

Contrast-enhanced Magnetic Resonance Imaging – A Method with Prospects

Satellite Symposium: 'Our Innovative, Comprehensive and Targeted Approach to Focal Liver Lesions'

Held at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL) on 24 April 2008, Milan

Convenor: Bayer Schering Pharma, Berlin

DOI: 10.17925/EOH.2008.04.1.77

The Clinical Management of Liver Tumours as an Interdisciplinary Task

At the 43rd annual meeting of the European Association for the Study of the Liver (EASL),¹ gastroenterologist Professor Peter Malfertheiner expressed the view that the clinical management of focal liver lesions requires close co-operation between clinicians and radiologists. He felt that of the imaging methods currently available, magnetic resonance imaging (MRI) with the liver-specific gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-containing contrast agent Primovist® provides the most precise detection, localisation and characterisation of focal liver lesions and permits effective planning of treatment.

Many focal liver lesions remain undiscovered throughout the patient's life and are an incidental finding in over 50% of autopsies. Most common are haemangiomas (20%), followed by focal nodular hyperplasia (3%), according to Professor Claudio De Angelis. Furthermore, he emphasised that given the multiplicity of benign, malignant and infectious changes that can occur, the precise localisation and characterisation of focal liver lesions requires a great deal of diagnostic intuition. In this regard, imaging techniques are an important instrument for confirming a clinical suspicion. Most focal liver lesions are incidental findings, especially during ultrasound examinations performed as part of the follow-up of tumour patients or in screening programmes for liver cirrhosis.

In the experience of Professor De Angelis, small lesions of less than 15mm in asymptomatic patients are generally benign, even in patients with a history of tumours. On the other hand, suspicion is called for in patients with advanced cirrhosis. A recent study by an Italian working group found that about 50% of lesions initially thought to be haemangiomas proved to be hepatocellular carcinomas. Other primary tumours are relatively rare. However, the liver is a preferred site of metastasis of other tumours, particularly gastrointestinal tumours.

What Comes After Ultrasound?

The quality of ultrasound findings varies with the experience of the examiner and the quality of the equipment. Contrast-enhanced ultrasound (CEUS) is generally the preserve of specialised centres. According to the EASL Barcelona guidelines, in this situation a computed tomography (CT) scan or a contrast-enhanced (CE)-MRI scan should also be performed before consideration is given to performing a liver biopsy. According to Professor De Angelis, "A biopsy is the diagnostic method of last choice."

CT, especially multidetector CT, provides significantly better diagnosis of abdominal lesions. However, in addition to radiation exposure a

high rate of false-positive findings and the relative imprecision with which small lesions (<1cm) are displayed are seen as significant disadvantages of this technique. The imaging modality that now provides the most sensitive and specific information is MRI. When used in combination with tissue-specific contrast agents it permits soft-tissue diagnosis in the various haemodynamic phases of tissue perfusion: arterial, portal venous and in equilibrium. In hepatocyte-specific contrast agents such as Gd-EOB-DTPA, gadolinium is bound to a chelate with both hydrophilic and lipophilic properties. Once in the liver, it is actively taken up by hepatocytes to an extent of 50%, and is subsequently excreted in equal amounts in the bile and urine.

