated by the differences in T1, T2 and proton-density in biologic tissue. However, magnetization transfer technique provides another kind of MR imaging contrast, thought to be based on biochemical properties due to the magnetization interaction between bulk water protons and macromolecular protons [4,12]. The MT technique consists of applying an off-resonance radiofrequency pulse

to selectively saturate the macromolecular protons [2,5]. MT saturation of these protons is then transferred to the bulk water protons through cross relaxation process and/or chemical exchange [2,12].

The tissue signal intensity on the MR image is decreased in relation to the magnitude of the magnetization exchange rate. This rate differs from tissue to tissue thus generating uniform contrast. MT imaging techniques have proved useful in many clinical applications [14,15]. Few works have been done using the MT technique to evaluate different hepatic neoplasms with promising results [7,8,10]. The complementary effects of MR techniques with paramagnetic contrast agents have recently been demonstrated and the use of contrast agents has become an essential part of MR imaging for characterizing hepatic tumors [10,11].

The purpose of this study is to define the usefulness of the MT imaging techniques combined with paramagnetic contrast agents in the evaluation of hepatic tumors.

PATIENTS AND METHODS

Study population:

Six healthy volunteers were imaged to obtain control data for the MT effect, 3 males and 3 females, their ages ranged from 20 to 42 years.

Twenty five patients with hepatic tumours were evaluated (12 females and 13 males), their age ranged from 37 to 63 years.

MR imaging:

MR imaging was performed with a superconducting magnet at 1.5 T (Signa Advantage:

GE Medical Systems, Milwaukee) T1-weighted spin-echo-(SE) images (TR/TE m sec = 400/11) and T2-weighted (SE) images (2000/30,90) were obtained with a 256 x 192 matrix, a 26-36 cm field of view, two signals acquired with respiratory compensation and saturation pulses superior and inferior to the section. Seven-eight mm section thickness was taken with 3-5 mm inter section gap.

- Fast spin-echo T1 weighted axial images TR/TE 500/13 msec.
- Fast spin-echo T2 weighted images TR/TE 3000/103 m sec.

Initially axial T1 and T2 weighted SE images were obtained through the entire liver. Two to three representative sections containing tumor were chosen for MT imaging. One section of which was used for evaluation. In this section GRE sequences without contrast agent enhancement and then with and without the off-resonance saturation pulse were performed. For the dynamic contrast enhanced study gadopentate dimeglumine (Magnevist/Scherring) was administered as an intra- venous bolus injection (0.1 m mol/Kg body weight dose at a rate of 2 ml/sec). Dynamic MR imaging was started immediately after injection and repeated every 20 seconds, with eight acquisition in the first 3 minutes and then three more acquisitions of 1 minute intervals.

After dynamic MR imaging patients underwent enhanced T1 weighted SE imaging followed by enhanced GRE and MT-GRE imaging. Gadolinium enhanced GRE imaging was performed at 13-24 minutes and enhanced MT-GRE imaging at 15-25 minutes, after contrast injection. In each patient enhanced images were obtained in the same plane used for the unenhancement images. Pre-contrast 3D MT GRE was performed using the following parameters.

MT frequency effect: 1200

TR: 10.2 MS

Flip angle : 20

TE: 1.7 ms

Band width: 15.6 kHz

Matrix: 256 x 128

Nex : 2 with respiratory triggering

Quantitative analysis:

GRE and MT- GRE images before and after contrast administration and enhanced T1

weighted SE images were analyzed on the basis of the signal intensity measurements in the defined region of interest.

Quantitative evaluations were available for all the included study population. In healthy volunteers, the region of interest was placed over the liver, spleen, skeletal muscles and subcutaneous fat. In patients with multiple hepatic lesions, a single representative lesion was sampled and a strongly enhanced area of the tumor was chosen for measurement. The size and position of all regions of interest were kept constant for the different sequences in each patient. Two to three measurements were obtained in each tissue. The mean value was recorded.

Quantitation of the amount of MT effect was expressed as the signal intensity on GRE image with the off-resonance saturation pulse (MS) divided by the signal intensity on the image without the off-resonance saturation pulse (MO).

Qualitative analysis:

Images were analyzed considering four characteristics:

Tumor conspicuity, sharpness of anatomic structure, image artifacts and overall quality.

