Randomized clinical trial

Randomized multicentre trial of gadoxetic acid-enhanced MRI *versus* conventional MRI or CT in the staging of colorectal cancer liver metastases

C. J. Zech[1,3], P. Korpraphong[4], A. Huppertz[2], T. Denecke[2], M.-J. Kim[6], W. Tanomkiat[5], E. Jonas[7] and A. Ba-Ssalamah[8] on behalf of the VALUE study group

[1]Institute of Clinical Radiology, University Hospital Munich – Grosshadern, Munich, and [2]Department of Radiology, Charité University Hospital, Berlin, Germany, [3]Clinic of Radiology and Nuclear Medicine, University Hospital Basle, Basle, Switzerland, [4]Department of Radiology, Faculty of Medicine, Siriraj Hospital, Bangkok, and [5]Department of Radiology, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand, [6]Yonsei University, Severance Hospital, Seoul, South Korea, [7]Department of Upper Abdominal Surgery, Karolinska University Hospital, Stockholm, Sweden, and [8]Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Vienna, Austria

Correspondence to: Dr C. J. Zech, Clinic of Radiology and Nuclear Medicine, University Hospital Basle, Petersgraben 4, CH-4031 Basle, Switzerland (e-mail: Christoph.Zech@usb.ch)

Background: **This multicentre international randomized trial compared the impact of gadoxetic acid-enhanced magnetic resonance imaging (MRI), MRI with extracellular contrast medium (ECCM-MRI) and contrast-enhanced computed tomography (CE-CT) as a first-line imaging method in patients with suspected colorectal cancer liver metastases (CRCLM).**

Methods: **Between October 2008 and September 2010, patients with suspected CRCLM were randomized to one of the three imaging modalities. The primary endpoint was the proportion of patients for whom further imaging after initial imaging was required for a confident diagnosis. Secondary variables included confidence in the therapeutic decision, intraoperative deviations from the initial imaging-based surgical plan as a result of additional operative findings, and diagnostic efficacy of the imaging modalities *versus* intraoperative and pathological extent of the disease.**

Results: **A total of 360 patients were enrolled. Efficacy was analysed in 342 patients (118, 112 and 112 with gadoxetic acid-enhanced MRI, ECCM-MRI and CE-CT respectively as the initial imaging procedure). Further imaging was required in 0 of 118, 19 (17·0 per cent) of 112 and 44 (39·3 per cent) of 112 patients respectively ($P < 0·001$). Diagnostic confidence was high or very high in 98·3 per cent of patients for gadoxetic acid-enhanced MRI, 85·7 per cent for ECCM-MRI and 65·2 per cent for CE-CT. Surgical plans were changed during surgery in 28, 32 and 47 per cent of patients in the respective groups.**

Conclusion: **The diagnostic performance of gadoxetic acid-enhanced MRI was better than that of CE-CT and ECCM-MRI as the initial imaging modality. No further imaging was needed in the gadoxetic acid-enhanced MRI group and comparison of diagnostic efficacy parameters demonstrated the diagnostic superiority of gadoxetic acid-enhanced MRI. Registration number: NCT00764621(http://clinicaltrials.gov); EudraCT number: 2008-000583-16 (https://eudract.ema.europa.eu/).**

Presented in abstract form to the 97th Scientific Assembly and Annual Meeting of the Radiological Society of North America, Chicago, Illinois, USA, December 2011

Paper accepted 21 January 2014

Published online 20 March 2014 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9465

Introduction

Colorectal cancer is the third leading cause of cancer death in the world[1]. Approximately 50 per cent of patients with colorectal cancer either have or will develop liver metastases at some stage of their disease[2,3]. In patients diagnosed with colorectal cancer, imaging of the liver is standard practice to exclude synchronous hepatic metastases[4]. For follow-up after colorectal resection, guidelines[5] suggest the use of hepatic imaging by ultrasonography or computed tomography (CT) at specified intervals, at the discretion of the surgeon or in the case of rising serum carcinoembryonic antigen (CEA) levels. The presence of colorectal cancer liver metastases (CRCLM) is an

important prognostic factor and changes the management of patients with colorectal cancer dramatically[6,7]. Liver resection can be performed in about 15 per cent of patients, with overall 5-year survival rates in the range of 35–58 per cent[8]. Although the surgical strategy in patients planned for surgery is devised before operation based on radiological imaging, surgical exploration with intraoperative ultrasonography (IOUS) is still regarded as the standard in establishing the extent of hepatic disease[9–11]. Deviations from the preoperative surgical plan as a result of additional intraoperative findings are undesirable, from both a patient and a logistical perspective. In patients with suspected CRCLM, imaging is used to detect liver lesions and characterize them to make the differential diagnosis between metastases, other malignant lesions or benign lesions. Magnetic resonance imaging (MRI) has been shown to be more sensitive than CT for the detection of liver lesions (especially for lesions smaller than 10 mm in size), and is now regarded as the superior technique for characterization[12,13]. Hepatobiliary contrast agents such as gadoxetic acid (gadolinium ethoxybenzyl diethylenetriamine penta-acetate) can further increase the detection rate[14–19]. However, no controlled trials exist comparing gadoxetic acid-enhanced MRI with MRI with extracellular contrast medium (ECCM-MRI) and contrast-enhanced CT (CE-CT) for hepatic staging (including detection and correct characterization of liver lesions) in patients with suspected CRCLM. In the setting of hepatic imaging, MRI is still widely regarded as a problem-solving modality in case of equivocal findings on CT or ultrasound imaging, rather than a first-line imaging modality. However, depending on the number of unclear cases, this might result in an overall increased number of imaging procedures for patients as well as suboptimal use of resources[20,21].

