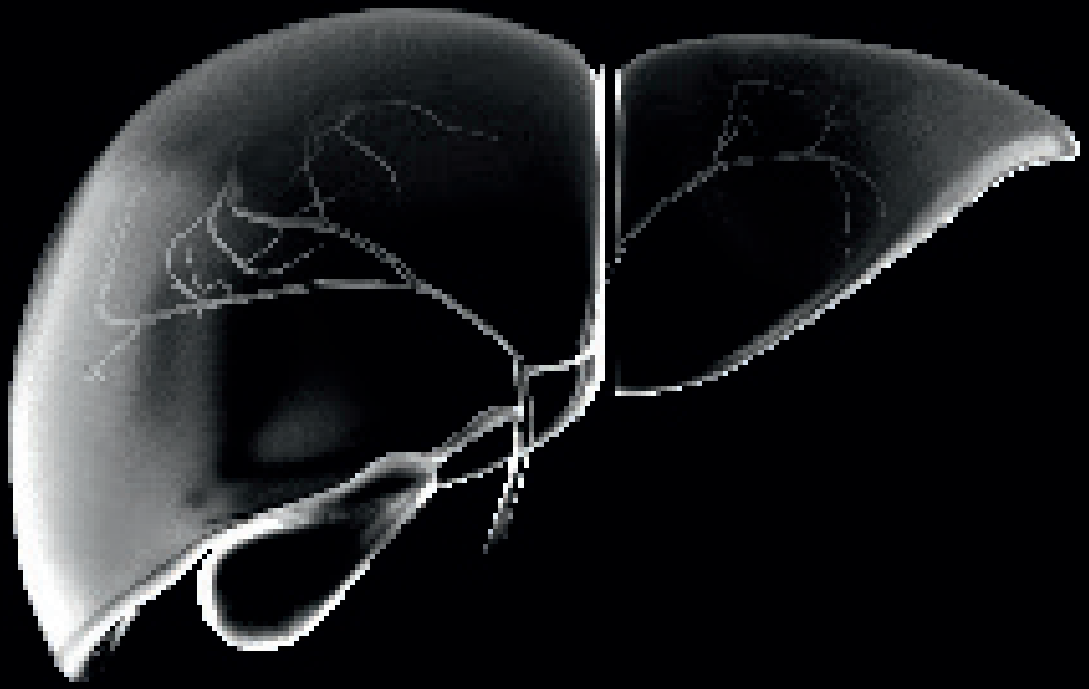
Primovist®
High Accuracy in Liver Lesion Detection[1] and Recommended by Oncologic Guidelines[2–5]



- **Liver specific MR contrast agent with hepatocyte-selective uptake[6]**
- **Higher accuracy for lesion detection, especially of small HCC and metastases **,[7–9]**
- **Improved differentiation between benign and malignant lesions ***, [10–12]**

* compared to CE-CT and unenhanced MRI
** compared to CE-CT

1. Zech CJ, Korpraphong P, Huppertz A, et al. Br J Surg. 2014;101:613–621.
2. Omata M, Cheng AL, Kokudo N, et al. Hepatol Int. 2017;11:317–370.
3. Kudo M, Matsui O, Izumi N, et al. Liver Cancer. 2014;3: 458–68.
4. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC). J Radiol. 2019;20(7):1042–1113.
5. Van Cutsem E, Cervantes A, Adam R, et al. Annals of Oncology 2016;27:1386–1422.
6. Bayer plc UK, SmPC Primovist. (2019). 11 May 2020
7. Bluemke DA, Sahani D, Amendola M, et al. 2005; 237:89–98.
8. Huppertz A, Balzer T, Blakeborough A, et al. Radiology 2004; 230:266–275.
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10. Raman SS, Leary C, Bluemke DA, et al. Comput Assist Tomogr 2010;34:163–72.
11. Chung YE, Kim MJ, Kim YE, et al. PLoS ONE 2013;8(6):e66141.
12. Halavaara J, Breuer J, Ayuso C, et al. J Comput Assist Tomogr 2006;30:345–354.

Clear Direction. From Diagnosis to Care.

