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LIVER MRI IN ONCOLOGICAL PATIENTS: WHAT BENEFITS CAN WE GET? A PRACTICAL MINIREVIEW

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Abstract: *Liver parenchyma could develop primary tumours or be involved by secondary metastases. Hepatocellular carcinoma (HCC) is the most frequently encountered primary tumour of the liver; intra-hepatic cholangiocarcinoma represents the second most common tumour which develops from the liver, less reported than HCC. Secondary involvement of hepatic parenchyma could be observed in several tumours, namely in case of colonic, pulmonary, breast, gastric, oesophageal, pancreatic or genitourinary cancer.*

Management of oncological patients requires the highest diagnostic accuracy, in order to obtain the most correct "oncological stage of disease", to adopt the optimal treatment and to identify – in case of non-surgical therapies – the early responder patients.

MRI fuelled high expectations in the evaluation of oncological liver, due to its high contrast resolution. The new recent advantages of liver MRI, predominantly represented by diffusion weighted imaging (DWI) and hepatospecific contrast agent are discussed in this paper, in order to help clinicians, oncologists and radiotherapists in the management of hepatic oncological disease.

Namely, we focused on main features of a liver MRI protocol in oncological patients: 1) dual-echo chemical shift gradient-echo sequences; 2) Gadoxetic-acid liver MRI and HCC; 3) Hepatocyte-specific contrast agents MRI in detection of liver metastases; 4) DWI for malignant lesions detection and response to treatments.

INTRODUCTION

Magnetic resonance imaging (MRI) plays an important role in liver imaging. In the last decades, the development of new sequences and the introduction of liver-specific contrast agents improved morphological and functional information provided by MRI[1,2]. These technical advances have been very useful in the assessment of oncological liver disease.

The role of liver MRI in oncological patients is not uniformly defined by different staging guidelines. Generally, ultrasonography (US) and multidetector-CT (MDCT) are used as first-line or second-line diagnostic procedures for staging oncological patients. Liver MRI has been previously considered only in cases of doubtful lesions encountered in the liver parenchyma. However, in the past decade, MRI has progressively increased its involvement, due to the very high-diagnostic performance in focal liver lesions detection and characterization.

Standard liver MRI protocol includes breath-hold unenhanced and dynamic (arterial, portal, and equilibrium or late phase) enhanced images; however, hepatospecific agents have been widely introduced in liver MRI imaging, in order to improve diagnostic accuracy especially in the management of oncological patients.

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Gd-EOB-DTPA (gadolinium-ethoxybenzyl-diethy-lenetriamine pentaacetic acid, Primovist®, Bayer Schering) and Gd-BOPTA (gadopentate dimeglumine, Multihance®, Bracco Imaging) are positive liver-specific contrast agents having a T1-shortening effect. They are administered by bolus injection, showing extracellular and hepatocellular pharmacokinetics properties. First, these contrast agents are distributed in the extravascular spaces, coming in the interstitial space from vessels lumen. Then, contrast molecules are taken up by normal liver parenchyma and by focal liver lesions with functioning hepatocytes, enabling differentiation of hepatocyte-containing from non-hepatocyte- containing lesions (metastases, cysts, hemangiomas and abscesses)[3].

The goal of this paper is to describe the diagnostic capability provided by liver MRI in the oncological liver disease; namely, we focused our attention on main advantages of liver MRI, represented by:

- Dual-echo chemical shift gradient-echo sequences: beyond the chemiotherapy-induced steatosis;
- Gadoxetic-acid liver MRI and HCC;
- Hepatocyte-specific contrast agents MRI in the detection of liver metastases;
- DWI: malignant lesions detection and response to the treatments.

DUAL-ECHO CHEMICAL SHIFT GRADIENT-ECHO SEQUENCES: BEYOND CHEMIO-THERAPY-INDUCED STEATOSIS

Since its introduction in late 1980s, dual-echo chemical shift gradient-echo sequences (Figure 1) have been routinely performed in a liver MRI protocol for assessment of diffuse liver disease[4-7]. These gradients-echo sequences were initially introduced to investigate the presence of fat in the parenchymal liver, thank to a "double echo-time"[8]. Using a 1.5 Tesla scanner, water and fat protons are generally in phase at an echo time of 4.5 msec, whereas they have opposite phase at 2.2 msec[4]. When fat and water protons are placed in "opposition phase", voxel with equal content of water and fat will exhibit a drop of signal intensity.

Hepatic steatosis consists in an increased accumulation of triglycerides within hepatocytes. Systemic chemotherapy is often performed as pre-operative treatment before liver resection[9-11]: unfortunately, chemotherapy treatment has been widely recognized as being responsible for several liver injuries, which include steatosis, steatohepatitis, sinusoidal dilatation and haemorrhage, perisinusoidal and veno-occlusive fibrosis[9,12-13]. However, steatosis could be a pre-existent condition in the parenchymal liver, not necessary related to the oncological treatment.