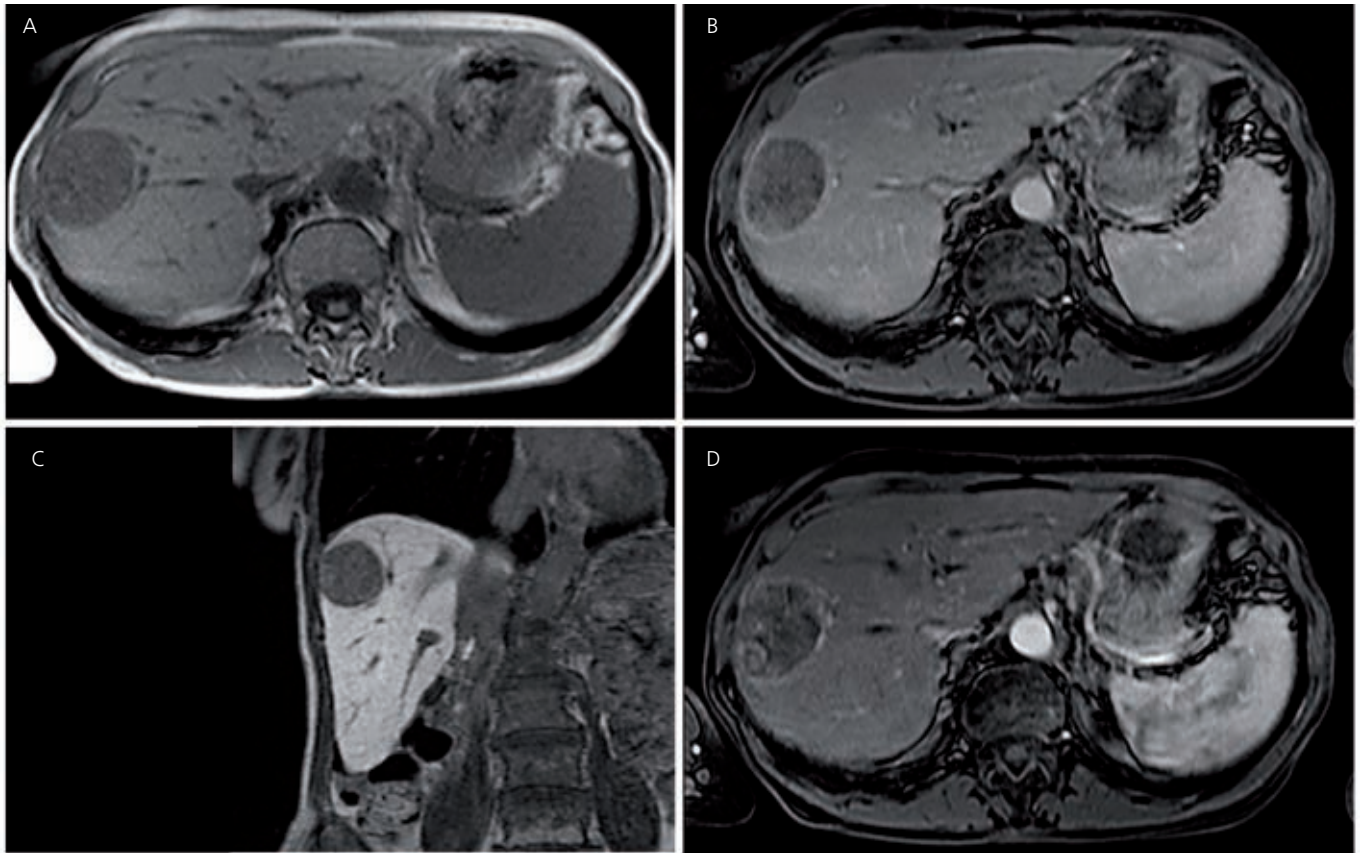
Native T1- and T2-weighted MRIs obtained before intravenous bolus administration of Gd-EOB-DTPA provide important information on the organ structure of the liver such as the proportions of fat and water (see *Figure 1*). During the vascular phase, healthy liver tissue, which is approximately 75% perfused via the portal vein, can be distinguished from tumours, which are 80–95% perfused via the hepatic artery. For example, hepatocellular carcinomas are hypervascularised and show high enhancement during the vascular phase. Similarly, haemangiomas and focal nodular lesions show typical enhancement patterns during the various phases. Professor Lennart Blomqvist explained that in the hepatocellular phase the liver parenchyma appears bright after taking up the contrast agent as a result of the increased signal intensity, whereas lesions without functional hepatocytes remain dark.

Superior Performance Profile

Use of Gd-EOB-DTPA makes it possible to distinguish benign lesions such as focal nodular hyperplasia from malignant lesions such as hepatocellular carcinoma, cholangiocarcinoma and metastases of other primary tumours on the basis of the phase-specific signal distribution, without the need for liver biopsies. It also provides important information about functional parameters such as the extent and haemodynamics of liver perfusion, for example, the rate of transfer between the various compartments (blood, hepatocytes, bile) and the functional status of the hepatocytes.