The objective of this randomized trial was to compare gadoxetic acid-enhanced MRI with ECCM-MRI or CE-CT for hepatic staging of patients with suspected CRCLM. The underlying hypothesis was that the higher accuracy of gadoxetic acid-enhanced MRI of the liver would lead to a reduced need for additional pretherapeutic staging examinations, a more precise surgical plan, and thus fewer instances of intraoperative modification of the plan designed before surgery.

Methods

Trial design and participants

The VALUE study (multicentre randomized comparison study to eVALUatE outcomes and resource needs of imaging and treatment following gadoxetic acid-enhanced MRI of the liver, in comparison with ECCM-MRI and CE-CT in patients with a history of colorectal cancer and known or suspected metachronous liver metastases) was a multicentre international randomized phase IV interindividual (parallel-group) trial (ClinicalTrials.gov identifier: NCT00764621; EudraCT number: 2008-000583-16). Between October 2008 and September 2010, patients with suspected CRCLM were recruited at 27 centres in eight countries (Austria, Germany, Italy, Korea, Spain, Sweden, Switzerland and Thailand). The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines, following approval by relevant ethics committees/institutional review boards at the participating centres. All participating centres had hepatobiliary units with experience in liver resection and affiliated radiology departments experienced in liver CT and MRI, including the use of gadoxetic acid. At recruitment of sites, a site selection questionnaire was completed to ensure adequate experience with all three tested diagnostic modalities.

Before inclusion in the study, written informed consent was obtained from each patient. Patients aged 18 years or above, for whom tomographic imaging of the liver (contrast-enhanced MRI or CE-CT) was planned, were included in the study. The decision to proceed to a dedicated liver examination was based on findings on screening imaging (ultrasonography or abdominal CT) diagnostic or suggestive of metastasis, and/or rising CEA values that prompted a liver examination. Patients scheduled for MRI with a liver-specific contrast agent other than gadoxetic acid were excluded, as the aim of the study was to compare gadoxetic acid-enhanced MRI with currently established imaging modalities not using liver-specific contrast. Detailed inclusion and exclusion criteria are presented in *Table S1* (supporting information).

Contrast-enhanced imaging

Patients were randomly assigned within the centres to one of the following imaging procedures: MRI using a single intravenous injection of gadoxetic acid (marketed as Primovist®, Eovist® and EOB-Primovist®; Bayer Pharma AG, Berlin, Germany), MRI using a single intravenous injection of an extracellular contrast medium, or CT using a single intravenous injection of iodinated low-osmolar or iso-osmolar contrast medium. The structure of the randomization list was developed by the study biometrician. The final randomization code was generated by the contract research organization Ecron Acunova (Frankfurt, Germany) using the validated program RANDOM as 1 : 1 : 1 randomization (block size 6). The randomization list included the randomization

codes, patient identifier and assigned imaging modality. The randomization information was provided in sealed envelopes that were kept securely in the radiology department at each study site.

All contrast media used in the study were commercially available products so, technically, no study drug was provided. Gadoxetic acid is administered as an intravenous bolus injection at a dose of 0·025 mmol Gd per kg bodyweight. For ECCM-MRI, a variety of Gd-based contrast agents are available that all behave as non-specific extracellular fluid space contrast medium with comparable imaging properties, pharmacokinetics and biodistribution. For contrast-enhanced MRI of the liver using extracellular Gd-based contrast, a dose of 0·1 mmol Gd per kg bodyweight administered as a single intravenous bolus injection is recommended. Finally, for CE-CT, a variety of iodinated contrast agents are available that are routinely administered in contrast-enhanced CT of the liver using a total volume of up to 100–150 ml (of contrast agents with an iodine concentration of 300 mg/ml or above).

There is no consensus on ideal protocols for the different imaging modalities. For this reason, rather than specifying the exact protocols for imaging with the different modalities, centres were allowed to use their routine liver-dedicated clinical protocols to reflect current clinical practice. However, to establish standardization in image quality, important imaging parameters were suggested and documented (*Table S2*, supporting information).

Consensus meetings and study objectives

Image assessment and therapy decisions were performed on site without blinding to create a realistic setting similar to that in routine clinical practice. Reviewing the initial imaging at a consensus meeting, the treating radiologist and surgeon assessed whether a confident therapy decision could be made (primary efficacy parameter), or whether further imaging was required to clarify equivocal findings and/or assess tumour proximity to anatomical structures. Secondary efficacy parameters included documentation of the level of confidence in the decision using a five-point scale (very low, low, moderate, high and very high confidence). In patients in whom diagnostic assessment of the liver was not sufficient to come to a therapy decision, the treating physicians were free to choose either of the two remaining imaging methods. The second imaging was performed within 2 weeks, but more than 24 h after the first, to allow sufficient washout of the contrast agent. It is important to note that the decision to proceed to a second imaging was not defined as a factor of the confidence in the treatment decision, but was left to the discretion of the treating radiologist and surgeon. After the second imaging procedure, the same parameters as at the first consensus meeting were recorded at a second consensus meeting.