RESULTS

The diagnosed hepatic tumors in our patients included 12 HCC, 9 secondaries, 2 haemangiomas and 2 simple cysts. The primary malignancy in patients with metastatic deposits was present in the colon in 5 cases, stomach in 2 cases and in the breast in 2 cases.

The diagnosis of HCC and liver metastases was documented by percutaneous needle biopsy, while the diagnosis of haemangiomas and simple cysts was supported by complementary US and/or CT examinations as well as follow up studies.

In healthy subjects (n=6), the MS/MO values were as follows: liver: 0.73, spleen: 0.75, muscles: 0.67, fat: 0.94. The off-resonance irradiation was found to have a strong effect on skeletal muscle but little effect on fat. Liver and spleen show intermediate MT effect.

In patients, the MT saturation pulse reduced the signal intensity of the liver and tumor on unenhanced GRE images. Visual distinction of tumors did not change between unenhanced MT GRE and GRE images.

After contrast injection the two cases of haemangiomata and 16 cases out of the 21 malignant liver tumors showed contrast enhancement with different patterns and to varying degrees.

Haemangiomata showed marked hyperintensity relative to the liver parenchyma on both enhanced T1 weighted SE and GRE images. They became more conspicuous on MT GRE images because the surrounding liver intensity was suppressed. In HCC (12 cases) 9 were hypointense to the liver on enhanced T1-weighted SE images and became isointense and less obvious on enhanced GRE and MT-GRE images.

A thin rim of hyperintensity was seen in 6 out of the 9 cases of hepatocellular carcinoma.

Table (1): Shows the degree of MT effect in hepatic tumors and liver parenchyma on unenhanced and enhanced images.

Table (1): Ms/MO values on unenhanced and enhanced GRE.

| Tissue | Ms/MO | |
|--------------------------|------------|----------|
| | Unenhanced | Enhanced |
| Liver parenchyma | 0.74 | 0.77 |
| Hepatocellular carcinoma | 0.75 | 0.79 |
| Metastasis | 0.75 | 0.87 |
| Haemangioma | 0.81 | 0.97 |
| Cysts | 0.85 | 0.85 |

On unenhanced images, no significant difference in MS/MO was found between liver parenchyma and hepatocellular carcinoma or metastasis, yet in haemangiomata and cysts MS/MO value is larger than that of the normal liver parenchyma.

On enhanced images there was a significant difference in Ms/MO between liver and haemangioma and between liver and metastasis.

Table (2) Shows the qualitative analysis of hepatic tumour imaging with enhanced MT GRE versus unenhanced MT GRE and enhanced GRE versus unenhanced GRE, as well as the enhanced MT GRE versus enhanced T1 WIs.

The table shows that enhanced MT GRE images were significantly better than enhanced GRE and T1 weighted images and the enhanced GRE and MT GRE images were both superior to unenhanced GRE, MT GRE and T1 weighted images.

Table (2): Qualitative analysis of hepatic tumor imaging with different MRI techniques (n=25).

| Comparison | Quality | |
|----------------------------|----------|-------|
| | Superior | Equal |
| <i>Tumour conspicuity:</i> | | |
| MT GRE Gd-Vs T1 Gd | 14 | 11 |
| MT GRE Gd-Vs MT GRE | 23 | 2 |
| GRE Gd-Vs GRE | 20 | 5 |
| <i>Anatomic details:</i> | | |
| MT GRE Gd-Vs T1 Gd | 13 | 12 |
| MT GRE Gd-Vs MT GRE | 24 | 1 |
| GRE Gd-Vs GRE | 20 | 4 |
| <i>Image quality:</i> | | |
| MT GRE Gd-Vs Gd | 15 | 5 |
| MT GRE Gd-Vs MT GRE | 22 | 3 |
| GRE Gd-Vs GRE | 19 | 6 |

Fig. (1): Hepatic cyst:

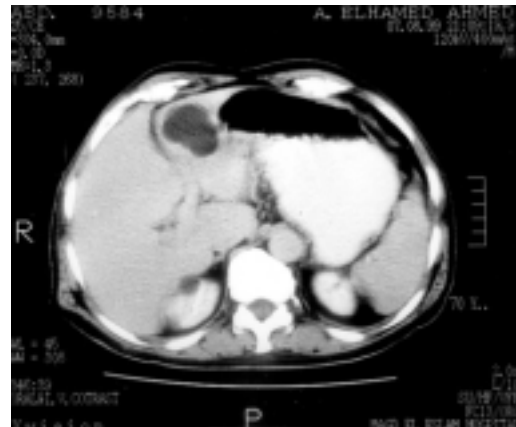


Fig. (1-A): Post contrast axial CT scan of the liver revealed a relatively well defined hypodense, cystic lesion implicating the lateral segment of the left lobe yet no definite demarcated capsule is noted.