Primovist®
Gadoxetic Acid

High Global Burden

- Hepatocellular carcinoma (HCC) is the most common primary liver cancer* and the sixth most common cancer worldwide with 840,000 new cases per year.[13]
- Every year, more than 780,000 patients die from primary liver cancer globally.[13] Primary liver cancer is currently the fourth most common cause of cancer-related death worldwide.[13]
- China accounts for almost half of global HCC numbers.[14]
- In addition, 1.8 million new cases of colorectal cancer (CRC) are reported annually.[13] In a German study ~ 23% of patients develop liver metastases within 3 years after diagnosis.[15]

Estimated primary liver cancer incidence worldwide among male and female population (2018)

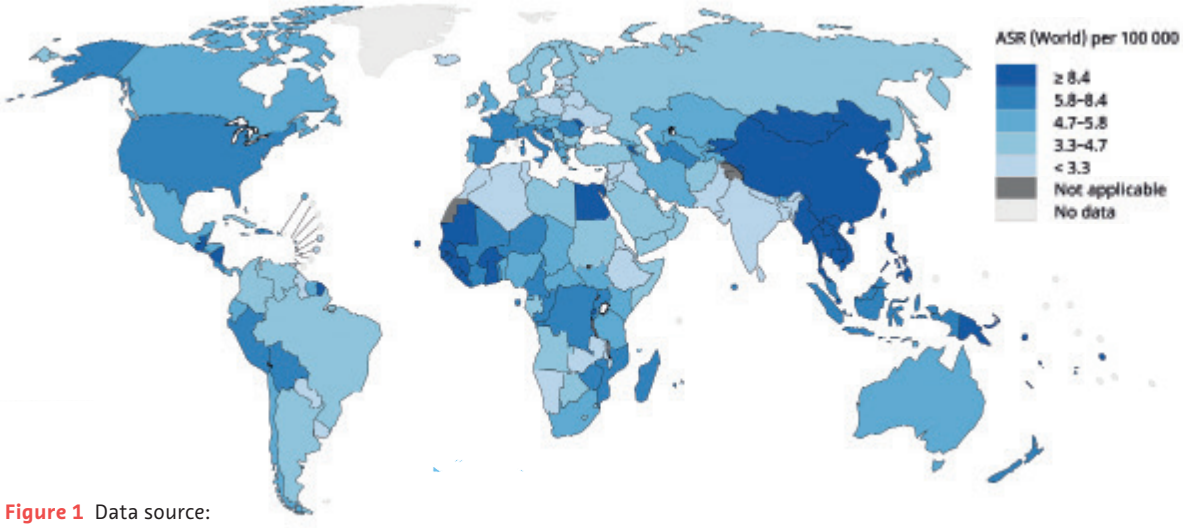


Figure 1 Data source:

* HCC (comprising 75–85% of cases) and intrahepatic cholangiocarcinoma (CC, comprising 10–15% of cases) as well as other rare types.

13. Bray F, Ferlay J, Soerjomataram I, et al. CA Cancer J Clin. 2018; 68:394–424.
14. Chen W, Zheng R, Baade PD, et al. CA Cancer J Clin 2016; 66:115–32.
15. Hackl C, Neumann P, Gerken M, et al. BMC Cancer. 2014;14:810.

Primovist® – First-Line in the Diagnostic Imaging Algorithm of Liver Cancer in Dedicated Countries

International diagnostic guidelines recognize Primovist® as one of the first-line imaging modality options for diagnosis of HCC

- Asian Pacific Association for the Study of the Liver (APASL)*,[2]
- Japan Hepatology*,[3]
- Korean Liver Cancer Study Group*,[4]
- European Association of the Study of the Liver (EASL)[16]
- American Association for the Study of Liver Diseases Group (AASLD/LI-RADS)[17]

The current European Society for Medical Oncology (ESMO) guideline for metastatic CRC recommends CT and MRI for detection of liver lesions and points out that Primovist® is more sensitive in lesions < 10 mm.[5]