A detailed assessment of the number, size and segmental involvement (according to the Brisbane 2000 nomenclature[22]) of suspected metastases was documented, together with details of the treatment plan. In patients considered primarily resectable – probably tumour-free following one operative intervention (surgery with or without concomitant interventional procedures) without the need for preoperative tumour or volume manipulation chemotherapy or portal vein embolization – and who underwent surgical exploration with the intent to perform liver resection, intraoperative deviation from the surgical plan originating from the consensus meeting(s) was recorded. The time interval between imaging and surgery was noted. To evaluate diagnostic performance of the preoperative imaging modality, the extent of disease as assessed at the consensus meeting(s) was compared with the standard of intraoperative assessment (visual inspection, palpation and IOUS) and, in cases where resection was performed, with the histopathological extent of disease in the resected liver. Furthermore, the number of segments planned to be completely or partially resected was compared with the actual number of segments resected.

Statistical analysis

Statistical evaluations were performed using the SAS® package, release 9.2 (SAS Institute, Cary, North Carolina, USA).

For evaluation of the primary efficacy parameter (proportion of patients requiring further imaging), the software ADDPLAN® 5 MC[23] (Adaptive Designs – Plans and Analyses; AptivSolutions®, Cologne, Germany) was used. The proportion of patients undergoing gadoxetic acid-enhanced MRI was tested one-sidedly in a hierarchical order against: pooled data from ECCM-MRI and CE-CT; CE-CT; and ECCM-MRI at an overall significance level of 2·5 per cent.

The sample size (initially planned for 600 patients) was determined based on an earlier health economic evaluation[21]. As the initial information on the difference in proportions between gadoxetic acid-enhanced MRI and the other imaging methods was limited, an interim analysis of the primary efficacy parameter was planned after inclusion of approximately 100 patients in each group for eventual adjustment of the sample size. For statistical analysis of the primary parameter, Fisher's combination test for multistage testing was used together with the approximate test for equality[23,24]. Depending on the interim analysis result and prespecified P values, it had to be determined whether there was a premature study termination due to

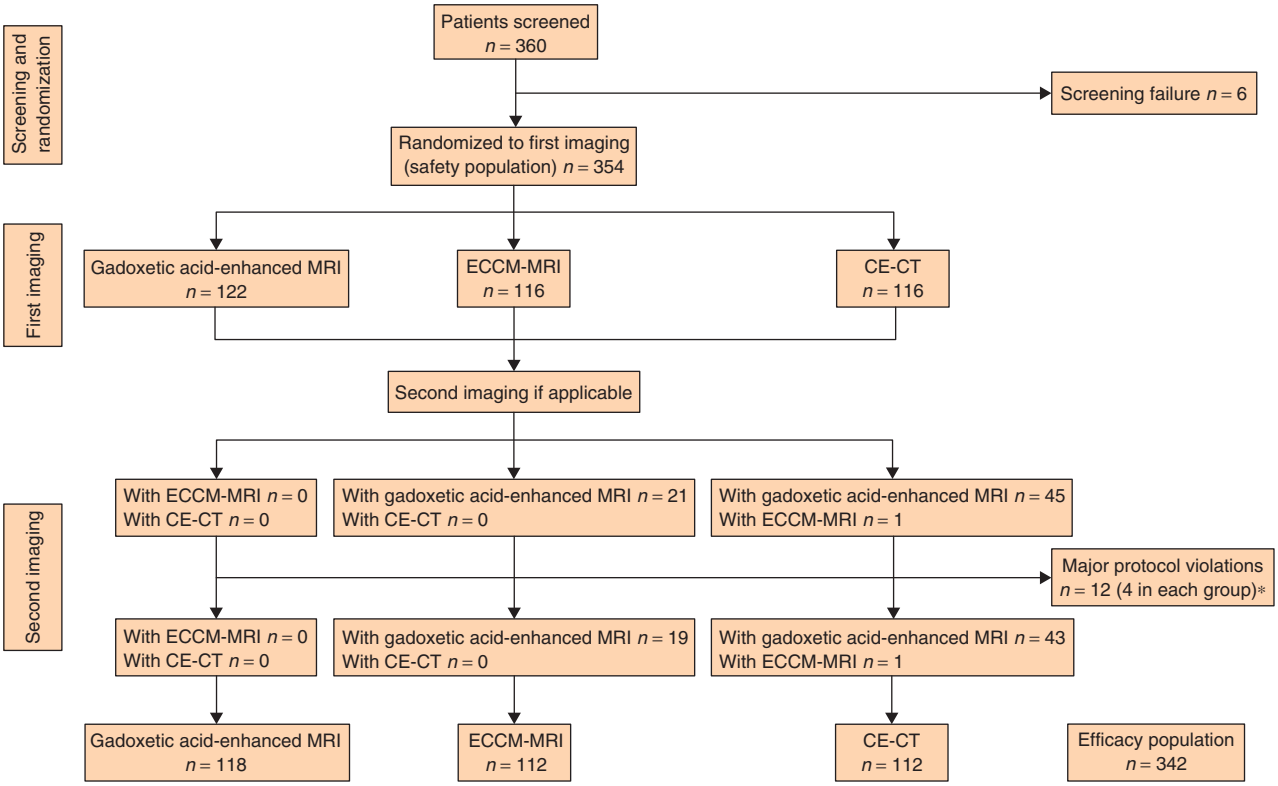

Fig. 1 Flow diagram of patients randomized to initial imaging using gadoxetic acid-enhanced magnetic resonance imaging (MRI), MRI with extracellular contrast media (ECCM-MRI) or contrast-enhanced computed tomography (CE-CT). *The 12 major protocol violations occurred in four patients who had a second imaging procedure and in eight patients who did not have a second imaging procedure