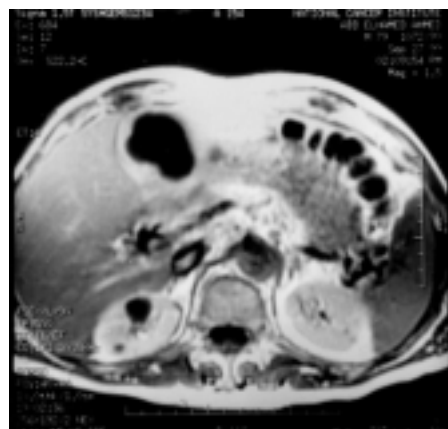


Fig. (1-B): Post contrast axial T1 weighted spin-echo image verifies the cystic nature of the lesion, with the border sharply demarcated.

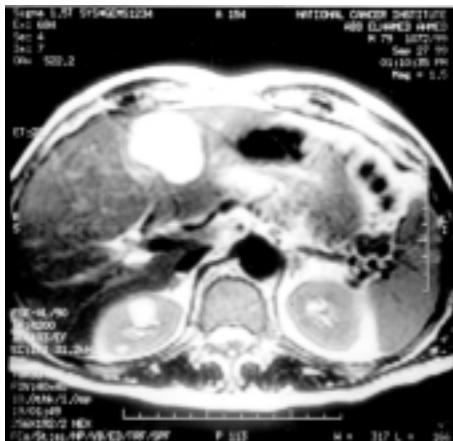


Fig. (1-C): Axial T2-weighted spin-echo image confirming the cystic nature of the lesion.

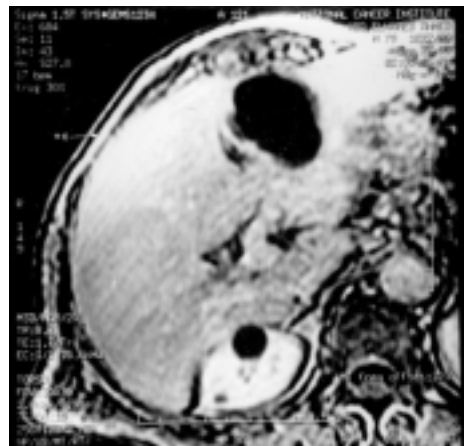


Fig. (1-D): Axial post contrast MT sequence demonstrates the lesion with better conspicuity, higher lesion to liver contrast ratio and better resolution.

Fig. (2): Metastatic bronchogenic carcinoma:



Fig. (2-A): Post contrast axial T1 spin-echo sequence demonstrates well-margined, regular rounded marginal enhancing focal hepatic parenchymal lesion implicating the ventral right hepatic lobe.



Fig. (2-B): Axial T2-weighted image demonstrates the lesion to be of high uniform signal intensity verifying its tumoral nature.



Fig. (2-C): Post contrast axial MT sequence exhibits sharp demarcation, better resolution, high contrast to noise ratio and better image quality.



Fig. (2-D): Non contrast axial MT sequence shows multiple, well defined, variable sized homogenous, hypointense lesions at the hepatic dome not readily visualized either by CT or conventional MR sequences.