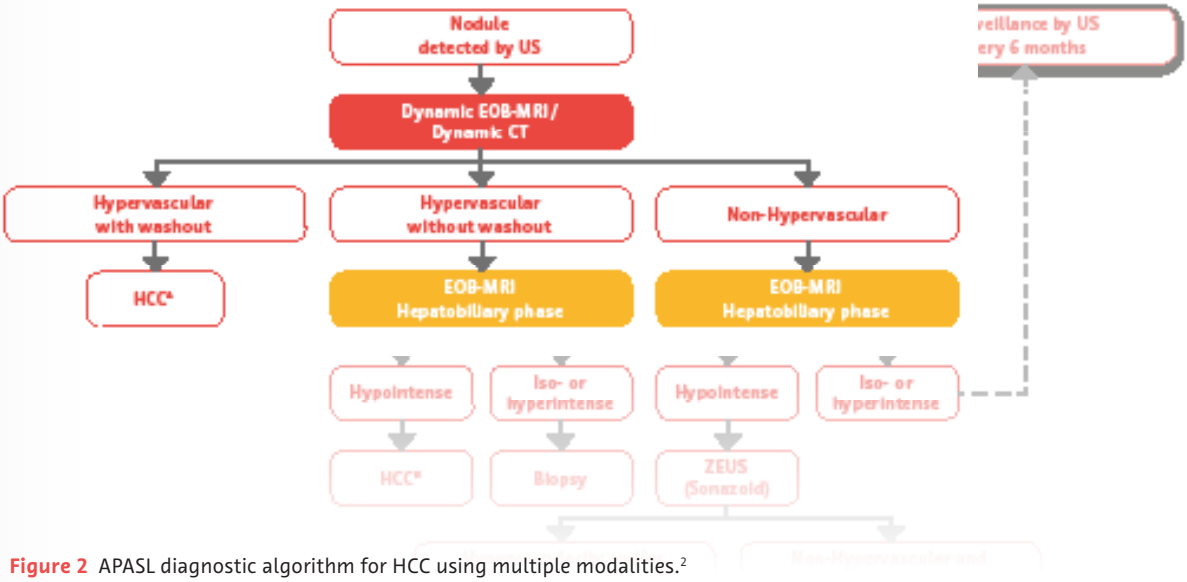


Figure 2 APASL diagnostic algorithm for HCC using multiple modalities.[2]

* APASL, Japanese and Korean Guidelines recognize hepatobiliary phase imaging features in their guidelines.

2. Omata M, Cheng AL, Kokudo N, et al. Hepatol Int. 2017;11:317–370.
3. Kudo M, Matsui O, Izumi N, et al. Liver Cancer. 2014;3: 458–68.
4. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC). J Radiol. 2019;20(7):1042–1113.
5. Van Cutsem E, Cervantes A, Adam R, et al. Annals of Oncology 2016; 27:1386–1422.
16. European Association for the Study of the Liver (EASL). J Hepatol. 2018; 69(1):182 – 236.
17. Marrero JA, Kulik LM, Sirlin CB, et al. Hepatology. 2018; 68(2):723 – 750.

Primovist® – Combined Perfusion and Hepatocyte-Selective MR Imaging

- With its unique EOB group, Primovist® is highly hepatocyte selective with up to 50% being taken up specifically by normal hepatocytes.[18]
- Hepatocyte-selective uptake is depicted in hepatobiliary phase imaging.[6]
- Primovist® enhanced MRI is a combination of vascular perfusion phase and hepatobiliary phase imaging.[6]