Hepatic metastases could be misdiagnosed in a steatotic liver using CT and US. Small metastases – appearing as small hypodense foci – could be missed during the enhanced phases of a CT study.

Dual-phase chemical shift sequences could help radiologists in the diagnosis of these small metastases, being able to detect the fatty liver and the hepatic lesions in the parenchyma. In a previous paper published by Chung et al[14], the presence of peritumoral fatty sparing areas surrounding metastases have been demonstrated. Local sparing areas are generally due to arterioportal shunt or reduced portal blood flow from intestine[14,15]. Fatty sparing areas are frequently observed in peritumoral regions: the neoplastic lesions cause compression of adjacent liver parenchyma, causing reduction of portal blood flow. In the assessment of focal liver malignancies, in-phase unenhanced spoiled gradient echo T1-weighted sequences, T2-weighted inversion recovery sequences and contrast-enhanced nonsuppressed spoiled gradient-echo images were not able to detect the "peritumoral fatty sparing areas", which were easily assessed on out-of-phase images[14].

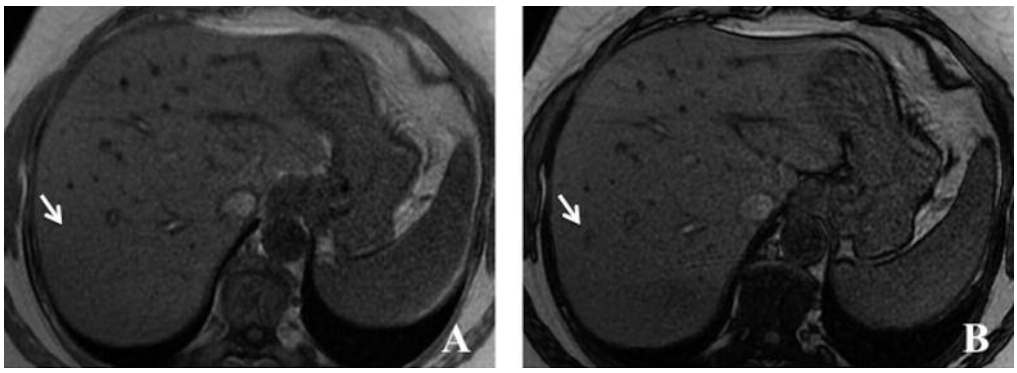

Figure 1. Patient with focal hepatic steatosis, appreciable in "in-phase" (**A**) and "out-of-phase" (**B**) GRE T1 sequences. A small area of focal steatosis shows a typical signal drop in out-of-phase image (**B**), suggesting its intracellular fat content.

Fatty liver show diffuse drop of signal intensity, except for peritumoral areas which generally appear as a hyperintense parenchymal rims which surround the metastatic lesion.

The hyperattenuating rim is not specific for metastatic lesions, being observed also in cases of benign lesions such as hemangiomas[4]; a combination of all MRI features obtained by the different sequences is mandatory to perform the correct diagnosis and characterization.

GADOXETIC-ACID LIVER MRI AND HCC

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related deaths[16]. The prognosis is poor because tumour has an aggressive behaviour. It usually occurs in the setting of cirrhosis and chronic liver disease.

Early HCC detection is very important to improve the possibility of therapeutic intervention and patient survival. In fact, when diagnosed at an advanced stage, HCC has a five-year survival rate of <5%[16]. Screening and surveillance are recommended in high-risk patients with chronic liver disease. An early detection of malignant nodules is important for a better therapy, such us surgical resection, transcatheter arterial chemoembolization (TACE), and chemical or thermal ablation[17-23].

As referred by Yu et al[23], contrast-enhanced CT and MRI are good techniques for detection and characterization of the majority of HCC lesions, with a sensitivity of 65% and 72%, respectively. The specificity of CT and MRI is about, respectively, 96% and 87%. According to Colli et al[24], the sensitivity of these two techniques is 68% and 81%, respectively. In previous studies, the specificity of CT is 93% and 81% for MRI.

Detection of HCCs smaller than 2 cm is still a problem using both dynamic MDCT and MRI, because identification of hypovascular and isovascular lesions, in the early stages of multistep hepatocarcinogenesis, remains difficult[17].

According to the European Association for the Study of Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC) 2012[25], nodules greater than 1 cm should be studied with one imaging technique (either 4-phase MDCT scan or dynamic contrast enhanced MRI).

On enhanced MRI, classic HCC features are the arterial enhancement and "wash-out" during portal venous or equilibrium phases, with or without delayed enhancing fibrous capsule. This appearance – reported as typical vascular behaviour (Figure 2) – is highly specific of HCC using extracellular contrast agents[18].