futility ($P > 0{\cdot}500$), an early termination due to a significant result ($P < 0{\cdot}0102$), or an adjustment of the sample size to reach a statistically significant result ($0{\cdot}0102 \leq P \leq 0{\cdot}500$).

Efficacy was further analysed descriptively in patients without major protocol violations and for whom primary parameter data were available (per-protocol population, further referred to as the efficacy population). To analyse diagnostic performance in the subgroup of patients who underwent liver surgery, a segment-wise analysis was performed in terms of detected metastases. This included a segment-based analysis of sensitivity and specificity using a variance calculation with corresponding confidence intervals (c.i.) following the Obuchowski method[25].

Results

A total of 360 patients were enrolled in the trial (*Fig. 1*). Excluding six screening failures, a total of 354 patients underwent an initial contrast-enhanced imaging procedure (the safety population). In four patients in each group there were major protocol violations (procedure deviations, treatment deviations and inclusion/exclusion errors at study entry). Hence, efficacy was evaluated for 342 patients: 118 in the gadoxetic acid-enhanced MRI group, 112 in the ECCM-MRI group and 112 in the CE-CT group. Demographic and baseline characteristics of

Table 1 Demographic and baseline patient features for patients in the three primary imaging groups (efficacy population)

	Gadoxetic acid-enhanced MRI ($n = 118$)	ECCM-MRI ($n = 112$)	CE-CT ($n = 112$)
Age (years)*	62 (37–82)	64 (33–87)	63 (32–88)
Weight (kg)*	73 (42–146)	72 (37–108)	71 (42–115)
Sex ratio (M : F)	80 : 38	73 : 39	74 : 38
Previous resection of liver segments	3	0	1
Underlying liver disease			
Hepatic cirrhosis	0	1	0
Hepatic steatosis	1	4	0

*Values are mean (range). MRI, magnetic resonance imaging; ECCM, extracellular contrast medium; CE-CT, contrast-enhanced computed tomography.

patients indicated satisfactory comparability of the three imaging groups (*Table 1*).

Imaging procedures

Gadoxetic acid-enhanced MRI was used as the initial imaging modality in 122 patients and ECCM-MRI in 116. Including the second imaging procedure, overall 188 patients in the safety population had gadoxetic acid-enhanced MRI and 117 had ECCM-MRI. For the 117 ECCM-MRI examinations, the following contrast agents were used: gadobutrol (Gadovist®; Bayer Pharma AG) in 66 (56·4 per cent); Gd-diethylenetriamine penta-acetate (Magnevist®; Bayer Pharma AG) in 38 (32·5 per cent); Dotarem® (Guerbet, Roissy CdG Cedex, France) in 12 (10·3 per cent); and Omniscan® (GE Healthcare, Chalfont St Giles, UK) in one (0·9 per cent). For the two MRI procedures, the majority of examinations were performed using a field strength of 3·0 Tesla (in 104 (55·3 per cent) of 188 gadoxetic acid-enhanced MRI and 60 (51·3 per cent) of 117 ECCM-MRI procedures) or 1·5 Tesla (in 83 (44·2 per cent) gadoxetic acid-enhanced MRI and 56 (47·9 per cent) ECCM-MRI procedures), with one imaging procedure for each MRI procedure performed on a 1·0-Tesla system. CE-CT was used in 116 instances as first imaging. All centres used spiral multidetector CT, with 45 examinations (38·8 per cent) being performed on 16-slice CT and 68 (58·6 per cent) on CT with 64 slices or more. Two examinations were performed on four-slice CT, and for one CT examination the slice number was not specified.

Table 2 Patients requiring further imaging to reach a diagnosis and therapy decision after initial imaging (efficacy population)

	No. of patients requiring further imaging*	Test result	
		P‡	Rate difference (%)†
Gadoxetic acid-enhanced MRI	0 of 118 (0)		
ECCM-MRI	19 of 112 (17·0)	< 0·001 ($H_0$3)	17·0 (11·4, 25·6)
CE-CT	44 of 112 (39·3)	< 0·001 ($H_0$2)	39·3 (30·7, 49·8)
Pooled ECCM-MRI–CE-CT	63 of 224 (28·1)	< 0·001 ($H_0$1)	28·1 (22·5, 34·6)

Values in parentheses are *percentages and †95 per cent repeated confidence intervals of the rate differences between gadoxetic acid-enhanced magnetic resonance imaging (MRI) and each of the comparators below, corresponding to the hierarchically ordered null hypotheses $H_0$1, $H_0$2, $H_0$3 (H_0i:$rate_{\text{gadoxetic acid-enhanced MRI}} \leq rate_{\text{comparator(i)}}$ with i = 1,2,3)[23,24]. ECCM, extracellular contrast medium; CE-CT, contrast-enhanced computed tomography. ‡One-sided Fisher's combination test of the entire population.