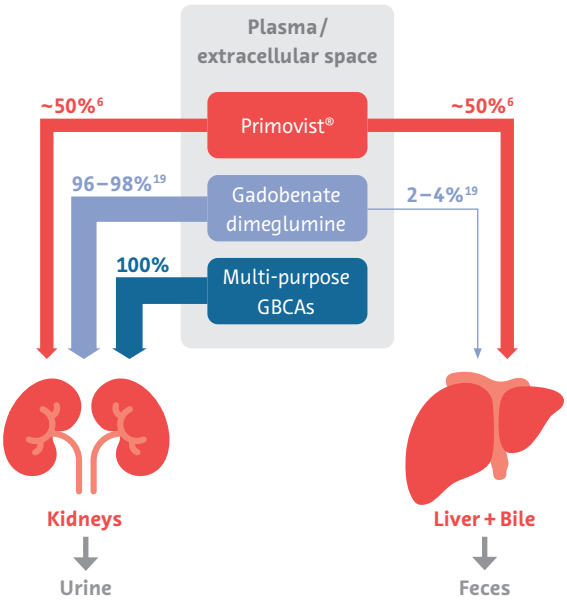
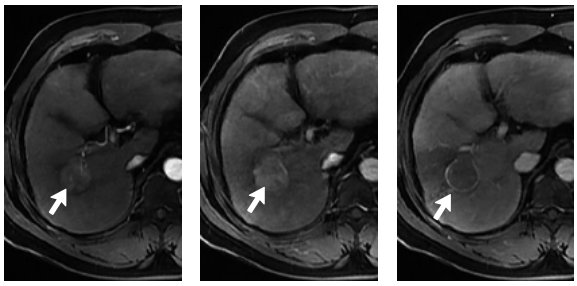


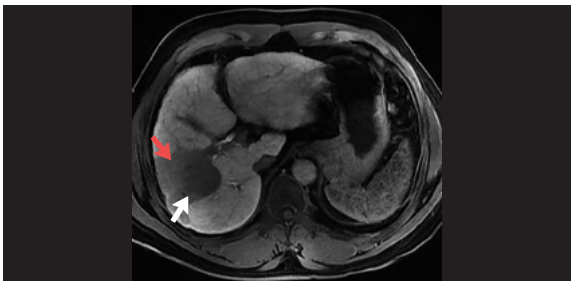
Figure 3 Excretion pathway for Primovist® and other GBCAs.

Vascular perfusion imaging



Early arterial phase | Late arterial phase | Portovenous phase

Hepatocyte-selective imaging



20 min, hepatobiliary phase

Figure 4 Comprehensive liver imaging with Primovist® in a patient with chronic hepatitis B: Typical imaging features of HCC in seg. VI/VII (white arrow) with strong arterial phase hyperenhancement, wash-out and enhancing capsule. Due to the lost function of the de-differentiated hepatocytes to take up Primovist®, the tumor appears hypointense (dark) in the hepatobiliary phase (HBP). In addition, the HBP reveals a geographic area around the tumor (red arrow) that also shows reduced hepatocellular uptake of Primovist® due to concomitant inflammation. Information on reduced cell function can be of high clinical relevance and help guide therapy planning before interventions.

Images courtesy of: Prof. Jin Wang, Third Affiliated Hospital, Sun Yat-Sen University (SYSU) and Liver Disease Hospital, Sun Yat-Sen University (SYSU), Guangzhou, China

6. Bayer plc UK, SmPC Primovist. (2019). 11 May 2020
18. Hamm B, Staks T, Mühler A, et al. Radiology. 1995;195(3):785–792.
19. Bracco UK Limited, SmPC Multihance. (2018). Accessed 15 Jan 2018