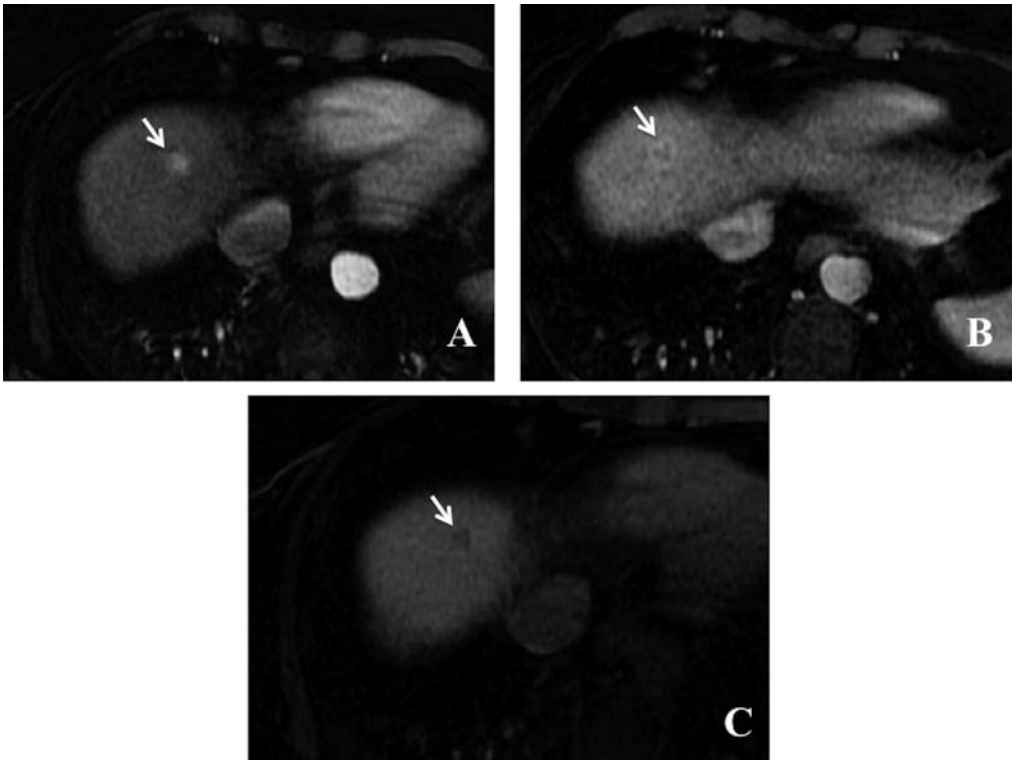

Figure 2. Patient with typical HCC appearance. Gd-EOB-DTPA MRI shows a lesion *(arrows)* that appears hypervascular in arterial phase (**A**), and hypointense in venous (**B**) and hepatobiliary (**C**) phases.

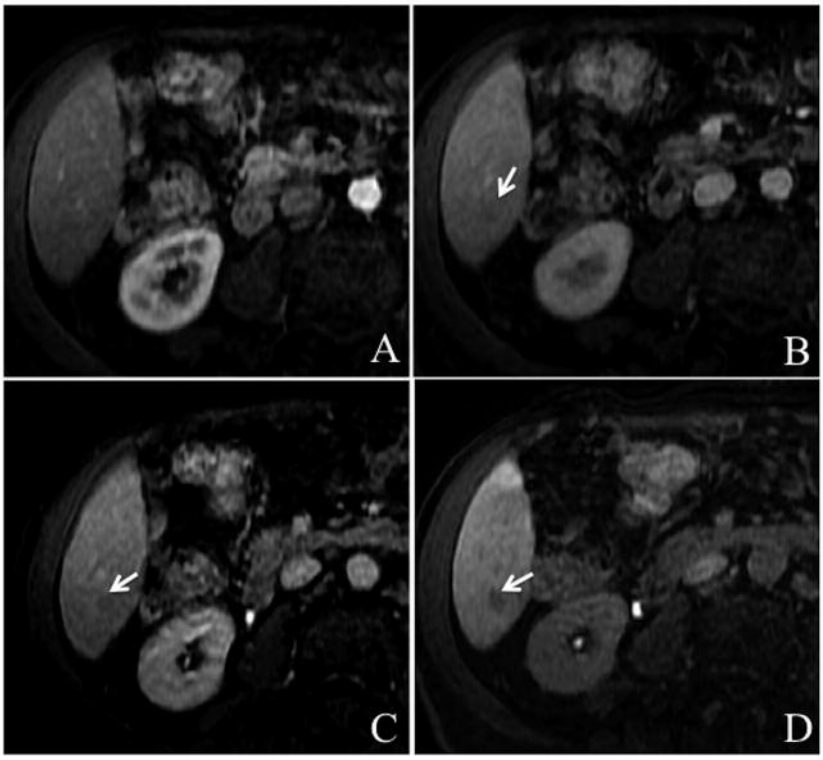

Figure 3. Patient with atypical HCC in Gd-EOB-DTPA MRI. The lesion *(arrows)* appears isointense in arterial phase (**A**), hypointense in venous (**B**) and tardive (**C**) phases; after 20 minutes, in the hepatobiliary phase (**D**), the lesion is also hypointense in comparison with the liver parenchyma.

