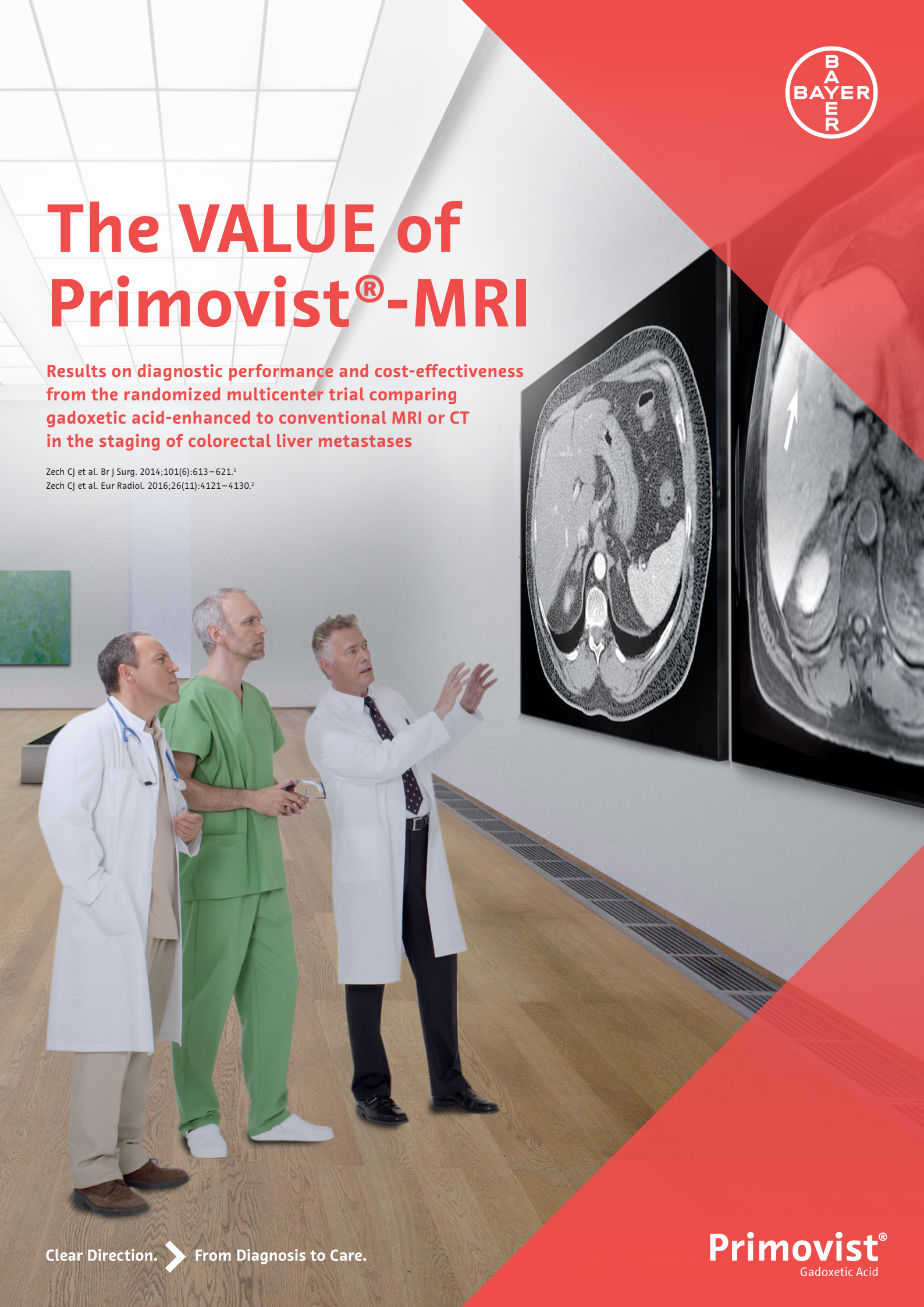
The VALUE of Primovist®-MRI

Results on diagnostic performance and cost-effectiveness from the randomized multicenter trial comparing gadoxetic acid-enhanced to conventional MRI or CT in the staging of colorectal liver metastases

Zech CJ et al. Br J Surg. 2014;101(6):613–621.[1]
Zech CJ et al. Eur Radiol. 2016;26(11):4121–4130.[2]



Clear Direction. From Diagnosis to Care.