In the clinical setting, CEMRI can produce images for about 30 minutes. Professor Blomqvist concluded that thanks to its superior performance profile, CEMRI has now superseded CT as the preferred imaging method for the differential diagnosis of local hepatic lesions, although he conceded that this will not always be achievable in routine clinical practice. Nevertheless, he felt that in view of the ever closer ties that are developing between the work of oncologists, hepatologists and (interventional) radiologists, preference should be given to a method that also opens up the best possibilities in terms of subsequent treatment.

Figure 1: Signal Pattern of Hepatocellular Tumours After Administration of the Gadolinium-containing Contrast Agent



The gadolinium-containing contrast agent Gd-EOB-DTPA was administered during the various haemodynamic phases and in the hepatocyte-specific late phase. A: T1-weighted magnetic resonance (MR) image; B: T1 arterial phase; C: T1 portal venous phase; D: T1 hepatocyte-specific phase (after 20 minutes). Photographs courtesy of: Dr Huppertz, Imaging Science Institute Charité-Siemens.

Diagnosis and Treatment Are Coming Closer Together

Professor Jens Ricke also felt that the future of highly sensitive and specific imaging techniques lies in complementing minimally invasive interventions in the treatment of liver tumours. According to Professor Ricke, "Diagnosis and treatment are coming closer together. I see the future for treatment as lying in a combination of minimally invasive and systemic tumour therapies." Experts are unanimous in their view that the potential of these methods is far from exhausted. In addition to thermoablative procedures such as radiofrequency ablation (RFA) and laser ablation (also known as laser-induced thermotherapy [LITT]), Professor Ricke's working group has had good experience with stereotactic irradiation, brachytherapy and yttrium-90 radioembolisation and selective internal radiation therapy (SIRT). Between 2001 and 2004, the number of such interventions performed by Professor Ricke more than tripled to a figure of 350. This development has been facilitated by the new generation of MR scanners, which in addition to short examination times due to their open design offer good access to the patient for local minimally invasive interventions.

An interim analysis of a prospective study that is under way in 17 of a scheduled total of 31 patients given brachytherapy for focal liver tumours shows not only that Gd-EOB-DTPA provides good differentiation of irradiated areas six weeks after the intervention, but also that this hepatocyte-specific contrast agent makes it possible to monitor regeneration and revascularisation of the liver parenchyma during subsequent treatment. In Professor Ricke's view, this provides important additional information on the questions of whether small metastatic foci have been eradicated and how well the chosen dose of radiation has been tolerated.

New Prospects

Good experiences have been achieved with CEMRI, such as the precise placement of the source of radiation or heat and rapid assessment of the degree of success. This has led Professor Ricke to wonder whether it may also be possible to predict impending liver failure due to radiation-induced hepatitis, which may occur after local treatment of multiple or large tumours or after a number of treatment cycles.

One diagnostic problem that remains is that of pseudotumours. At present, these cannot be demonstrated using any of the clinically available imaging techniques. Professor Malfertheiner sees a need in such situations to generate hard data for evidence-based recommendations, especially in relation to the effectiveness and tolerability of the various local surgical and minimally invasive therapeutic procedures, both alone and in combination with systemic chemotherapy such as with sorafenib (Nevaxar®). Currently, according to the experts systemic palliative therapy with sorafenib – possibly in combination with local tumour therapies – would be the treatment of choice for multifocal hepatocellular carcinoma with lung metastases, such as Child-Pugh B. ■

Source

Preprint of: Kretzschmar A, Contrast-enhanced MRI – a method with prospects – The Clinical Management of Liver Tumours as an Interdisciplinary Task, Med Welt, 2008;59(7–8). © Schattauer GmbH, Stuttgart.