A crucial step in the carcinogenesis is the increase of arteriolar vascularization and reduction of the portal supply. These vascular changes differentiate a regenerative nodule from a dysplastic nodule and an early-HCC[26].

Atypical nodules (Figure 3) show enhancement in arterial phase, without evident wash-out in the portal or equilibrium phase or with wash-out only in the portal phase; small lesions (< 2 cm) often do not show typical behavior of HCC[26]. As previously reported in literature, these atypical nodules require the use of 2 techniques or alternatively a biopsy[22].

The sensitivity and specificity for diagnosis of HCC are better increased by hepatobiliary phase in a liver MRI protocol. According to several authors, liver imaging with Gd-EOB-DTPA allows a higher detection rate of small HCC lesions and lower false positives in comparison to CT[18].

Gadoxetic acid is a recently developed MR contrast agent that is specifically taken up by hepatocytes and has a higher sensitivity than dynamic CT for detecting HCC, especially lesions smaller than 2 cm in diameter. Gd-EOB-DTPA is "a second generation hepatocytes-directed gadolinium-based paramagnetic media"[19]; it is known as "dual agents" because dynamic contrast and liver-specific imaging (15 to 20 min after administration of contrast) are possible[17,19].

Gd-EOB-DTPA has urinary and biliary excretion rates (about 41.6-51.2% in urine and 43.1-53.2% in bile); the enterohepatic recirculation rate is about 4%[27]. During dynamic vascular phases, hepatocytes increase the uptake of gadoxetic acid and discharge it through the bile canaliculi. The functional hepatocytes achieve the contrast agent through cloned organic anion transporting polypeptides (OATPs) and excrete it via multidrug resistance-associated proteins (MRPs) to bile canaliculi (MRP2 = apical transporter) or sinusoidal space (MRP3, MRP4 = basolateral transporters)[18]. The molecular regulation and expression of OATPs and MRPs are atypical in neoplasms, metastases and pathological conditions, such us cirrhosis[2].

In cases of malignant nodules, OATP8 expression decreases, and the uptake of gadoxetic acid is reduced; as a consequence, the lesion appears hypointense on hepatobiliary images[16]. In less than 5% of HCCs an over-expression of OATP8 and MRP3 is possible, and the lesions are seen hyperintense in the hepatospecific phase, because of retention of contrast.

According to Leoni et al[28], about 20% of small HCCs do not appear with the typical vascular pattern at imaging. In the initial phases of carcinogenesis, the small lesions show an arterial hypovascularity with portal perfusion and then the

portal blood supplies decrease[29]. Hypointensity in the HB-phase indicates the malignant nature of the lesion, and it gradually increases as the nodule evolves towards malignancy[19,30-32]. According to Joo I[16], about 10% of HCCs are iso or hyper intense in the hepatobiliary phase, because of genetic alteration resulting in the over-expression of OATP8 e MRP2. In cases of HCCs (about 5-10%) iso- or hyperintense in the hepatobiliary phase, a low MRP2 or high MRP3 expression at the luminal membrane of pseudoglands are demonstrate[16,18].

According to Bolog[3], the degree of enhancement of the lesion in the hepatobiliary phase is correlated with the degree of differentiation of the HCC. The well-differentiated HCCs display uptake of hepatobiliary contrast agents and appear either iso- or hyperintense to liver parenchyma; moderately and poorly differentiated HCCs do not take up hepatobiliary contrast agent and they appear hypointense.

As referred by Kogita[33], low or absence of Gd-EOB-DTPA uptake precedes reduction of portal vascularization in malignant differentiation.

According to Golfieri et al[19], the addition of the hepatobiliary phase to dynamic MRI improves sensitivity up to 99,4% in detection of HCCs of < 2 cm; another study[32] refers a maximum increase in sensitivity from 85,7% to 91,7%.

Contrast-enhanced MR imaging – with dynamic and hepatobiliary images – shows a higher sensitivity (0,72) for HCC detection, especially for nodules < 2 cm diameter, compared with dynamic MR images alone (0.63) or MDCT (0.61)[34]. Hepatobiliary images also best differentiate small hypervascular HCCs (≤ 2 cm) from arterially enhancing pseudo-lesions; the latter demonstrate iso-signal intensity on the hepatobiliary phase[22,35-36].