Primovist®
Gadoxetic Acid

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The VALUE of Primovist®

The Primovist® VALUE Study

Primovist®-MRI demonstrates the VALUE of accurate diagnosis[1]

Objective

- Accurate staging of secondary liver cancer from colorectal cancer (CRC) is essential for identifying patients who are most likely to benefit from surgery
- Increasing cost pressures on healthcare systems require optimal use of resources, including the avoidance of unnecessary imaging[3]

Hypothesis

Using Primovist®-MRI as a first-line imaging modality in the diagnostic workup of patients with colorectal cancer liver metastasis (CRCLM) might therefore

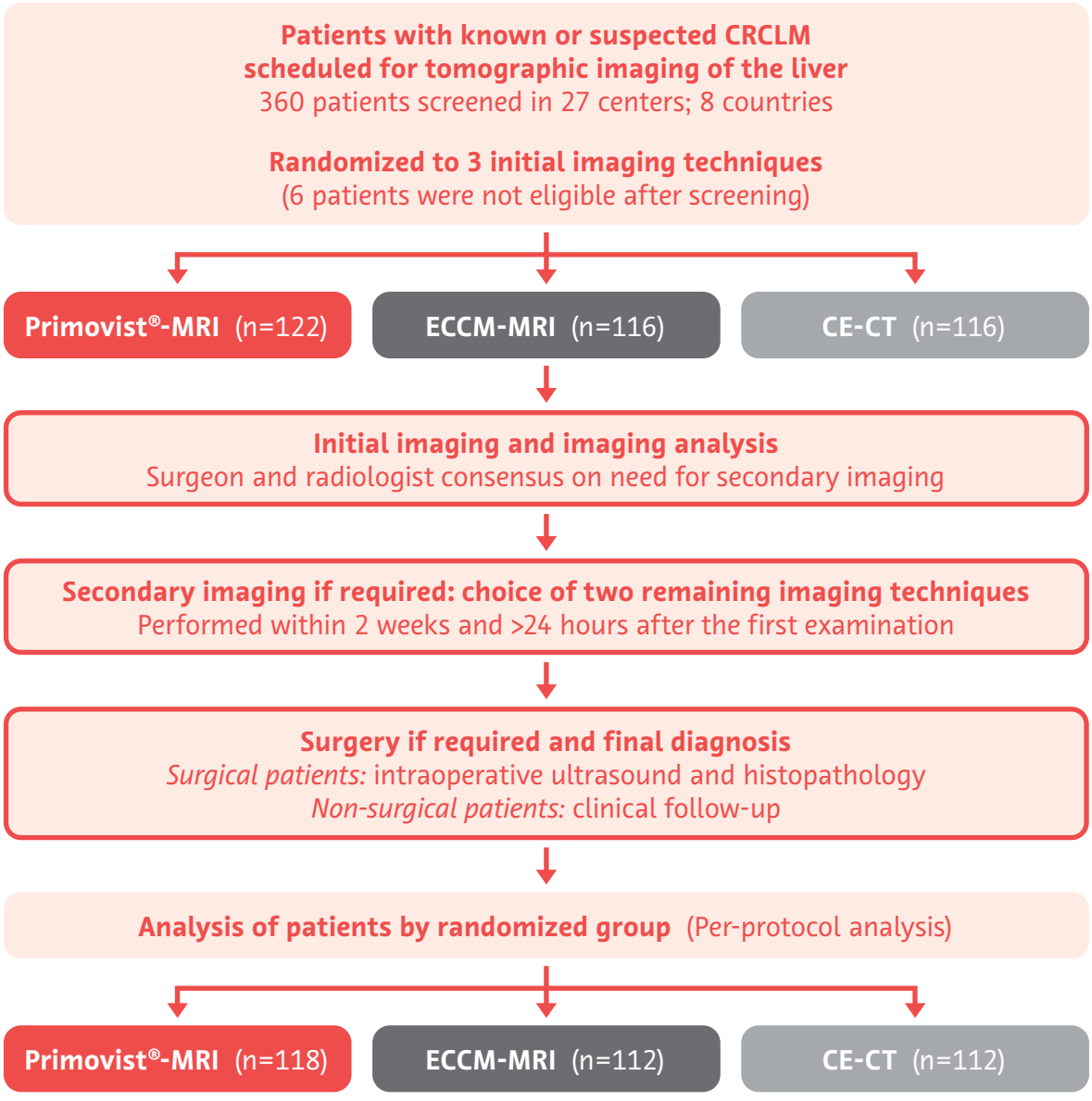
- decrease the number of unnecessary additional pre-therapeutic imaging for patients
- allow more precise surgical planning and reduce the need for intra-operative modifications
- optimize the use of healthcare resources