Requirement for further imaging and confidence assessment

Additional imaging was not deemed necessary for any patient in the gadoxetic acid-enhanced MRI group, but was required in 19 (17·0 per cent) of 112 patients in the ECCM-MRI group and in 44 (39·3 per cent) of 112 in the CE-CT group (*Fig. 1*). In this respect, comparisons of gadoxetic acid-enhanced MRI *versus* ECCM-MRI and CE-CT, and *versus* pooled data for ECCM-MRI and CE-CT, were highly significant (*Table 2*). A statistically significant difference in favour of gadoxetic acid-enhanced MRI was already reached in the interim analysis, including results for 281 patients ($P < 0{\cdot}0102$ – below the prespecified threshold laid down in the study protocol, based on a requirement of further imaging for 0, 14·0 and 37·4 per cent of 97, 93 and 91 patients in the gadoxetic acid-enhanced MRI, ECCM-MRI and CE-CT group respectively), leading to early termination of the study. Confidence ratings for the diagnosis and treatment plan were high or very high in 98·3 per cent of patients in the gadoxetic acid-enhanced MRI group, compared with 85·7 and 65·2 per cent in the ECCM-MRI and CE-CT group respectively. Exploratory testing (using the Wilcoxon 2-sample test) of the differences in confidence between gadoxetic acid-enhanced MRI and the other two imaging techniques resulted in *P* values of less than 0·001 (*Table 3*).

For the 63 patients undergoing a second imaging procedure, gadoxetic acid-enhanced MRI was the preferred imaging modality in all patients initially randomized to ECCM-MRI (19) and in all but one patient (43) initially randomized to CE-CT. For one patient in the CE-CT group, ECCM-MRI was chosen as a second imaging procedure.

Modification of the treatment plan in patients undergoing liver surgery

Of the 342 patients in the efficacy population, 223 were assessed as having liver metastases: 85 (70·0 per cent) of 118, 72 (64·3 per cent) of 112 and 66 (58·9 per cent) of 112 in the gadoxetic acid-enhanced MRI, ECCM-MRI and CE-CT group respectively. A total of 112 of these patients had liver surgery, 47 (55 per cent) of 85 patients in the gadoxetic acid-enhanced MRI group, 35 (49 per cent) of 72 in the ECCM-MRI group and 30 (45 per cent) of 66 in the CE-CT group.

In the per-patient evaluation of patients who had one imaging procedure, the surgical plan was modified in 13 (28 per cent) of 47 patients with initial gadoxetic acid-enhanced MRI, eight (32 per cent) of 25 with initial ECCM-MRI and eight (47 per cent) of 17 with initial CE-CT examinations.

Table 3 Confidence in diagnosis and therapeutic decision after initial imaging (efficacy population)

Initial imaging technique	All patients	Confidence				
		Very low	Low	Moderate	High	Very high
Gadoxetic acid-enhanced MRI*	118	0 (0)	0 (0)	2 (1·7)	36 (30·5)	80 (67·8)
ECCM-MRI*	112	0 (0)	1 (0·9)	15 (13·4)	48 (42·9)	48 (42·9)
CE-CT*	112	0 (0)	13 (11·6)	26 (23·2)	44 (39·3)	29 (25·9)

Values in parentheses are percentages. MRI, magnetic resonance imaging; ECCM, extracellular contrast medium; CE-CT, contrast-enhanced computed tomography. *Wilcoxon two-sample tests resulted in two-sided $P < 0·001$ for the comparisons of gadoxetic acid-enhanced MRI *versus* ECCM-MRI and CE-CT.

The modified surgical plan was considered to have resulted in an increased duration of surgery in 13 per cent of patients with gadoxetic acid-enhanced MRI and 16 per cent of patients with ECCM-MRI, compared with 29 per cent of patients with CE-CT examinations. Completely or partially resected segments were correctly identified by imaging in 114 (91·9 per cent) of 124, 83 (91 per cent) of 91 and 71 (83 per cent) of 86 segments in the gadoxetic acid-enhanced MRI, ECCM-MRI and CE-CT group respectively. Although there was almost no difference with regard to identification of completely or partially resected segments between ECCM-MRI and gadoxetic acid-enhanced MRI (−0·7 percentage points, 95 per cent c.i. −9.8 to 8.4 per cent), an advantage, although not statistically significant, was seen for the hepatocyte-specific contrast agent compared with CE-CT (−9·4 percentage points, 95 per cent c.i. −23·3 to 4·5 per cent).

Three patients who had surgery did not undergo resection. One patient examined first with ECCM-MRI followed by gadoxetic acid-enhanced MRI was found to have unresectable hepatic disease at surgical exploration. Two patients, one in the gadoxetic acid-enhanced MRI group and one in the ECCM-MRI group, had unresectable extrahepatic disease.