Fig. (3-A)

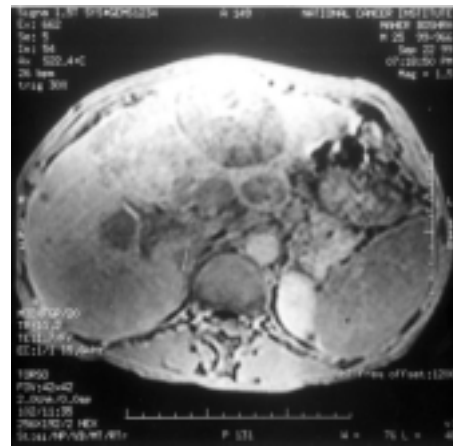


Fig. (3-B)

Fig. (3): Multi centric H.C.C.:

- A: Non contrast axial T1-weighted spin-echo sequence revealed a well defined homogenously hyperintense, regular, rounded, soft tissue tumoral mass lesion implicating the lateral segment of the left hepatic lobe with small satellites scattered parenchymal foci.
- B: Axial contrast enhanced MT sequence verified the visualized lesion with higher conspicuity, image contrast, in addition to the precise highlight of the satellite lesions at the portal bifurcation.

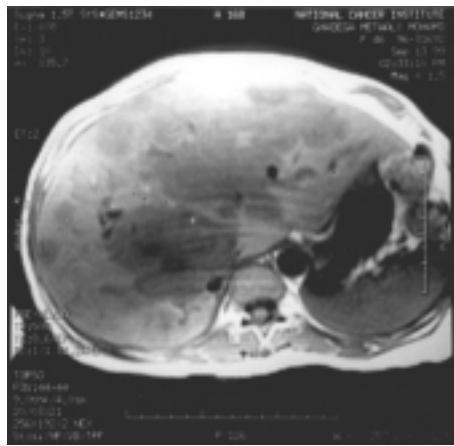


Fig. (4-A)



Fig. (4-B)

Fig. (4): Multi centric H.C.C.:

- A: Non contrast axial T1-weighted spin-echo sequence demonstrates the liver to be studded by multiple variable sized, irregular, relatively demarcated, map like, hypointense, heterogenous mass lesions scattered in both hepatic lobes.
- B: Contrast enhanced axial MT sequences depicts the well delineated lesions with high spatial resolution, less noise, better image quality, higher conspicuity and high lesion to liver ratio.

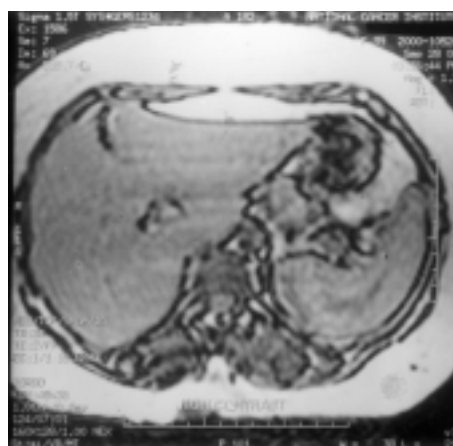
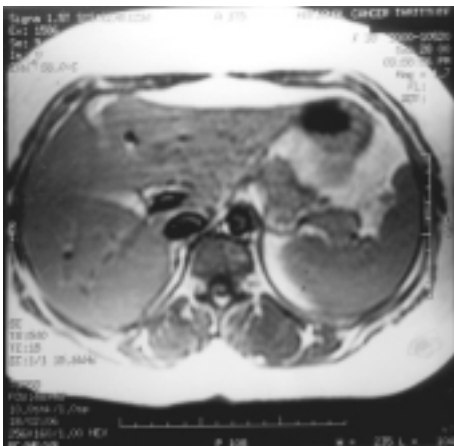


Fig. (5): Capillary haemangioma:

- Fig. (5-A,B): Non contrast axial T1-weighted and MT sequence. showing no definite abnormality.



Fig. (5-C): Post contrast axial MT sequence clearly depicts a well defined focal lesion (haemangioma) in the posterior segment of the right lobe with sharp demarcation and even the feeding vessel is also well seen.

DISCUSSION

The high inherent tissue contrast of MR is well known, however further augmentation of tissue contrast can now be achieved by introducing contrast agents such as Gd-DTPA [1].

The effect of Gd-DTPA is not pronounced in the reduction of T1 which results in enhancement of T1 weighted images [2]. The contrast enhancement is supposed to be increased by using off-resonance irradiation which reduces the signal emitted by tissue with high efficiency of water/macromolecule interaction and a low concentration of paramagnetic substance, while having less effect on tissues with considerable paramagnetic concentration and/or weak water/macromolecule interaction [3].