Demonstrating the VALUE of accurate initial diagnosis on CRCLM in a prospective, randomized phase IV trial

Goals

- To prospectively assess the impact of Primovist®-MRI versus extracellular contrast media-enhanced MRI (ECCM-MRI); or contrast-enhanced CT (CE-CT) as first-line imaging methods for staging of patients with suspected CRCLM
- To compare costs for diagnostic workup and surgery of the three imaging strategies

VALUE Study Design



Demographic and baseline characteristics of patients in the three primary imaging groups were matched with satisfactory comparability

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
- Safety (The study confirmed the overall good safety profile of Primovist®. Detailed results available are in the full study)[1,4-7]

Cost analysis

- Assess the cost for diagnostic workup and surgery of the three imaging strategies

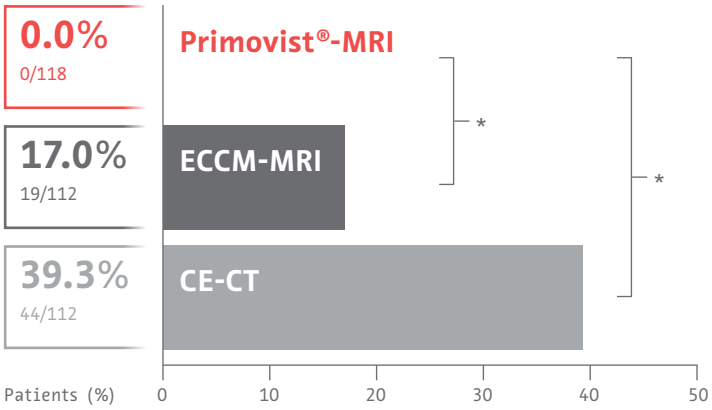
Significantly fewer secondary liver imaging procedures

PRIMARY ENDPOINT

Primovist®-MRI significantly reduces the need for additional liver imaging to confirm the diagnosis and decide on therapy

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



- Comparisons of Primovist®-MRI versus ECCM-MRI and CE-CT, and versus pooled data of ECCM-MRI and CE-CT, were highly significant (p<0.0001)
  - A significant difference favouring Primovist®-MRI was already reached by the interim analysis (results of 281 patients; p<0.0102) leading to early termination of the study.
- Primovist®-MRI was chosen in 98% (62/63) of cases requiring secondary imaging to resolve diagnostic uncertainties from first-line imaging with ECCM-MRI or CT-CT**

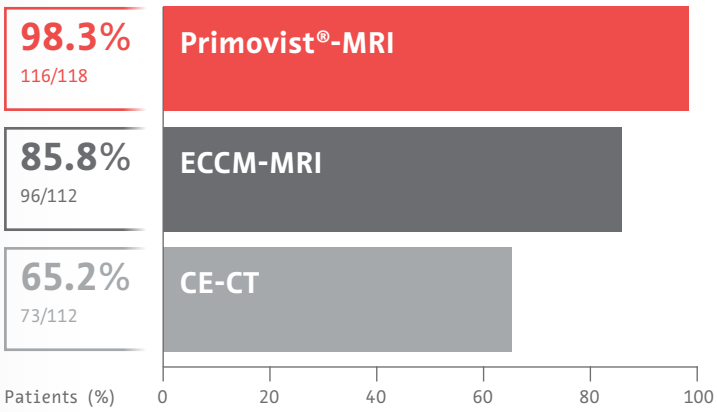
* p<0.001, from per protocol set analysis
** For 1/63 cases, CE-CT was used, secondary to ECCM-MRI

Improved confidence in diagnosis and therapeutic decision

SECONDARY ENDPOINT

In almost all patients (98.3%), Primovist®-MRI resulted in high or very high ratings regarding confidence in diagnosis and treatment planning

Pooled rates of high and very high diagnostic confidence after first-line imaging.