Of the 112 patients operated on, 23 had a second imaging procedure before liver surgery (10 patients with the sequence ECCM-MRI followed by gadoxetic acid-enhanced MRI, and 13 who had CE-CT followed by gadoxetic acid-enhanced MRI). In eight patients (3 in the ECCM-MRI group and 5 in CE-CT group), the investigators required a second imaging modality despite an initial high-confidence treatment decision. One patient was assigned to surgery based on the second imaging modality. In this patient, lesions considered unresectable by initial CE-CT (high number of metastases and unfavourable segmental location) were found to be primarily resectable as predicted by subsequent gadoxetic acid-enhanced MRI. Conversely, in five patients deemed resectable after first imaging, unnecessary surgery was avoided by the second imaging modality. In four of these patients this was achieved by second imaging with gadoxetic acid-enhanced MRI (additional metastases detected (2); suspected metastases (1) and suspected hepatocellular carcinoma (1) according to initial CE-CT findings, eventually diagnosed as benign lesions), whereas in one patient suspected metastases by CE-CT were confirmed as benign by ECCM-MRI.

Table 4 Diagnostic performance of imaging techniques in patients undergoing surgery with an assessable total number of lesions (efficacy population)

Initial imaging technique	Total no. of lesions at final diagnosis* compared with initial imaging		
	Lower	Equal	Higher
Gadoxetic acid-enhanced MRI	2 of 42 (5)	37 of 42 (88)	3 of 42 (7)
ECCM-MRI†	14 of 34 (12)	25 of 34 (74)	4 of 34 (12)
CE-CT	4 of 29 (14)	18 of 29 (62)	7 of 29 (24)

Values in parentheses are percentages. *On intraoperative or pathological examination. †For one patient the comparison was considered 'failed' owing to a 'not assessable' number of total lesions at the first consensus meeting. MRI, magnetic resonance imaging; ECCM, extracellular contrast medium; CE-CT, contrast-enhanced computed tomography. Results of the exact Pearson χ^2 test (2-sided at significance level of 0·050) were $P = 0·033$ for gadoxetic acid-enhanced MRI *versus* CE-CT and $P = 0·316$ for gadoxetic acid-enhanced MRI *versus* ECCM-MRI.

Diagnostic performance

In operated patients, comparison of the total number of lesions detected at initial imaging *versus* the number recorded by intraoperative examination and pathological examination of resected specimens showed the greatest number of patients with equal assessments (88 per cent) in the gadoxetic acid-enhanced MRI group (compared with 74 and 62 per cent in ECCM-MRI and CE-CT groups respectively) (*Table 4*).

Discussion

In the investigation of patients with confirmed or suspected CRCLM, the need for additional imaging as a result of an inadequate first imaging procedure is undesirable. It has economic implications and may result in a prolongation of

the workup and delayed treatment decisions and therapy. An accurate assessment of the extent of liver metastases is crucial for planning of an optimal and individualized treatment strategy. Ideally, the method used should be highly sensitive and specific regarding the extent of metastatic disease, while at the same time generating high-resolution images, depicting the segmental anatomy and vascular and biliary structures in the liver. Current liver resection guidelines, where limitations due to tumour characteristics such as number, size and location are not absolute contraindications, underscore the importance of correct assessment of the extent of the liver disease in patients considered for curatively intended therapy[1,26].

Deviation from the preoperative surgical plan owing to additional findings during intraoperative assessment is suboptimal, for example when preoperative knowledge of the true extent of the disease would have resulted in a different multimodality approach. If the intraoperative findings preclude curative resection, patients are exposed to an unnecessary invasive procedure. For the healthcare provider, a change in the surgical plan can cause logistical problems and generate unforeseen costs[27].

Detection rates of various imaging modalities, including CE-CT and MRI with ECCM or liver-specific contrast agents, have been compared in patients with CRCLM in several studies[13–19,28]. This study assessed prospectively the impact of imaging findings on the preoperative patient work flow and planned liver resection. The results suggest that gadoxetic acid-enhanced MRI is superior as a first imaging method compared with CE-CT and ECCM-MRI with regard to the primary efficacy parameter, namely whether a confident treatment decision can be made on information supplied by the chosen modality. With no patient initially examined by gadoxetic acid-enhanced MRI needing any additional imaging, the outcome was even better than predictions based on a previous health economic evaluation[21]. The choice of gadoxetic acid-enhanced MRI as second imaging modality in all patients but one could be due to a presumed better performance of the method in terms of the detection and characterization of lesions[15–19]. This is in line with clinical practice, where gadoxetic acid-enhanced MRI is seen as a problem-solving modality in equivocal cases.

An important aspect addressed by the present study is the evaluation of changes in the surgical plan as a result of unexpected findings at surgical exploration. Based on the proportion of patients for whom the initial surgical plan was modified at actual surgery, CE-CT was the least suitable imaging procedure, with modifications of the surgical plan in 47 per cent of patients undergoing surgery after CE-CT as a single imaging modality. Not only was gadoxetic acid-enhanced MRI assessment associated with the lowest proportion of patients for whom the surgical plan had to be modified, but as the second imaging modality after CE-CT it prevented unnecessary surgery in four patients and contradicted the initial CE-CT assessment of unresectability in one patient, who subsequently underwent successful resection. This is in line with data from multicentre trials[15,16], where liver-specific MRI with gadoxetic acid showed advantages for detection of metastases and lesion characterization. Diagnostic performance of the different imaging modalities was included as a secondary parameter in patients who had surgery. Hepatic assessment using gadoxetic acid-enhanced MRI differed least from the intraoperative assessment compared with ECCM-MRI and CE-CT.

