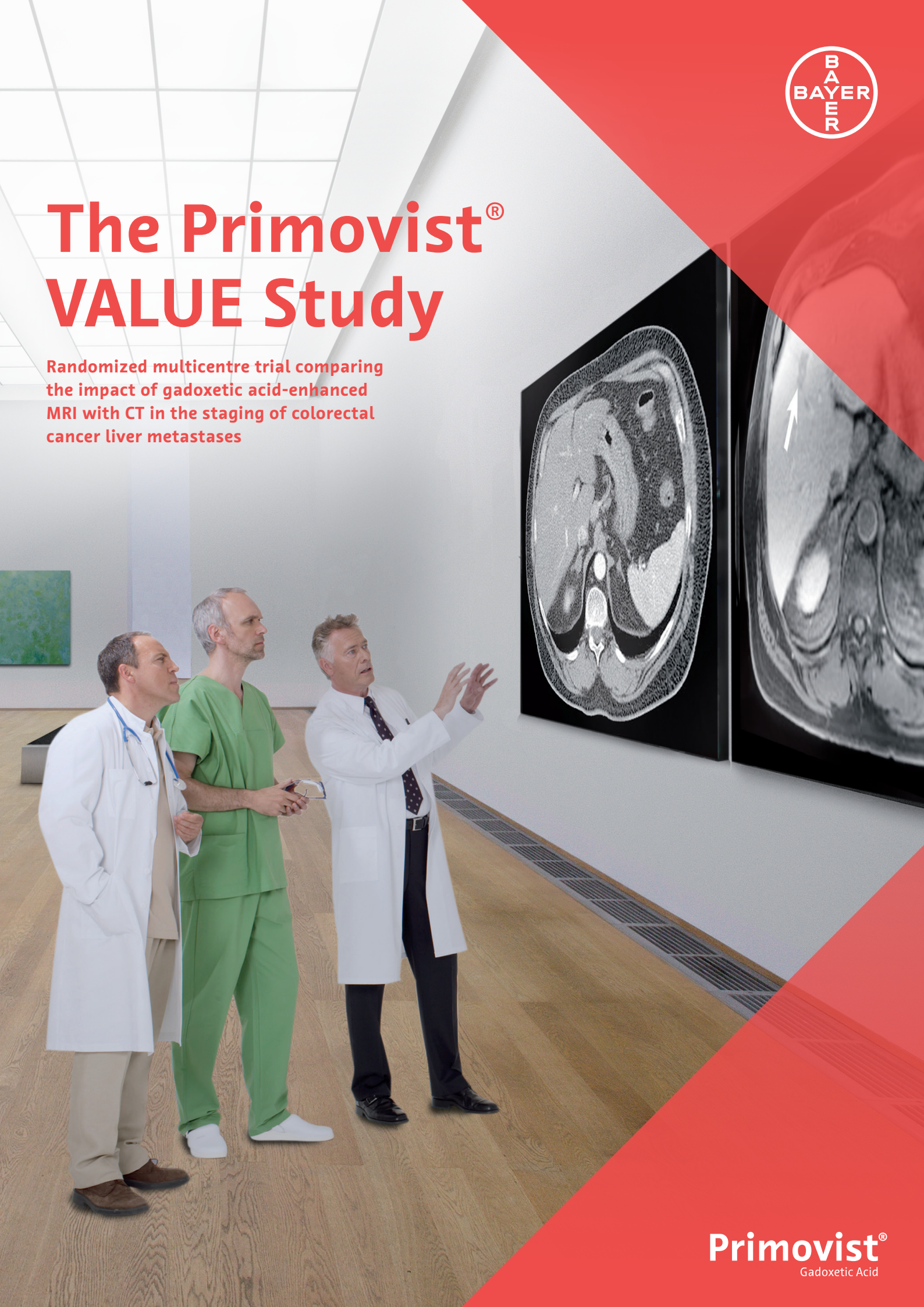
The Primovist® VALUE Study

Randomized multicentre trial comparing the impact of gadoxetic acid-enhanced MRI with CT in the staging of colorectal cancer liver metastases



Primovist®
Gadoxetic Acid

The Primovist® VALUE Study

The need for accurate radiological staging

- Accurate staging is essential for identifying patients with liver metastases secondary to CRC who are most likely to benefit from surgery[1,2]
- Primovist® (Gd-EOB-DTPA)-MRI may provide higher diagnostic accuracy than CE-CT2-4 for imaging liver lesions

Aim

- A prospective, randomized phase IV trial to evaluate the outcomes & resource needs of imaging & treatment following gadoxetate enhanced MRI of the liver versus CE-CT in patients with suspected CRCLM[5]