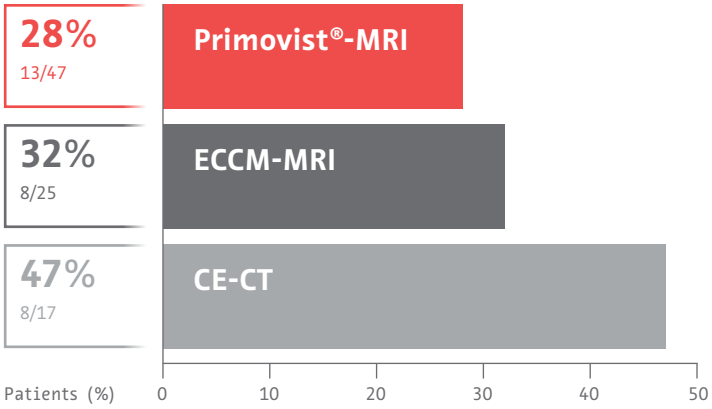
- Exploratory testing of the differences between Primovist®-MRI and the other two imaging techniques resulted in p-values <0.0001
- A higher confidence rating for the initial imaging modality likely means a decreased need for additional procedures when establishing a diagnosis and treatment plan

Fewer intra-operative modifications of surgical plan

SECONDARY ENDPOINT

Primovist®-MRI leads to fewer intra-operative modifications of the surgical plan (28%) compared to ECCM-MRI (32%) and CE-CT (47%) owing a better pre-operative planning

Patients requiring modifications to surgical plan after staging with a single imaging modality



- 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%
  - ECCM-MRI: 16%
  - CE-CT: 29%
- Completely or partially resected segments were correctly identified by imaging, as follows (p>0.05):
  - Primovist®-MRI: 92%
  - ECCM-MRI: 91%
  - CE-CT: 83%

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

Primovist®-MRI prevented unnecessary surgery in **4** out of **13** patients who were scheduled for surgery based on the initial staging CE-CT but turned out to be

- unresectable after secondary imaging with Primovist®-MRI due to the finding of additional metastases (n=2)
- unnecessary surgery because Primovist®-MRI identified the lesion as benign (n=2)

Conversely, one patient initially classified as primarily unresectable by CE-CT, was found to be resectable after secondary imaging with Primovist®-MRI

Primovist®-MRI leads to better diagnostic performance

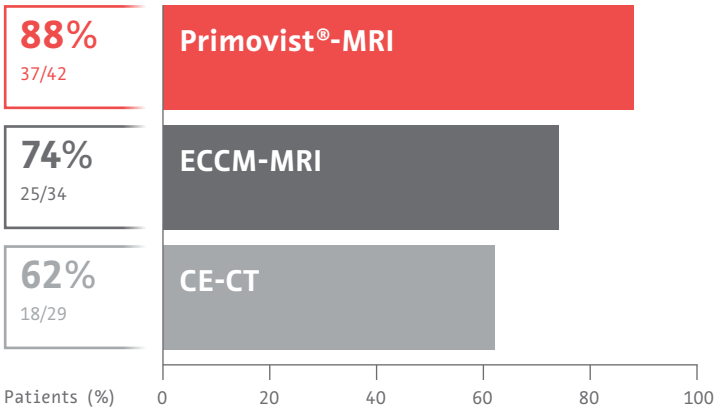
SECONDARY ENDPOINT

Primovist®-MRI leads to improved diagnostic performance, owing to more accurate lesion detection

Total number of lesions recorded following initial imaging was compared with the total number of lesions recorded during and after surgery

- Primovist®-MRI resulted in the highest number of patients with equal assessments (88%)

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



- The difference between imaging methods was significant for Primovist®-MRI vs. CE-CT (p=0.033) but not for Primovist®-MRI vs. ECCM-MRI (p=0.316)

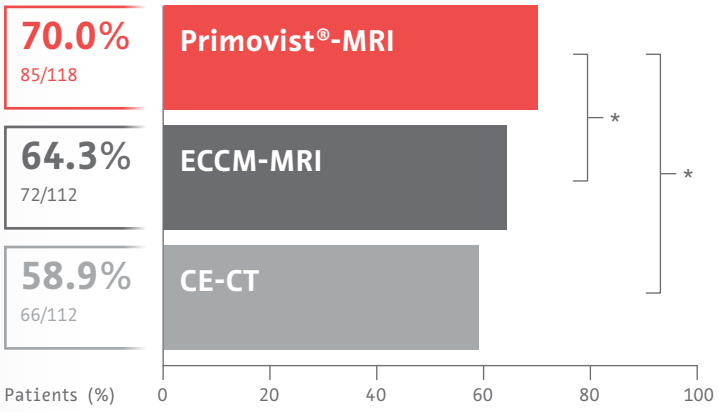
Superior sensitivity of Primovist®- MRI for detection of CRCLM

SECONDARY ENDPOINT

Imaging with Primovist-MRI results in significantly higher lesion detection rates compared to ECCM-MRI and CE-CT