In the gadoxetic acid-enhanced MRI group, liver metastases were detected in a higher number of patients compared with CE-CT and ECCM-MRI. This is likely to be the result of a higher sensitivity of gadoxetic acid-enhanced MRI for lesion detection. The interesting finding that a higher proportion of patients with metastases in the gadoxetic acid-enhanced MRI group were operated on might be due to greater confidence in the preoperative imaging findings.

Some points concerning the design of the study need to be discussed. Not only were patients with confirmed metastases included, but also patients with a suspicion of metastases, based on screening imaging and/or increased CEA level. This was deliberate, as it reflects the reality of current clinical practice in terms of screening[5]. Reflecting clinical reality, a variety of protocols for hepatic imaging were in place in the participating centres for examining patients with CRCLM, and a variety of MRI and CT scanners were in use, including 1·0-Tesla MRI systems and four-slice CT scanners. However, at recruitment of sites, a site selection questionnaire was completed to ensure adequate experience with all three tested diagnostic modalities. Imaging protocols were not standardized or specified, apart from suggesting and documenting important imaging parameters to establish a reasonable standardization in image quality. As there is no clear evidence in the literature that liver imaging with 1·0-Tesla MRI systems or four-slice multidetector CT is considerably inferior to more recent technology, the small number of patients who were examined with these systems were not excluded. These facts, together with the multicentre design with 27 centres in Europe and Asia, were accepted deliberately in order to represent clinical reality. MRI and CT procedures were of comparably high quality, as reflected in the detailed description of the imaging procedures. Similarly, to reflect clinical routine, assessments were performed in consensus by the

local clinical investigators (a radiologist and a surgeon), rather than by external review of imaging results and clinical decision-making. Centralized reading might, to a certain extent, have ruled out bias, especially regarding the decision to request a second imaging and choice of second imaging procedure. It is, however, debatable whether such a setting would have allowed generalization of results to the same extent. Furthermore, central clinical decision-making without the contribution of the treating surgeon is not really feasible. In cases where a second imaging procedure was requested, the study protocol did not assess the motivation. Drawing from clinical experience, equivocal findings was probably the most common reason.

Finally, measurement of the performance of different imaging strategies goes beyond the arbitrary endpoints used in this study, namely end of imaging and end of surgery. Follow-up of the operated group and patients assessed as not having metastases to the time of death or time-tested confirmation of a tumour-free state will generate more evidence regarding the sensitivity of the different imaging modalities. Such data could support or refute the theory that MRI with gadoxetic acid enabled detection of disease that would have remained undetected had either of the other treatment modalities been used. Long-term follow-up of these patients (for more than 5 years) is desirable and likely to answer this question.

Collaborators

Members of the VALUE study group were as follows: C. J. Zech (Munich, Germany and Basle, Switzerland), P. Korpraphong (Bangkok, Thailand), A. Huppertz (Berlin, Germany), T. Denecke (Berlin, Germany), M.-J. Kim (Seoul, South Korea), W. Tanomkiat (Songkhla, Thailand), S. H. Kim (Seoul, South Korea), Y. K. Kim (Seoul, South Korea), J. Ricke (Magdeburg, Germany), C.–H. Lee (Seoul, South Korea), R. Hammerstingl (Frankfurt/Main, Germany), J. C. Monsalve (Seville, Spain), P. Reimer (Karlsruhe, Germany), J. M. Lee (Seoul, South Korea), L. Grazioli (Brescia, Italy), S. Gschwend (Berlin, Germany), S. Baroud (Vienna, Austria), E. Jonas (Stockholm, Sweden), A. Ba-Ssalamah (Vienna, Austria).

Acknowledgements

This study was funded by Bayer Pharma AG. The authors thank K. Bergmann for administrative support and project management. Special thanks go to S. Gschwend from Bayer Pharma AG for continuous support and her dedicated work on this multicentre trial.

The authors also thank Ecron Acunova, Frankfurt, Germany, which provided services on behalf of Bayer Pharma AG, especially to K. Schmidt for coordinating the study and maintaining contact between the study centres, A. Hammes and E. Blümner for performing the statistical evaluation and many helpful discussions, and B. Glocker for medical writing services. Technical editing of the manuscript was provided by A. Bothwell of inScience Communications, Springer Healthcare, with funding from Bayer Pharma AG.

C.J.Z. is a member of the 'Liver Imaging' advisory board (Bayer) and has received honoraria for travel and lectures from Bayer and Bracco. A.H. has received speaker's honoraria from Bayer Healthcare for specific speeches. T.D. has received honoraria for presentations and travel funding for congresses from Bayer Schering. E.J. has received honoraria for lectures from Bayer Schering.

Disclosure: The authors declare no further conflicts of interest.

References

1 Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F *et al.*; Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of LIver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; **17**: 1225–1239.

2 Ballantyne GH, Quin J. Surgical treatment of liver metastases in patients with colorectal cancer. *Cancer* 1993; **71**(Suppl): 4252–4266.