According to Phongkitkarun[37], hepatobiliary phase images should be considered an adjunct tool, which increase the lesion detection of about 13.5%, in comparison with conventional dynamic MRI.

HEPATOCYTE-SPECIFIC CONTRAST AGENTS MRI IN THE DETECTION OF LIVER METASTASES

The liver parenchyma is one of the most common organs involved by metastases; in fact, secondary lesions are more frequent than primary ones[2]. In oncological patients, detection of liver metastases is an important diagnostic step in choosing the best treatment and management, in order to improve patient survival[38]. Frequently, in these patients, the first imaging modality is CT and the use of MRI is limited to cases of doubtful focal liver lesions.

Several studies have recently emphasized role of hepatocyte specific contrast agents (such us Gd-BOPTA and Gd-EOB-DTPA) in the evaluation of hepatic metastases.

Gd-BOPTA is approximately excreted via glomerular filtration for about 96%; the remaining 3-5% is eliminated in the bile, by functioning hepatocytes. The recommended dose is 0.1 mmol/kg body weight. Gadobenate dimeglumine has an excellent dynamic phase because of the lipophilic structure and transitory interaction with serum albumin[2].

The liver-specific imaging of Gd-EOB-DTPA is due to the lipophilic EOB part, linked to the gadolinium complex. The gadolinium concentration is low (about 0.25 mol/L) and the recommended dose is 0.025 mmol/kg body weight[39]. Gd-EOB-DTPA MRI protocol is the same as conventional MRI, but hepatobiliary phase is added. To optimize the acquisition time, T2-weighted, heavily T2-weighted, and diffusion-weighted images are generally acquired after unenhanced T1-weighted and T1 dynamic phases[39-40]; "alternative examination protocol" – with T2-weighted images acquired after dynamic phases – has been proposed by "consensus statement from the first International Primovist User Meeting[41]".

Hepatobiliary phase is generally acquired 20 minutes after Gd-EOB-DTPA injection, and 1-2 hours after Gd-BOPTA administration.

During the dynamic study, liver metastases show typical peripheral rim enhancement and central hypointensity due to necrosis. In the hepatobiliary phase (Figures 4 and 5), characterized by enhancement of normal hepatic parenchyma, lesions with deteriorated hepatocytes or non-hepatocytes remain unenhanced[18]. Metastatic lesions do not contain functional hepatocytes and the physiological carries for the uptake of the contrast agents, so they result hypointense in the hepatobiliary phase[2].

Some Authors[42-44] reported a "target appearance of liver metastases" in the hepatobiliary phase, with a central hyperintense round area, and a relatively hypointense peripherical rim. This appearance could be explained by desmoplastic reaction with an interstitial central portion, retaining contrast on delayed imaging. The hyperintense signal of the central area is usually lower than that of normal liver parenchyma.

Gd-EOB-DTPA imaging could be limited by several artifacts, with a poor dynamic image quality; dynamic phases could be damaged by motion artifact and ringing artifact. The latter origins from rapid concentration change of gadolinium, especially during the arterial phase, and it can be reduced, selecting square matrix and slower injection rate (1 ml/s)[2].