Total number of lesions detected was higher (70.0%) compared to ECCM-MRI (64.3%) and CE-CT (58.9%)

Higher lesion detection rate with Primovist®-MRI



* p<0.001, (Fisher's exact test, pairwise)

The impact of accurate radiological staging

Case study from the VALUE study

Clinical history

- Patient was included in the VALUE study
  - History of CRC and suspected liver metastases

First Imaging: CE-CT

- Staging CT images demonstrated a potentially resectable metastasis in the right liver lobe (1A)
- Several additional unclear lesions were observed in the right liver lobe of the CE-CT (1B)
- This resulted in a second imaging modality being requested, and Primovist®-MRI was chosen as secondary imaging

Secondary Primovist®-MRI to resolve diagnostic uncertainties from CE-CT

- The unclear small lesion could be clearly defined in the hepatocyte-specific phase of Primovist®-MRI and characterized as an additional metastasis in combination with dynamic phase T1w and T2w images (2B red arrow)
- Hepatocyte-specific images revealed several additional liver metastases
  - One was located rather central in liver segment 1 (2A red arrow), so that surgery was not possible
- In addition, several of the hypodense lesions seen in CE-CT were identified as cysts by T2w images (2B white arrow)
  - Several hypodense lesions found on CE-CT could clearly be identified as cysts by T2w images from the Primovist®-MRI (white arrow Fig. 2B, lesions not shown on CE-CT images)

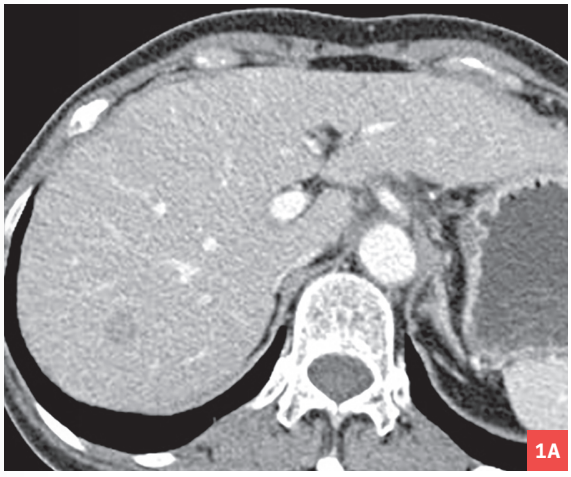
Impact on treatment and follow-up

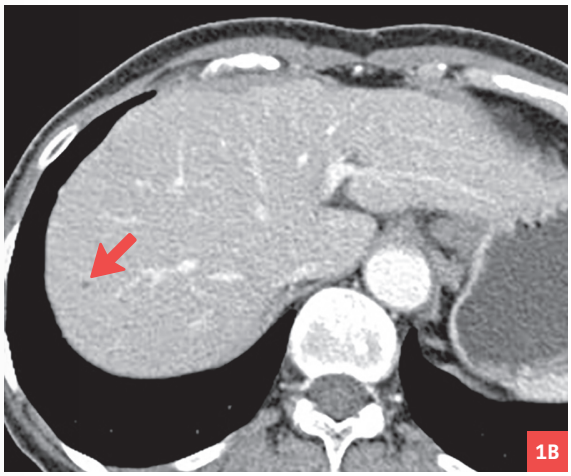
- Due to the unresectable lesion in segment 1 found only by Primovist®-MRI, the patient was shifted from surgery to neoadjuvant systemic chemotherapy to downstage the lesions before receiving re-assessment for surgery.

Take-Home Messages

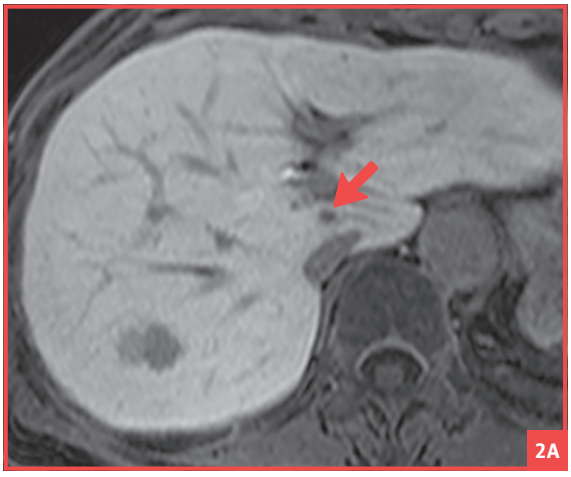
- The high liver-to-lesion contrast of Primovist®-MRI's hepatocyte-specific phase allows for the detection of additional lesions. In combination with the other MR-sequences, Primovist®-MRI can also improve lesion characterization.
- Ultimately, the overall increased diagnositic accuracy of Primovist®-MRI can be decisive for correct treatment stratification and avoid unnecessary surgery - This demonstrates high clinical VALUE of imaging with Primovist®-MRI.