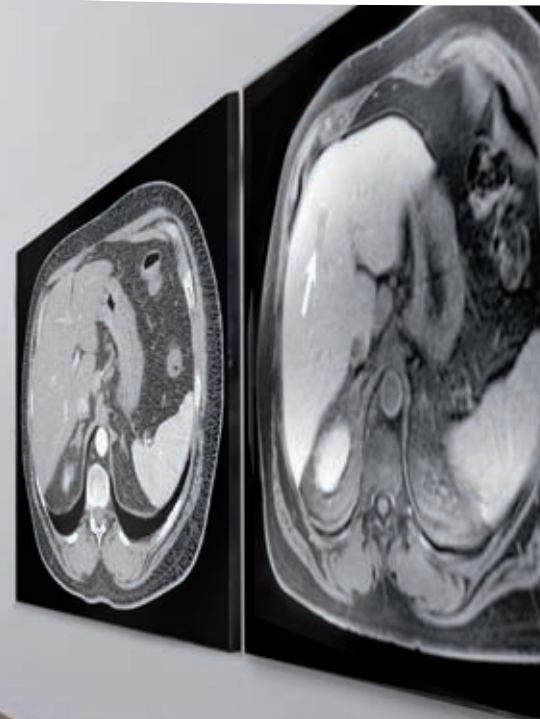
Disclosure

With the generous support of Bayer Schering Pharma, Berlin.



Bayer HealthCare
Bayer Schering Pharma

The Fine Art of Liver Imaging



Gadoxetic acid

▼ **Primovist**®
Defining Liver Imaging

Mastery in detection, delineation and characterization

- especially of small liver lesion (< 10 mm)¹
- sharpened distinction of lesions and liver parenchyma^{2,3}
- increased diagnostic confidence by dynamic & hepatocyte specific imaging⁴



EU2007.1042
August 2008 8PRIM012

Convening a community
dedicated to advancing
research in the pathogenesis,
prevention and treatment
of liver cancer