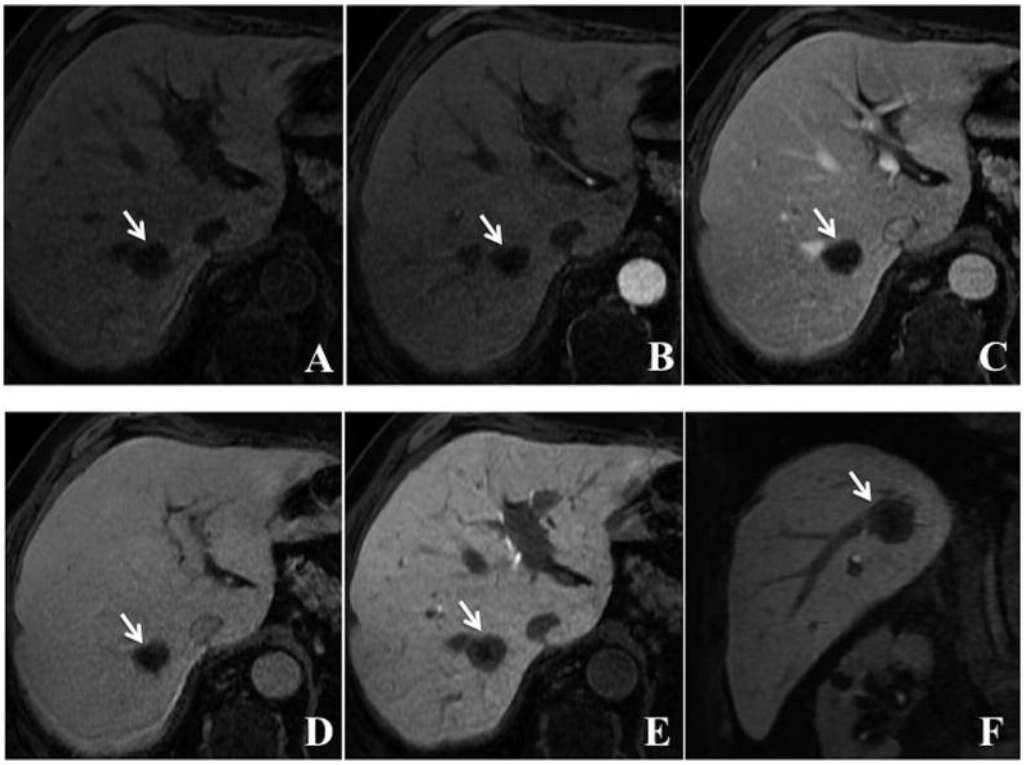

Figure 4. Patient with hepatic metastasis from colic cancer studied with Gd-EOB-DTPA MRI. We illustrate unenhanced acquisition (**A**), arterial (**B**), venous (**C**) and tardive (**D**) phases after contrast agent injection. Axial (**E**) and coronal (**F**) acquisition in hepatospecific phase, after 20 minutes after administration, show hypointense focal lesion.

As referred by Jeong HT[40], MRI is the first-line technique for evaluation of liver metastases, but the use of optimal pulse sequences and appropriate MR contrast agent is important. According to the literature, a scan delay of 20 minutes is optimal for peak liver enhancement; some studies demonstrate that a 10-minute delay time may be sufficient to have the same results, allowing a shorter examination time. In fact, other authors demonstrated that there are no significant differences between hepatobiliary phase images acquired at 10 minutes and after a delay of 20 minutes[40,45].

As reported by Lee[46], the combination of gadoxetic acid-enhanced dynamic extracellular and hepatobiliary phases shows better sensitivity than dynamic phases alone, and triple-phase multi-detector-CT (MDCT)[46]. CT examination is limited in localization and characterization of small and low-attenuated hepatic lesions[46].

According to Motosugi et al[47], gadoxetic acid-enhanced liver MRI allows both vascular dynamic study of the liver, and the hepatospecific phase, increasing the sensitivity in comparison with MDCT (85% for MRI and 69% for MDCT), in studying liver metastases from pancreatic carcinoma. Also in a work by Böttcher et al[48], Gd-EOB-DTPA-enhanced MRI is better than MDCT for the detection of liver metastases. MRI has a sensitivity of 86.8% (compared to 66.2% for MDCT) and a specificity of 94.4% (against 72.3% of MDCT). Other studies reported better accuracy for liver-MRI in the detection of liver metastasis from colorectal carcinoma and hepatocellular carcinoma[18].

In recent papers, the detection of the small liver lesions on the hepatobiliary phase images has been improved by the rising of value of flip angle. In the hepatobiliary phase, a flip angle up to 30-35 increases the signal of the liver parenchyma and decreases that of enhanced lesions, with a better visualization of small nodules[49,50].

Also hepatospecific-images obtained with Gd-BOPTA added a significant role in the detection of liver metastasis[51,52]. In fact, according to Kim, hepatobiliary phase with Gd-BOPTA has a sensitivity of 95.5% in the detection of liver metastasis, better than the sensitivity of Gd-BOPTA dynamic images only (77.4%)[52].

LIVER MRI WITH DWI: MALIGNANT LESIONS DETECTION AND RESPONSE TO THE TREATMENTS

Diffusion-weighted imaging (DWI) is an additional, unenhanced MRI sequence that is very sensitive to the microscopic random motion of water