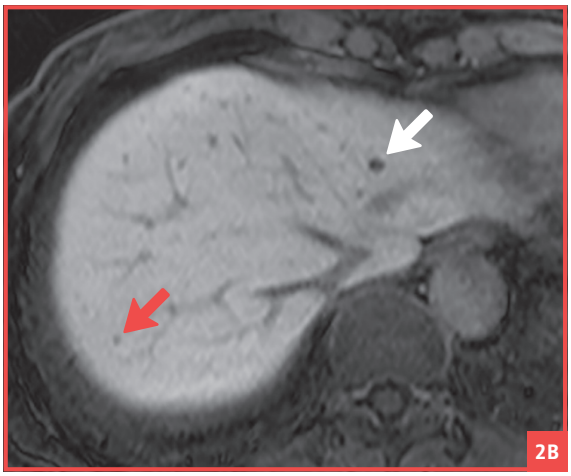
Initial Imaging: CE-CT


1A


1B

Secondary Imaging: Primovist®-MRI


2A


2B

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

In the diagnostic workup of CRCLM: Primovist®-MRI improves treatment decision making at no additional cost

Objective

Secondary cost-evaluation study:

- A secondary evaluation of a sub-group of 54 patients from eight countries of the VALUE trial compared the three imaging strategies (Primovist®-MRI versus ECCM-MRI versus CE-CT) in terms of cost for imaging workup and surgery.[1]

Results

Liver-specific imaging with Primovist®-MRI for CRCLM:

- Avoids additional imaging procedures and thus decreases total imaging costs before surgery in most countries
- Detects significantly more liver lesions compared to CE-CT and ECCM-MRI, thus improving treatment decision-making and surgical planning
- May increase the number of patients eligible for curative surgery and is recommended as imaging modality of choice to clarify lesion resectability

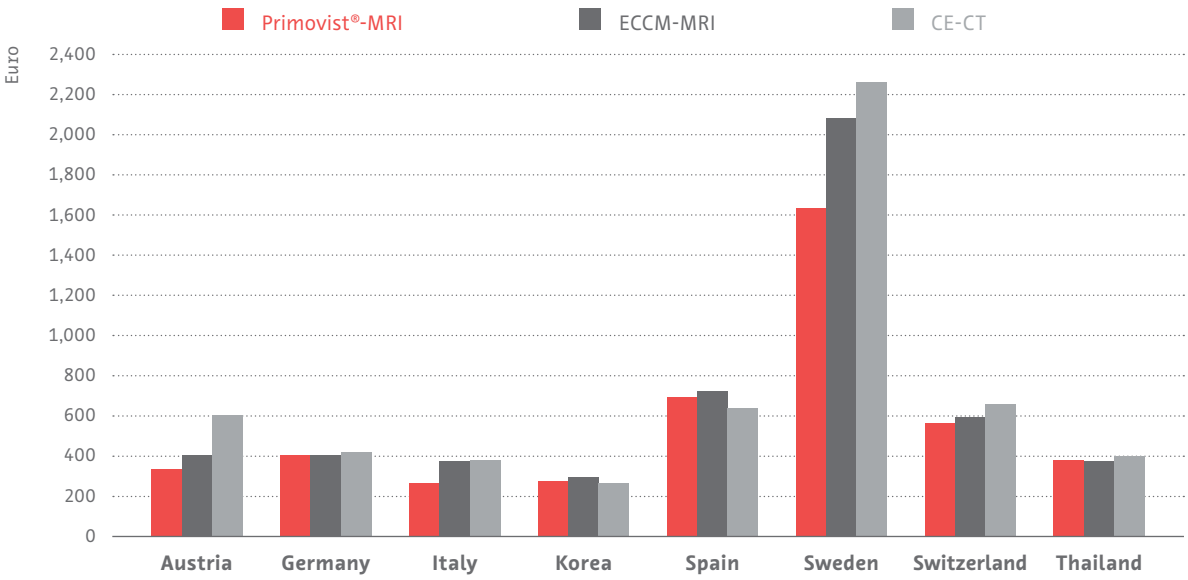


Figure 1 Costs of diagnostic work-up of patients with CRC liver metastases per country (expected per-patient costs in Euro, 2013)
Adapted from Zech CJ, et al. Eur Radiol. 2016;26(11):4121–4130. Table 4[2]