Objective

- To compare Primovist®-MRI with CE-CT for hepatic staging of patients with suspected CRCLM

Hypothesis

The higher accuracy of Primovist®-MRI could lead to reduced resource usage compared with CE-CT by:

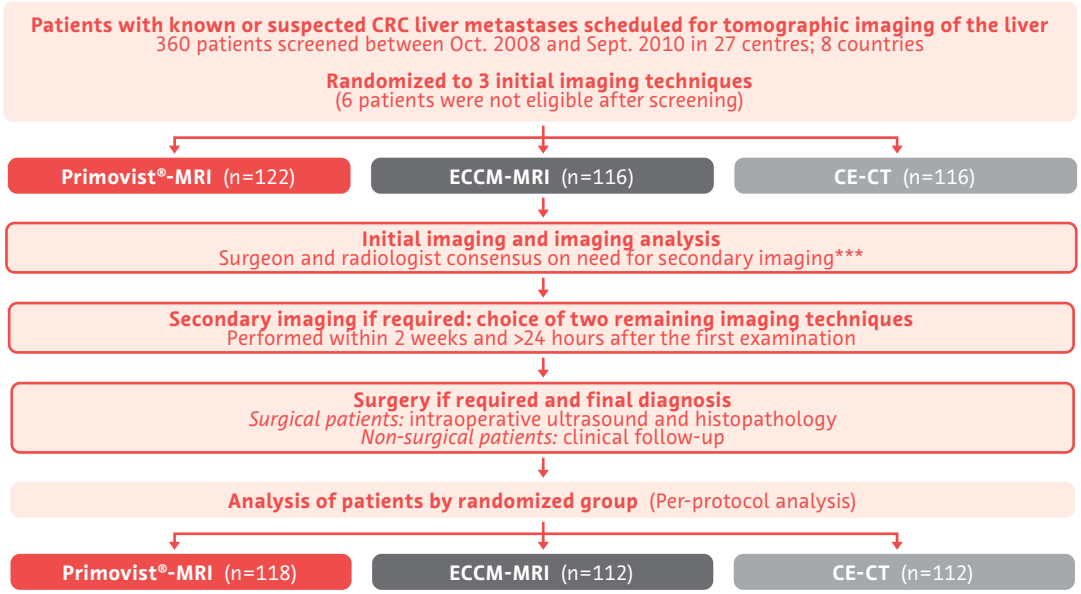
- Reducing the need for additional pre-therapeutic staging examinations
- Providing a more precise surgical plan
  - Reduces the instances of intra-operative modification of the plan designed before surgery

CE-CT, contrast-enhanced multidetector computed tomography; CRC, colorectal cancer; CRCLM, colorectal cancer liver metastasis; ECCM-MRI, extracellular contrast media-enhanced MRI; Gd-EOB-DTPA-MRI, gadoxetic acid (Gd-EOB-DTPA)-enhanced MRI
VALUE, Multi-centre, randomised comparison study to eVALUatE outcomes and resource needs of imaging and treatment following Primovist-enhanced MRI of the liver, in comparison to ECCM-MRI and CE-MDCT in patients with a history of CRC and known or suspected metachronous liver metastases.

1. Bipat S et al. Radiology 2005;237:123; 2. Ruers TJ et al. J Nucl Med 2009;50:1036; 3. Hammerstingl R et al. Eur Radiol 2008;18:457; 4. Halavaara J et al. J Comput Assis Tomogr 2006;30:345; 5. Zech CJ et al. Br J Surg. 2014. doi: 10.1002/bjs.9465.

The VALUE Study – a randomised multicentre trial.
Zech et al. Br J Surg. 2014; 101(6):613-21

VALUE Study Design



* ECCM agents used were: Gadovist, Magnevist, Dotarem, and Omniscan. (Gadovist, Magnevist, and Dotarem are not approved for hepatic imaging in Canada). The results of ECCM-MRI are not presented in this document.
**CE-CT was performed using a single injection of iodinated low-osmolar or iso-osmolar contast medium.
***External review of the imaging results may have ruled out bias caused by the assessments being performed in consensus by the local clinical investigators.