Magnetization transfer contrast entails the use of an off-resonance radio-frequency (RF) irradiation which presaturates selectively the protons of the immobile macromolecules and saturates indirectly via cross-relaxation, the magnetization of the water protons, which can be monitored by MRI [11].

Thus, the MT contrast is additive to the enhancement of contrast achieved by paramagnetic substances and T1 weighted imaging sequences. This phenomenon is utilized in this study using a set of sequence parameters to assess the clinical efficiency of MT contrast imaging in differentiation of hepatic tumors.

The adult liver contains many extracellular matrix component such as collagen, non collagenous glycoproteins and protoglycons. These

structures and their hydrodynamics are the key factors in determining cross-relaxation rates between mobile water protons and the motion restricted protons, thus it was assumed that the liver is particularly susceptible to MTC effect [10].

Our results showed that simple fluids such as bile and cyst contents as well as fat suffered little signal loss on the images obtained with the off resonance saturation pulse which means little transfer of longitudinal magnetization, while muscles transferred the most magnetization and showed some variability possibly due to terrible amount of intra muscular fatty tissues. The liver and spleen have similar magnetization transfer values. Similar results have been reported by several investigators who agreed that tissues rich in fat or water show weak MT indices [4]. They also showed that the MT saturation pulse has resulted in decrease of the signal intensity of the normal hepatic parenchyma as well as liver tumors specially metastasis and haemangiomas which coincides with our findings on enhanced images. However, the comparison of magnetization transfer and spin echo sequences should be based on signal intensity measurements not on morphologic criteria only since the use of morphologic criteria would presumably favor the use of standard SE images with long TR-TE over MT sequences because the higher signal-to-noise ratio are better edge definition of the former [8]. This hypothesis was found to be correct as we observed no improvement in anatomic details or tumour conspicuity of different hepatic focal tumours by using the unenhanced MT saturation sequences compared to the original SE images.

On the other hand we noticed that MT GRE imaging combined with gadolinium administration has significantly improved the qualitative analysis of haemangioma which had paramagnetically enhancing region compared with enhanced GRE and T1 weighted SE images Fig. (5). The MT saturation pulse reduces the signal intensity of liver parenchyma on enhancing GRE images to the same degree as on unenhanced images because liver showed weak enhancement. Whereas, the saturation pulse provided little or no reduction in the signal intensity of the enhanced region in which the paramagnetic contrast agents accumulated. It is thought that the off-resonance saturation pulse that produces MT contrast has little effect on

relaxation mechanism caused by paramagnetic agents [4,13].

Haemangiomas tend to transfer magnetization considerably more than fluids but less than malignant lesions since blood and plasma demonstrate more saturation with the off-resonance pulse than does water, based on the protein contrast [9]. Also, haemangiomas have internal stroma that may add considerably to the degree of saturation transfer [10].

For hepatocellular carcinoma we noticed that MT pulse provided no significant improvement in tumor conspicuity on enhanced GRE or unenhanced images, because hepatocellular carcinoma showed almost the same M_s/M_0 values as the surrounding normal liver parenchyma. MT-GRE imaging improved contrast between the well enhanced region of tumors and the poorly enhanced liver in the enhancement phases and therefore seems useful for contrast enhancement studies of the liver, Fig. (3). These findings coincide with those reported by Onaya et al. [9], who stated that for hepatocellular carcinoma, the MT pulse produces no improvement in contrast to noise ratio or tumor conspicuity on enhanced GRE or unenhanced images. Hepatocellular carcinoma shows a thin rim of late enhancement, which could be barely measured, in the enhancement phases and has almost the same M_s/M_0 values as the surrounding liver on both unenhanced and enhanced GRE images [7] Fig. (4).

Several reports [7,9,10] showed that hepatomas did not demonstrate improved lesion contrast with MTC imaging specially in cirrhotic liver, that was explained by the disease spectrum which accompanies cirrhosis such as hepatitis and fatty infiltration. Hepatomas may also contain high concentrations of copper binding proteins such as metallothionin which can easily account for T1 shortening and the strong MT effect [9].

The results of previous studies using the double contrast (Gd-DTPA and MTC) technique denied the diagnostic value of this combination referring to the great variations in the factors controlling the final image including the transit time of the contrast agent and its clearance rate, its susceptibility to MT effect and the interplay of relaxation rate enhancement and cross relaxation [6]. These, factors have been evaluated on a large scale to gain meaningful results

concerning the diagnostic ability of MTC to detect hepatic lesions [9].