The VALUE of Primovist®

Conclusion

Compared to CE-CT and ECCM-MRI

The high diagnostic accuracy and superior sensitivity of MR-imaging with Primovist®-MRI in patients with suspected CRCLM resulted in

- Higher confidence in diagnostic and therapeutic decision
- Fewer additional imaging procedures
- Improved surgical planning
- No additional cost for diagnostic workup

Higher
diagnostic confidence

Fewer
imaging procedures

Improved
surgical planning

Cost-efficient
diagnostic workup

References

1 **Zech CJ, Korpraphong P, Huppertz A, et al.** Randomized multicentre trial of gadoxetic acid-enhanced MRI versus conventional MRI or CT in the staging of colorectal cancer liver metastases. Br J Surg. 2014;101(6):613–621.

2 **Zech CJ, Justo N, Lang A, et al.** Cost evaluation of gadoxetic acid-enhanced magnetic resonance imaging in the diagnosis of colorectal-cancer metastasis in the liver: Results from the VALUE Trial. Eur Radiol. 2016;26(11):4121-4130

3 **Zech CJ, Grazioli L, Jonas E, 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.

4 **Endrikat JS, Dohanish S, Balzer T, Breuer JA.** Safety of gadoxetate disodium: Results from the clinical phase II-III development program and postmarketing surveillance. J Magn Reson Imaging. 2015;42(3):634–643.

5 **Endrikat J, Kim SY, Sakaguchi T, et al.** Safety of gadoxetate disodium: results from six clinical phase IV studies in 8194 patients. Acta Radiol. 2016;57(11):1326–1333.

6 **Endrikat J, Schwenke C, Vogtlaender K, et al.** Safety profile of gadoxetate disodium in elderly patients (≥65 years). Acta Radiol. 2018;59(1):81-88.

7 **Geller J, Kasahara M, Martinez M, et al.** Safety and Efficacy of Gadoxetate Disodium-Enhanced Liver MRI in Pediatric Patients Aged >2 Months to <18 Years-Results of a Retrospective, Multicenter Study. Magn Reson Insights. 2016;9:21–28.