Primary endpoint

- Proportion of patients for whom further imaging after initial imaging was required for a confident diagnosis

Secondary endpoints

- Confidence in diagnosis and therapeutic decision
- Proportion of patients with intra-operatively modified surgical plans
- Diagnostic performance of imaging techniques in comparison with final diagnosis

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VALUE Study
Patient Populations

	Imaging technique	
	Primovist®-MRI (n=118)	CE-CT (n=112)
Age (years), mean ±SD	62	63
Range	37 – 82	32-88
Weight (kg), mean ±SD	73	71
Range	42 – 146	42-115
Male / Female	80 / 38	74/38
Patients with previously resected liver segments, (n)	3	1
Patients with underlying liver disease (n), hepatic cirrhosis / hepatic steatosis	0 / 1	0/0

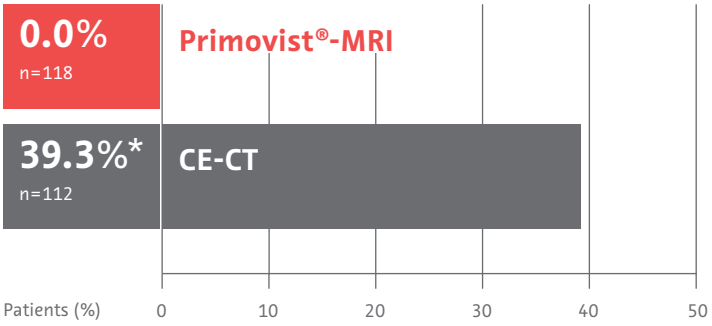
Primary Endpoint

Fewer secondary liver imaging procedures compared to CE-CT

The use of Primovist®-MRI as an initial imaging technique reduced the need for additional liver imaging to make a confident therapy decision compared to CE-CT

Additional imaging was not deemed necessary for any of the patients in the Primovist®-MRI group to establish a diagnosis and confident therapy decision by their surgeon and radiologist

Patients requiring further imaging for diagnosis and therapy decision[a]



[a] Per-protocol set analysis. * p<0.001

- Comparison of Primovist®-MRI versus CE-CT was statistically significant (p<0.001)
- Primovist®-MRI was the technique chosen in 98% (62/63) of patients who underwent a second imaging procedure

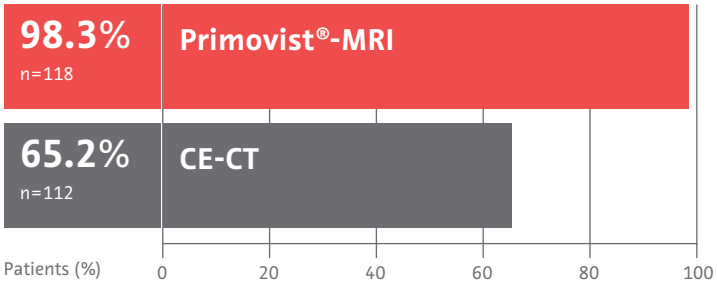
Secondary Endpoint

High diagnostic confidence in imaging technique compared to CE-CT

Primovist®-MRI provided better diagnostic confidence than CE-CT

High or very high confidence ratings for the diagnosis and treatment plan were given in 98.3% of the patients in the Primovist®-MRI group

High and very high diagnostic confidence after initial imaging technique (rated by radiologists and surgeons)

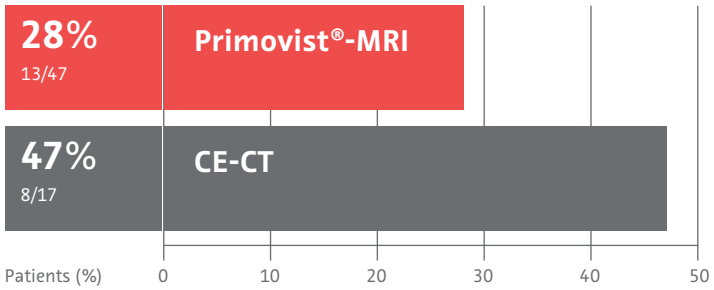


- Exploratory testing of the differences between Primovist®-MRI and CE-CT resulted in p-values <0.001
- A higher confidence rating for the initial imaging modality might be the reason why a higher proportion of patients with metastases in the Primovist®-MRI group were operated on

A lesser percentage of patients for whom intra-operative surgical planning had to be modified compared to CE-CT

In the per-patient evaluation of patients with one imaging procedure, the surgical plan was modified in 28% patients in the Primovist®-MRI group, compared with 47% for CE-CT

Patients requiring modifications to surgical plan (Patients with one imaging procedure)*



- The modified surgical plan was considered to have caused an increase in the duration of the surgery in the following proportions of patients:
  - Primovist®-MRI: 13%
  - CE-CT: 29%
- Completely or partially resected segments were correctly identified by imaging, as follows:
  - Primovist®-MRI: 92%
  - CE-CT: 83%

The VALUE Study – a randomised multicentre trial.