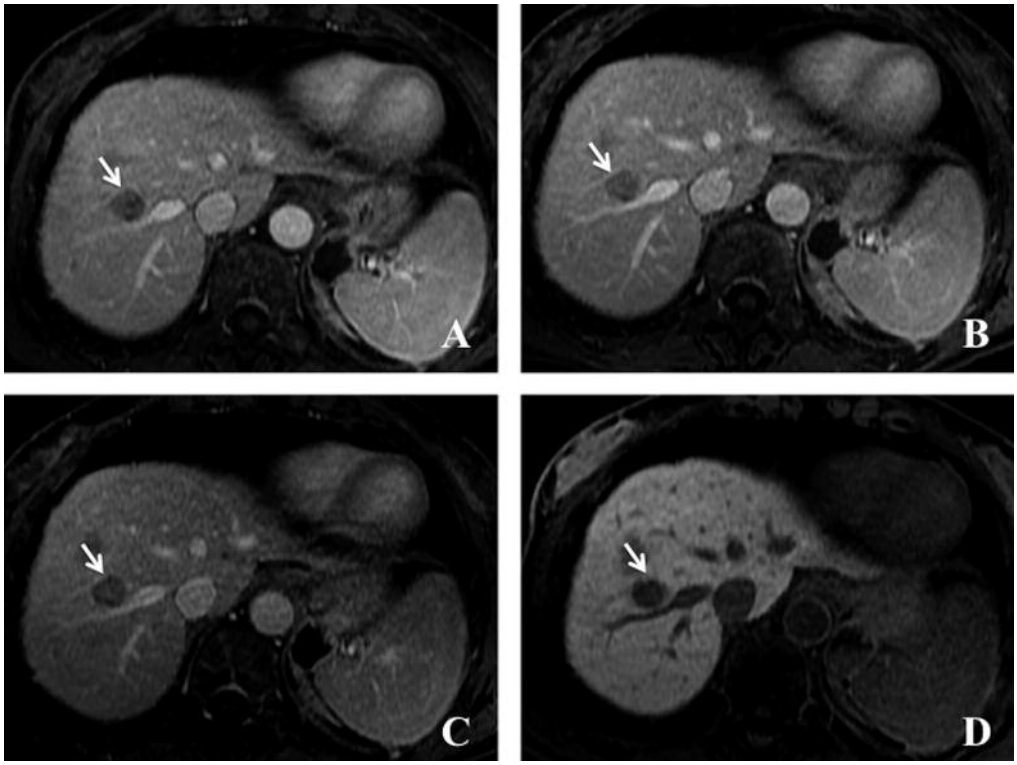

Figure 5. Patient with hepatic metastasis from colic cancer studied with Gd-BOPTA MRI. Metastasis (arrows) appeare hypointense in arterial (**A**), venous (**B**) and tardive (**C**) phases after contrast agent injection. It maintains hypointensity also in hepatospecific phase (**D**), acquired after 2 hours after administration.

protons, driven by their thermal energy, known as Brownian motion[3,53-54]. It can differentiate tissues based on cellular density, architectural changes and vascularization[45,55].

Diffusion imaging is a valuable tool in the detection and characterization of liver lesions[53] and it is usually performed in the standard liver MRI protocol, between dynamic and hepatobiliary phases obtained after Gd-EOB-DTPA administration[45,57].

The sensitivity of DWI is related to the *b*-value, measured in s/mm^2. The *b*-value sets the degree of weighting in diffusion[54,58]. DWI sequences are performed with at least two b values[54]. Diffusion weighted single-shot echo-planar (DW SS-EP) sequences with a low *b*-value are important for the detection of liver lesions, especially the smallest ones; high values of *b* sequences are useful for the characterization, even if they are determine low signal-to-noise ratio (SNR)[58].

DWI provides a qualitative/quantitative information, and they should be compared with un-enhanced and contrast- enhanced images. On DWI, in fact, solid benign lesions can demonstrate restricted diffusion and cystic or necrotic malignant lesions preserve unrestricted diffusion[54].

For a quantitative analysis, the apparent diffusion coefficient (ADC) is used; it is expressed in units of mm^2/s[3,54].

Liver tumors are hyperintense, in contrast to the surrounding normal liver parenchyma which is hypointense. Malignant liver lesions have a lower ADC values on diffusion-weighted images than benign ones[59]. The apparent diffusion coefficient is important in the distinction between the different tumor grades[60].

DWI increases the detection of small liver metastases (Figure 6) of about 40%[3]. Diffusion sequences report higher rates in the detection and characterization of focal liver lesions compared with other T2-conventional sequences, as referred by several Authors[59,61]. According to Lowenthal et al[53], DWI has a sensitivity of 0,98 in the detection of liver metastases. The sensitivity for the lesion smaller than 1 cm is 0.92 and it is better than conventional enhanced MRI (0.71). The detection rates of liver metastases on DWI is 97.5%, against 100% of conventional images.

Some Authors[60,62] demonstrate that DWI improves the HCCs detection, especially for lesions smaller than 2 cm. DWI has a high sensitivity (91.2%) and positive predictive value (81.6%) in comparison with conventional enhanced-MRI (respectively, 67.6% and 59.0%).