The study performed by Outwater et al., 1992 comprising 26 patients with benign and malignant hepatic focal lesions underwent MR imaging showed that hepatic malignancies demonstrate magnetization transfer similar to that of the liver, while hemangiomas and cysts show significantly less magnetization transfer than malignant lesions. We have reached similar findings in spite of the differences in the frequency offset and field strength.

In this work we have demonstrated that magnetization transfer can increase the lesion-to-liver contrast of hemangiomas Fig. (5) and cysts Fig. (1). Compared to the usual SE techniques, while MT dose not increase the contrast between malignant lesions and liver parenchyma since these have very similar degrees of transfer Fig. (2). The use of contrast agent with MT imaging may increase its value in diagnosis of malignant lesions in spite of the lack of consensus existing in the literature concerning this value.

REFERENCES

- 1- Adjel O.N., Tamura S. and Sugimara H.: Contrast-enhanced MR imaging of intrahepatic cholangiocarcinoma. *Clin. Radiol.*, 50: 6-10, 1995.
- 2- Balaban R.S. and Ceckler T.L.: Magnetization transfer contrast in magnetic resonance imaging. *Magn. Reson.*, 8: 116-137, 1992.
- 3- Dupuis K., Thangaraj V. & Edelman R.R.: Practical MRI for the technologists and imaging specialists. In Edelman R.R., Hesselink J.R. and Zlatkin M.B. (eds). *MRI Clinical magnetic resonance imaging*. Philadelphia. W.B. Saunders Company, 52-87, 1996.
- 4- Eng J., Ceckler T.L. and Balaban R.S.: Quantitative H magnetization transfer imaging in vivo. *Magn. Reson. Med.*, 17: 304-314, 1991.
- 5- Hajnal J.V., Baudouin C.J. and Oatridge A.: Design and implementation of magnetization transfer pulse sequence for clinical use. *J. Comp. Assist Tomogr.*, 16: 7-18, 1992.
- 6- Jukka I., Tantt, Sepponen R.E. and Martin J.L.: Synergetic enhancement of MRI with Gd-DTPA and magnetization transfer. *J. of Comp. Assist Tomogr.*, 16: 19-24, 1992.
- 7- Kahn C.E., Perra S.D. and Sepponen R.E.: Magnetization transfer of the abdomen at 0.1 T. De-

- tection of hepatic neoplasms. *Magn. Reson. Imaging*, 11: 67-71, 1993.
- 8- Loesberg A.C., Kormano M. and Lipton M.S.: Magnetization transfer of normal and abnormal liver at 1.0 T. *Invest Radiol.*, 28: 725-731, 1993.
 - 9- Onaya H., Yoshioka H., Itai Y. and Niitsu M.: Hepatic tumors: Magnetization transfer MR imaging with gadolinium enhancement. *JMRI*, 5: 273-279, 1995.
 - 10- Outwaterd E., Schnall M.D. and Braitman L.E.: Magnetization transfer of hepatic lesions: Evaluation of a novel contrast technique in the abdomen. *Radiology*, 182: 535-540, 1992.
 - 11- Pierce W.B., Harms S.E. and Flaming D.P.: Three dimensional gadolinium-enhanced MR imaging of the breast: Pulse sequence with fat suppression and magnetization transfer contrast-work in progress. *Radiology*, 181: 757-763, 1991.
 - 12- Wolf S.D. and Balaban R.S.: Magnetization transfer contrast (MTC) and tissue water proton relaxation in vivo. *Mag. Reson Med.*, 10: 135-144, 1989.
 - 13- Wolf S.D. and Balaban R.S.: Magnetization transfer contrast and tissue water proton relaxation in vivo. *Magn. Reson Med.*, 10: 135-144, 1989.
 - 14- Wolf S.D., Chesnick S., Frank J.A. and Balaban R.S.: Magnetization transfer contrast: MR imaging of the knee. *Radiology*, 179: 623-628, 1991.
 - 15- Wolf S.D. and Balaban R.S.: Magnetization transfer contrast: method for improving contrast in gradient recalled echo images. *Radiology*, 179: 133-137, 1991.