* Patients in the per-protocol set who had surgery

Primovist®-MRI improves diagnostic performance when used as secondary imaging

Primovist®-MRI prevented unnecessary surgery in 4 out of 23 patients all of for whom had had CE-CT as initial imaging[1]

- Additional metastases (n=2)
- Suspected metastases classified as benign (n=1)
- Diagnosis change from HCC to benign lesion after initial imaging with CE-CT (n=1)

One patient was assigned to surgery on the strength of the second imaging modality with Primovist®-MRI

- Lesions were considered unresectable following initial imaging using CE-CT

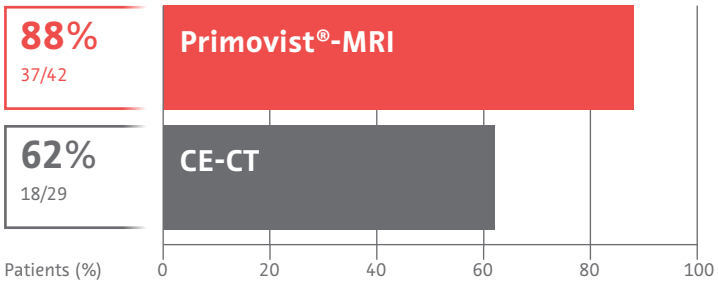
1. Zech CJ et al. Br J Surg. 2014. doi: 10.1002/bjs.9465

Secondary Endpoint

The highest percentage of patients with an equal assessment of lesions detected at initial imaging versus intra-operative examination compared to CE-CT

Primovist®-MRI showed the highest number of patients with equal assessments (88%) compared to CE-CT (62%) when the total number of lesions detected at initial imaging was compared to the number of lesions recorded during and after surgery

Percentage of patients with equal numbers of lesions at final diagnosis versus initial consensus



	Total number of lesions at final diagnosis compared to initial imaging		
Initial imaging technique	Lower	Equal	Higher
Primovist®-MRI (n=42)	5%	88%	7%
CE-CT (n=29)	14%	62%	24%

Take-Home Messages

- Additional findings can be of high clinical relevance in patients scheduled for liver surgery, reducing the occurrence of unnecessary surgery
- MRI may offer additional and accurate information for lesion characterisation, with the hepatocyte-specific phase allowing for better contrast for further lesion detection

1. Zech CJ et al. Br J Surg. 2014. doi: 10.1002/bjs.9465

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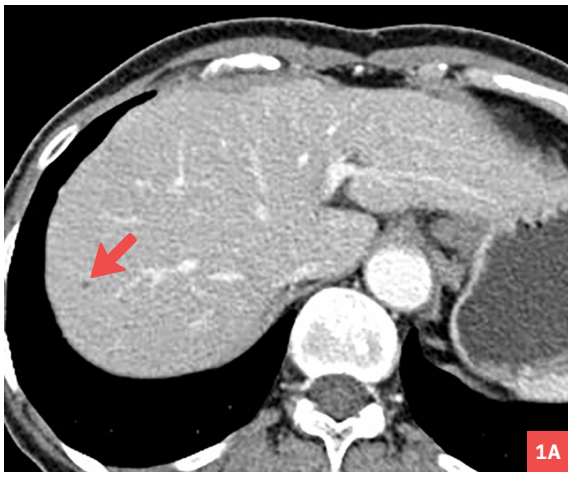
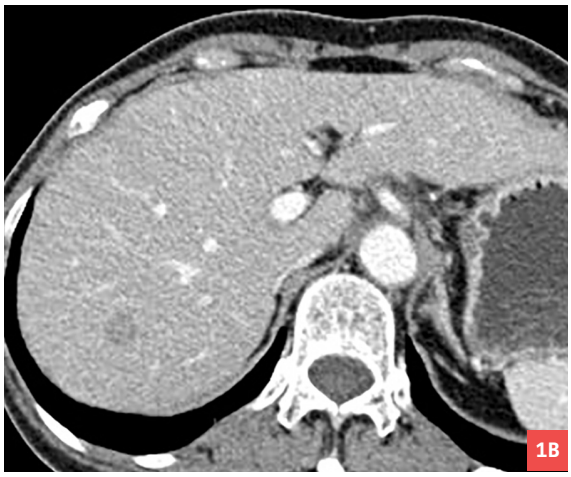
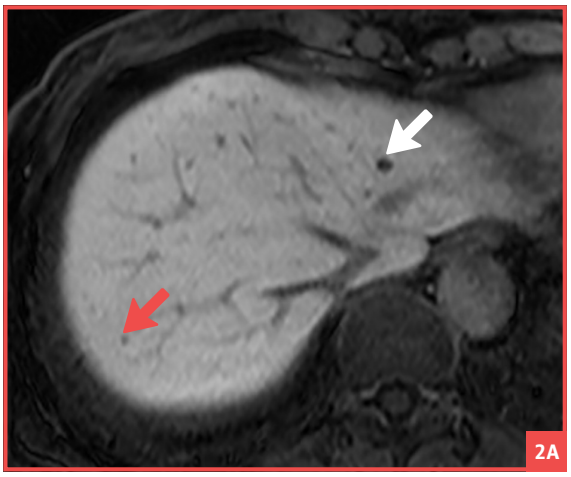
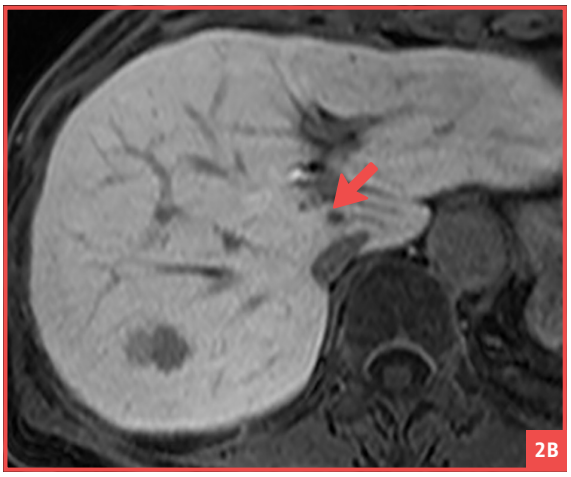
Initial Imaging: CE-CT