ILCA 2009

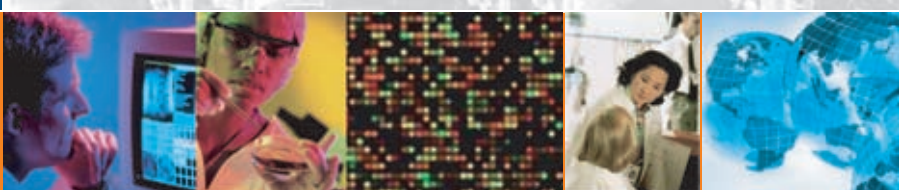
4 ▶ 6 September 2009

Milan, Italy

Multidisciplinary approach to HCC

Basic research - clinical practice link

Excellent networking opportunities



Priming Knowledge in Liver Cancer across Disciplines

www.ilca-online.org



Bayer HealthCare
Bayer Schering Pharma

Primovist 0.25 mmol/mL solution for injection. **Composition** 1 mL solution for injection contains 181.43 mg gadoxetic acid, Gd-EOB-DTPA disodium, equivalent to 0.25 mmol Gd-EOB-DTPA disodium. **Indications** Primovist is indicated for the detection of focal liver lesions and provides information on the character of lesions in T1-weighted magnetic resonance imaging (MRI). This medical product is for diagnostic use only. **Contraindications** Hypersensitivity to the active substance or to any of the excipients. **Undesirable effects** During the clinical development phase the overall incidence of adverse reactions which were classified as related was below 5%. Most of the undesirable effects were transient and of mild to moderate intensity. No individual adverse reaction reached a frequency greater than 1/100. **Nervous system disorders** headache, dizziness, paresthesia, taste disturbance, vertigo, akathisia, tremor, parosmia. **Cardiac disorders** bundle branch block, palpitation. **Vascular disorders** flushing, hypertension. **Respiratory, thoracic and mediastinal disorders** dyspnea, respiratory distress. **Gastrointestinal disorders** vomiting, nausea, dry mouth, oral discomfort, salivary hypersecretion. **Skin and subcutaneous tissue disorders** rash, pruritus, maculopapular rash, hyperhidrosis. **General disorders and administration site conditions** chest pain, injection site reactions, feeling hot, chills, discomfort fatigue, malaise, feeling abnormal. Laboratory changes as elevated serum iron, elevated bilirubin, increases in liver transaminases, decrease of hemoglobin, elevation of amylase, leucocyturia, hyperglycemia, elevated urine albumin, hyponatremia, elevated inorganic phosphate, decrease of serum protein, leucocytosis, hypokalemia, elevated LDH were reported in clinical trials. ECGs were regularly monitored during clinical studies and transient QT prolongation was observed in some patients without any associated adverse clinical events. In very rare cases anaphylactoid reactions leading to shock may occur. **Precautions** **General information** The usual safety precautions for MRI must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants. Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. The patient should refrain from eating for two hours prior to examination to reduce the risk of aspiration, as nausea and vomiting are known possible adverse reactions. Whenever possible, the contrast agent should be administered with the patient lying down. After the injection, the patient should be kept under observation for at least 30 minutes, since experience with contrast media shows that the majority of undesirable effects occur within this time. Caution should be exercised in patients with severe renal impairment due to reduced elimination capacity of Gd-EOB-DTPA. Patients with renal impairment: There have been reports of Nephrogenic Systemic Fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with - acute or chronic severe renal impairment (GFR < 30ml/min/1.73 m²) or - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. As there is a possibility that NSF may occur with Primovist, it should therefore only be used in these patients after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). All patients should be screened, in particular patients over the age of 65, for renal dysfunction by obtaining a history and/or laboratory tests. Haemodialysis shortly after Primovist administration in patients currently receiving haemodialysis may be useful at removing Primovist from the body. There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis. Caution should be exercised in patients with severe renal impairment due to reduced elimination capacity of Gd-EOB-DTPA. Caution should be exercised when Primovist is administered to patients with severe cardiovascular problems because only limited data are available so far. It cannot be excluded that Gd-EOB-DTPA may cause torsade de pointes arrhythmias in an individual patient. **Hypersensitivity** Allergy-like reactions, including shock, are known to be rare events after administration of gadolinium-based MRI contrast media. Patients with a history of allergic/allergoid reactions or bronchial asthma might be at higher risk for severe reactions. Most of these reactions occur within half an hour after administration of contrast media. However, as with other contrast media of this class, delayed reactions may occur after hours to days in rare cases. Adequate measures for resuscitation should be made readily available prior to administration of contrast agents. Hypersensitivity reactions can be more intense in patients on beta-blockers, particularly in the presence of bronchial asthma. It should be considered that patients on beta-blockers may be refractory to standard treatment of hypersensitivity reactions with beta-agonists. If hypersensitivity reactions occur, injection of the contrast medium must be discontinued immediately. **Local intolerance** Intramuscular administration may cause local intolerance reactions including focal necrosis and should therefore be strictly avoided. Date of preparation of the text October 2007. Please note! For current prescribing information refer to the package insert and/or contact your local BSP organisation. **Bayer Schering Pharma AG, 13342 Berlin, Germany. Adverse reactions can be reported to GPV. CaseProcessing@bayerhealthcare.com**

EU2007.1042 August 2008 8PRIM012

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to BayerSchering Pharma;
Tel: 01635 563500, Fax: 01635 563703, Email: phdsguk@bayer.co.uk

¹ Huppertz A. et al, Improved detection of focal liver lesions at MR imaging: Multicenter comparison of Gadoxetic acid enhanced MR images with intraoperative findings, *Radiology* 2004; 230:266-275

² Huppertz A, Haraida S, Kraus A et al. Enhancement of Focal Liver Lesions at Gadoxetic Acid-enhanced MR Imaging: Correlation with Histopathologic Findings and Spiral CT - Initial Observations. *Radiology* 2005; 234: 468-478

³ Halavaara J, Breuer J, Ayuso C et al. Liver Tumor Characterization: Comparison Between Liver specific Gadoxetic Acid Disodium-enhanced MRI and Biphasic CT - A Multicenter Trial. *J Comput Assist Tomogr* 2006; 30: 345-354

⁴ Hammerstingl R. et al, Diagnostic efficacy of gadoxetic acid (Primovist)-enhanced MRI and spiral CT for a therapeutic strategy. Comparison with intraoperative and histopathologic findings in focal liver lesions. *European Radiology* 2008 (18) 457-467