DWI has a lower spatial resolution than the conventional MRI. The physiological movements, especially in subcardiac and subphrenic areas,

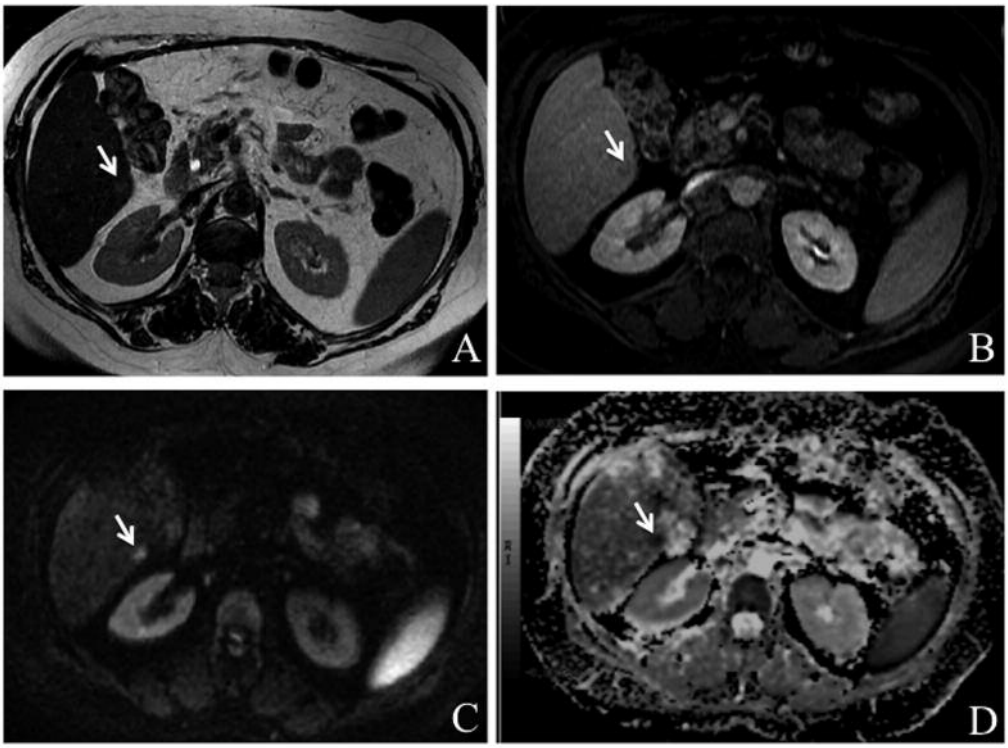

Figure 6. Patient with metastatic breast cancer. Gd-EOB-DTPA MRI demonstrates a metastatic lesion (*arrows*) in the V liver segment that shows a weak hyperintensity in T2-weighted image (**A**) and appears weakly hypointense in portal phase (**B**). This focal lesion is better showed in DWI and ADC map, because of its restricted diffusion, showing hyperintensity in DWI (**C**) and hypointensity in ADC map (**D**).

cause artifacts that can decrease the detection of small metastases in the lateral segment and the upper edge of the liver. The image quality can also be compromised by gastric peristaltic motion. In the upper edge of the liver, magnetic susceptibility artifacts, due to heterogeneity of the magnetic field between the lung and the liver parenchyma, are also possible[63]. These artifacts can also be induced in the caudal portion of the right liver by the air in the stomach and by meteoric colonic loop[58,61]. According to Chung[64], on DWI, small metastases next to the diaphragm or in the left hepatic lobe can also be overlooked because of cardiac-respiratory artifacts. The application of respiratory trigger enables us to obtain better image quality because of high spatial resolution and an adequate SNR[65]; unfortunately, triggered sequences are conditioned by a length time of acquisition. High pretreatment ADC values (mean ADC150-500 value $\geq 1.69 \times 10^{-3}$ mm^2/s) in tumors seem to be associated with a poor response to chemiotherapy, as referred by Koh[66] and Cui[67]. According to Koh[66], a significant increase in mean ADC is shown by metastatic lesions, responding to chemotherapy. DWI demonstrate promising results in the follow-up after local ablative treatment, especially in the detection of site recurrences[54].

CONCLUSIONS

Liver MRI provides high diagnostic capability. In oncological patients, liver MRI protocol should be more possible completed, including unenhanced sequences (predominantly represented by T1-weighted imaging, conventional T2 sequences, DWI, long-echo T2-weighted images) and enhanced acquisitions. Most important technical features of a protocol study – have been discussed in our paper – in order to emphasize the role of MRI imaging in the evaluation of hepatic oncological disease.

Namely, liver-specific contrast agents are needed in patients with doubtful lesions previously discovered in other radiological procedures; in addition, they should be performed in MRI examinations – including hepatobiliary phase – before surgical resection of liver metastases.

In the management of HCC, and in patients with suspicious lesions reported on surveillance examinations, gadoxetic-enhanced liver MRI is generally recommended to improve lesion detection and characterize typical and atypical lesions. Finally, all patients affected by chemiotherapy-induced steatosis, should be candidates for MRI examinations, in order to make a correct follow-up of disease.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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