Secondary Imaging: Primovist®-MRI





Study courtesy of the Department of Clinical Radiology,
University of Munich Hospitals, Grosshardern Campus, Munich, Germany

The Primovist® VALUE Study: Conclusion

- Imaging of the liver for metastases in patients with CRC has become standard practice[1,2]
- Additional imaging as a result of an inadequate first procedure is highly undesirable due to
  - Economic implications
  - Prolongation of work-up and delayed treatment decisions
- Therefore accurate assessment of the extent of disease is essential

1. Wald C et al. Surg Clin North Am 2006;86: 819
2. Scheer A, Auer RA. Clin Colon Rectal Surg 2009;22: 242

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Primovist®

gadoxetate disodium

Important Safety Information

- PRIMOVIST (gadoxetate disodium injection) is a gadolinium-based contrast agent (GBCA) indicated for intravenous use in T1-weighted magnetic resonance imaging (MRI) of the liver to detect and characterize l esions in adults with known or suspected focal liver disease.
- Safety and effectiveness in pediatric patients have not been established.

Most serious warnings and precautions:

- **Nephrogenic systemic fibrosis (NSF):** GBCAs increase the risk for NSF in patients with chronic severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m2) or acute renal failure / acute kidney injury. In these patients, avoid use of GBCAs unless the diagnostic information is essential and not available with noncontrast-enhanced MRI. NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a GBCA, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration.
- **Not for intrathecal use:** PRIMOVIST is not approved for intrathecal use. Intrathecal administration of GBCAs can cause serious, life-threatening, and fatal reactions, primarily with neurological reactions (e.g., coma, encephalopathy, seizures).

Other relevant warnings and precautions:

- Avoid intramuscular administration due to local intolerance reactions including focal necrosis
- Severe renal or hepatic failure may impair PRIMOVIST imaging performance
- Gadolinium may accumulate in the brain after multiple administrations of GBCAs. Use the lowest effective dose and perform a benefit risk assessment before administering repeated doses.
- Exercise caution when administering to patients with severe cardiovascular problems
- Hypersensitivity reactions including anaphylactoid reactions with cardiovascular, respiratory, and cutaneous manifestations, ranging from mild to severe reactions including shock have occurred very rarely following administration. Prior to administration assess all patients for a history of reaction to contrast media; bronchial asthma; allergic disorders. Administer only where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions.
- Use only during pregnancy if the clinical condition of the woman requires its use.

Adverse reactions:

Most adverse drug reactions reported with PRIMOVIST were of mild to moderate severity, and did not require a discontinuation of the procedure. The most frequently reported adverse reactions in clinical trails were headache (0.6%; mild), nausea (0.7%; usually occurring just after injection and resolving quickly), and a feeling hot (0.7%; usually occurring during injection).

For more information:

Consult the product monograph https://www.bayer.com/sites/default/files/2020-11/primovist-pm-en.pdf for important information about for adverse reactions, interactions, and dosing. The Product Monograph is also available by calling Bayer Medical Information at 1-800-265-7382.

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