3 Bengtsson G, Carlsson G, Hafstrom L, Jonsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981; **141**: 586–589.

4 Wald C, Scheirey CD, Tran TM, Erbay N. An update on imaging of colorectal cancer. *Surg Clin North Am* 2006; **86**: 819–847.

5 Scheer A, Auer RA. Surveillance after curative resection of colorectal cancer. *Clin Colon Rectal Surg* 2009; **22**: 242–250.

6 Crucitti F, Sofo L, Doglietto GB, Bellantone R, Ratto C, Bossola M *et al.* Prognostic factors in colorectal cancer: current status and new trends. *J Surg Oncol Suppl* 1991; **2**: 76–82.

7 LeGolvan MP, Resnick M. Pathobiology of colorectal cancer hepatic metastases with an emphasis on prognostic factors. *J Surg Oncol* 2010; **102**: 898–908.

8 Pawlik TM, Choti MA. Surgical therapy for colorectal metastases to the liver. *J Gastrointest Surg* 2007; **11**: 1057–1077.

9 Cervone A, Sardi A, Conaway GL. Intraoperative ultrasound (IOUS) is essential in the management of metastatic colorectal liver lesions. *Am Surg* 2000; **66**: 611–615.

10 Conlon R, Jacobs M, Dasgupta D, Lodge JP. The value of intraoperative ultrasound during hepatic resection compared with improved preoperative magnetic resonance imaging. *Eur J Ultrasound* 2003; **16**: 211–216.

11 Sietses C, Meijerink MR, Meijer S, van den Tol MP. The impact of intraoperative ultrasonography on the surgical treatment of patients with colorectal liver metastases. *Surg Endosc* 2010; **24**: 1917–1922.

12 Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L *et al.* Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging* 2010; **31**: 19–31.

13 Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010; **257**: 674–684.

14 Donati OF, Hany TF, Reiner CS, von Schulthess GK, Marincek B, Seifert B *et al.* Value of retrospective fusion of PET and MR images in detection of hepatic metastases: comparison with 18 F-FDG PET/CT and Gd-EOB-DTPA-enhanced MRI. *J Nucl Med* 2010; **51**: 692–699.

15 Hammerstingl R, Huppertz A, Breuer J, Balzer T, Blakeborough A, Carter 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. *Eur Radiol* 2008; **18**: 457–467.

16 Huppertz A, Balzer T, Blakeborough A, Breuer J, Giovagnoni A, Heinz-Peer G *et al.*; European EOB Study Group. 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.

17 Lowenthal D, Zeile M, Lim WY, Wybranski C, Fischbach F, Wieners G *et al.* Detection and characterisation of focal liver lesions in colorectal carcinoma patients: comparison of diffusion-weighted and Gd-EOB-DTPA enhanced MR imaging. *Eur Radiol* 2011; **21**: 832–840.

18 Muhi A, Ichikawa T, Motosugi U, Sou H, Nakajima H, Sano K *et al.* Diagnosis of colorectal hepatic metastases: comparison of contrast-enhanced CT, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, and gadoxetic acid-enhanced MRI. *J Magn Reson Imaging* 2011; **34**: 326–335.

19 Seo HJ, Kim MJ, Lee JD, Chung WS, Kim YE. Gadoxetate disodium-enhanced magnetic resonance imaging *versus* contrast-enhanced 18 F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of colorectal liver metastases. *Invest Radiol* 2011; **46**: 548–555.

20 Annemans L, Lencioni R, Warie H, Bartolozzi C, Ciceri M, Müller U. Health economic evaluation of ferucarbotran-enhanced MRI in the diagnosis of liver metastases in colorectal cancer patients. *Int J Colorectal Dis* 2008; **23**: 77–83.

21 Zech CJ, Grazioli L, Jonas E, Ekman M, Niebecker R, Gschwend S *et al.* Health-economic evaluation of three imaging strategies in patients with suspected colorectal liver metastases: Gd-EOB-DTPA-enhanced MRI *vs*. extracellular contrast media-enhanced MRI and 3-phase MDCT in Germany, Italy and Sweden. *Eur Radiol* 2009; **19**(Suppl 3): S753–S763.

22 Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 2005; **12**: 351–355.

23 AptivSolutions®. *ADDPLAN® 5 MC. Adaptive Designs – Plans and Analyses Release 5*. http://www.aptivsolutions.com/addpdlan-software/ [accessed 24 September 2012].

24 Kieser M, Bauer P, Lehmacher W. Inference on multiple endpoints in clinical trials with adaptive interim analyses. *Biometrical Journal* 1999; **41**: 261–277.

25 Obuchowski NA. On the comparison of correlated proportions for clustered data. *Stat Med* 1998; **17**: 1495–1507.

26 Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 2008; **13**: 51–64.

27 Bipat S, van Leeuwen MS, Ijzermans JN, Comans EF, Planting AS, Bossuyt PM *et al.* Evidence-base guideline on management of colorectal liver metastases in the Netherlands. *Neth J Med* 2007; **65**: 5–14.

28 Mainenti PP, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A *et al.* Detection of colo-rectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. *Abdom Imaging* 2010; **35**: 511–521.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Inclusion and exclusion criteria (Word document)

Table S2 Imaging parameters (MRI procedures) (Word document)