Primovist® 0.25 mmol/mL, solution for injection, prefilled syringe (gadoxetate disodium). Prescribing Information (Refer to Full Summary of Product Characteristics (SmPC) before prescribing). **Presentation:** Each mL solution for injection contains 181.43 mg/mL gadoxetate disodium. **Indication:** Detection of focal liver lesions and providing information on the character of lesions in T1-weighted magnetic resonance imaging (MRI). **Posology and method of administration:** Primovist® should be used only when diagnostic information is essential and not available with unenhanced MRI and when delayed phase imaging is required. Observe usual safety precautions for MRI (e.g. exclude cardiac pacemakers and ferromagnetic implants). Use lowest dose that provides sufficient enhancement for diagnostic purposes calculated based on the patient's body weight, and do not exceed the recommended dose. Administer dose undiluted as an intravenous bolus injection at a flow rate of about 2 mL/sec. After injection, flush cannula/line with 0.9% saline. Observe patients for at least 30 minutes after the injection. **Recommended doses are:** *Adults:* 0.1 mL/kg body weight. *Impaired renal function:* Use of Primovist® should be avoided in patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) and in patients in the perioperative liver transplantation period unless the diagnostic information is essential and not available with non-contrast enhanced MRI. If use cannot be avoided, dose should not exceed 0.025 mmol/kg body weight. Do not use more than one dose per scan. Do not repeat the dose for at least 7 days. *Patients with hepatic impairment:* No dose adjustment necessary. *Paediatric population:* The safety and efficacy of Primovist® have not been established in patients under 18 years old. However, an observational study was performed in 52 paediatric patients (aged >2 months and <18 years). Patients were referred for Primovist® contrast-enhanced liver MRI to evaluate suspected or known focal liver lesions. Additional diagnostic information was obtained when combined unenhanced and enhanced liver MR images were compared with unenhanced MR images alone. Serious adverse events were reported, however none were assessed by the investigator to be related to Primovist®. Due to the retrospective nature and small sample size of this study, no definitive conclusion can be made regarding efficacy and safety in this population. No dose adjustment necessary. *Elderly population (≥ 65 years):* No dose adjustment necessary. Exercise caution. *Accumulation in the body:* After administration of Primovist® gadolinium (Gd) can be retained in the brain and in other tissues of the body and can cause dose-dependent increases in T1w signal intensity in the brain, particularly in the dentate nucleus, globus pallidus, and thalamus. Signal intensity increases and non-clinical data show that Gd is released from linear GBCAs. Clinical consequences are unknown. he possible diagnostic advantages of using Primovist® in patients who will require repeated scans should be weighed against the potential for deposition of Gd in the brain and other tissues. **Contraindications:** Hypersensitivity to active substance or to any excipients. **Warnings and precautions:** It is recommended to screen all patients for renal dysfunction by obtaining laboratory tests, particularly patients over 65 years. Nephrogenic systemic fibrosis (NSF) has been reported with some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR <30 mL/min/1.73 m^2); Patients undergoing liver transplantation are at particular risk since incidence of acute renal failure is high in this group. Use should be avoided in patients with severe renal impairment and in patients in perioperative liver transplantation period unless diagnostic information is essential and not available with non-contrast enhanced MRI. Haemodialysis shortly after Primovist® administration may be useful at removing Primovist® from the body. There is no evidence to support initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis. *Use with caution in patients:* with severe cardiovascular problems; with, or with a family history of, congenital long QT syndrome; with drugs known to prolong cardiac repolarisation, particularly in patients with previous arrhythmias. Should not be used in patients with uncorrected hypokalaemia. Primovist® may cause transient QT prolongation. Allergy-like reactions, including shock, reported rarely. Patients with a history of allergic disorders or bronchial asthma or who have previously reacted to contrast media are at higher risk of hypersensitivity reactions. Most reactions occur within 30 minutes of administration but rarely delayed reactions may occur after hours to days. Appropriate drugs and instruments for treatment of hypersensitivity must be readily available. Hypersensitivity reactions can be more intense in patients on beta-blockers, particularly in patients with asthma. Patients taking beta-blockers who experience hypersensitivity may be resistant to treatment effects of beta-agonists. If hypersensitivity reactions occur, stop injection immediately. Do not administer intramuscularly due to risk of local intolerance reactions including focal necrosis. Consider the sodium content (11.7 mg/mL) for patients on controlled sodium diet. **Interactions:** Potent OATP inhibitors could cause drug interactions reducing the hepatic contrast effect. No clinical data exists to support this theory. Elevated levels of bilirubin or ferritin can reduce the hepatic contrast effect of Primovist®. Primovist® may interfere with serum iron determinations for up to 24 hours after administration. **Pregnancy and lactation:** There are no data from use in pregnant women. Animal studies have shown reproductive toxicity at repeated high doses. Should not be used in pregnancy unless clinical condition of the woman requires the use of Primovist®. Gd-containing contrast agents are excreted into breast milk in very small amounts. Continuing or discontinuing breast feeding for 24 hours after administration should be at discretion of the doctor and lactating mother. **Undesirable effects:** (please refer to the *Contraindications and the Warnings and Precautions* sections). Usually mild to moderate and transient. The most serious adverse reaction is anaphylactoid shock. Delayed allergoid reactions (hours later up to several days) are rare. *Common:* Headache, nausea. *Uncommon:* Vertigo, dizziness, dysgeusia, paraesthesia, parosmia, increased blood pressure, flushing, dyspnoea, respiratory distress, vomiting, dry mouth, rash, pruritus, back pain, chest pain, injection site reactions, feeling hot, chills fatigue. *Rare*: Tremor, akathisia, bundle branch block, palpitation, maculopapular rash, hyperhidrosis, malaise. Additionally, altered laboratory tests and transient QT prolongation were reported. *Frequency not known:* Hypersensitivity/anaphylactoid reaction (including shock*, hypotension, pharyngolaryngeal oedema, urticaria, face edema, rhinitis, conjunctivitis, abdominal pain, hypoesthesia, sneezing, cough, pallor), tachycardia and restlessness.*Life-threatening and/or fatal cases have been reported post marketing. Prescribers should consult the SmPC in relation to other side effects. **Overdose:** In excessive inadvertent overdose, monitor patient including cardiac monitoring (for possible induction of QT prolongation); remove by haemodialysis. However there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF). *Reporting of suspected adverse reactions:* Adverse events can be reported to DrugSafety.GPV.US@bayer.com. **Date of revision text:** December 2017. **Please note:** For current prescribing information refer to the package insert and/or contact your local Bayer AG.

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