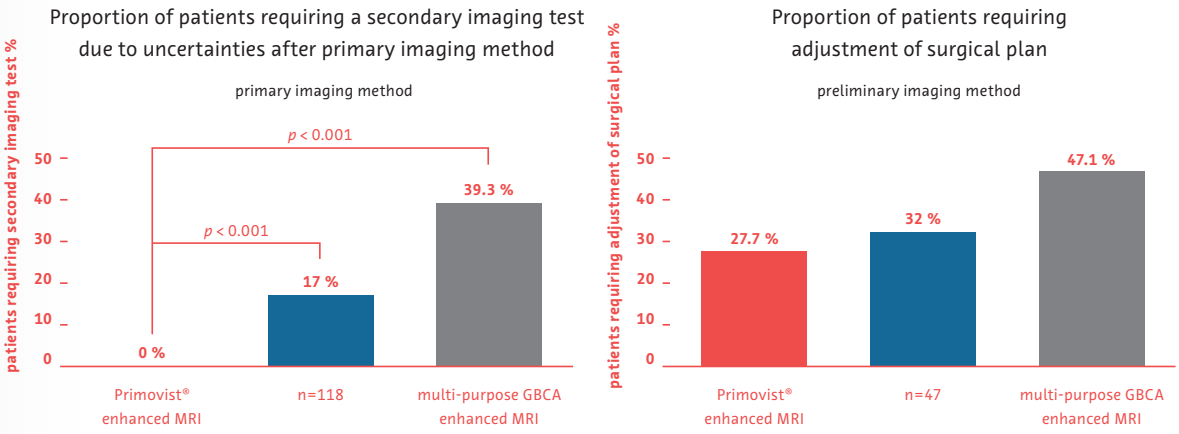
Metastasis and Therapy Planning

Increased Sensitivity of Detection in Liver Metastases

Specificity comparable to CT

- Primovist® enhanced MRI provides a higher detection rate compared to CT or multi-purpose GBCA without an increase in the false positive rate.[1]
- Primovist® enhanced MRI increases confidence in the therapeutic plan.[1]
- Primovist® enhanced MRI provides a confident diagnosis and surgical plan when used as the primary imaging modality and further imaging is not required.[1]
- Primovist® enhanced MRI is superior to CE-CT in patients post chemotherapy in detecting small CRLM with significantly higher sensitivity.[20]

VALUE study: Patients with suspected liver metastases in colorectal cancer (CRC) do not require further imaging for a confident diagnosis and surgical plan using Primovist® enhanced MRI.



n: patients who only received one imaging study and ultimately underwent surgery

Figure 5 Necessity of a second imaging study and adjustment of surgical plan [1]

1. Zech CJ, Korpraphong P, Huppertz A, et al.Br J Surg. 2014;101:613–621.
20. Jhaveri KS, Fischer SE, Hosseini-Nik H, et al. HPB (Oxford). 2017;19:992–1000.

Increased Sensitivity of Detection in HCC and Improved Patient Outcome

- Primovist® has the highest overall sensitivity and PPV, and may be the single optimal modality when diagnosing HCC*.[21]
- Significantly higher sensitivity compared to multi-purpose GBCAs for lesions < 20 mm in diameter.[21]
- Identification of HCC < 20 mm is paramount for clinical management and transplant allocation in patients with solitary HCCs.[21]
- Detection of additional small HCC nodules in 16% of patients, thereby reducing the risk of disease recurrence and decreasing overall mortality.[22]

Improved overall HCC survival when diagnosed with CT and Primovist® enhanced MRI[22]

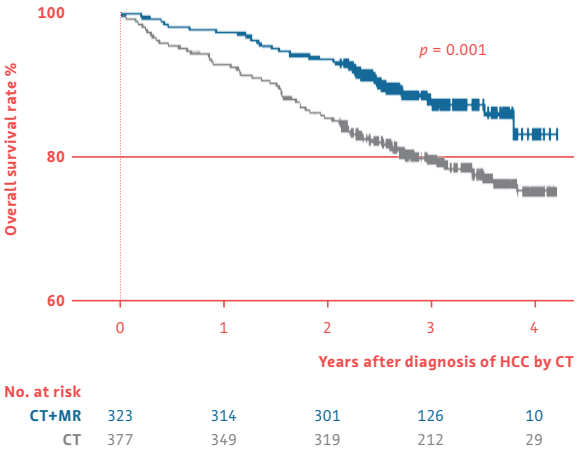


Figure 6 Overall survival of patients evaluated with CT alone or with CT and Primovist® enhanced MRI

* compared to ultrasonography, CT, extracellular contrast-enhanced MRI

21. Hanna RF, Miloushev VZ, Tang A. Abdom Radiol (NY). 2016;41:71–90.
22. Kim HD, Lim YS, Han S, et al. Gastroenterology. 2015;148: 1371–1382.

Reliable Assessment of Focal Lesion Characterization

- Primovist® enhanced MRI can characterize focal lesions more accurately than CT.[12,23]
- The enhancement in arterial and portal venous phases is comparable to CT.[24]
- In the hepatobiliary phase, the enhancement of focal lesions is hepatocyte-selective. This gives valuable information for lesion characterization.[24]

Comparison of the percentage of correctly characterized lesions*

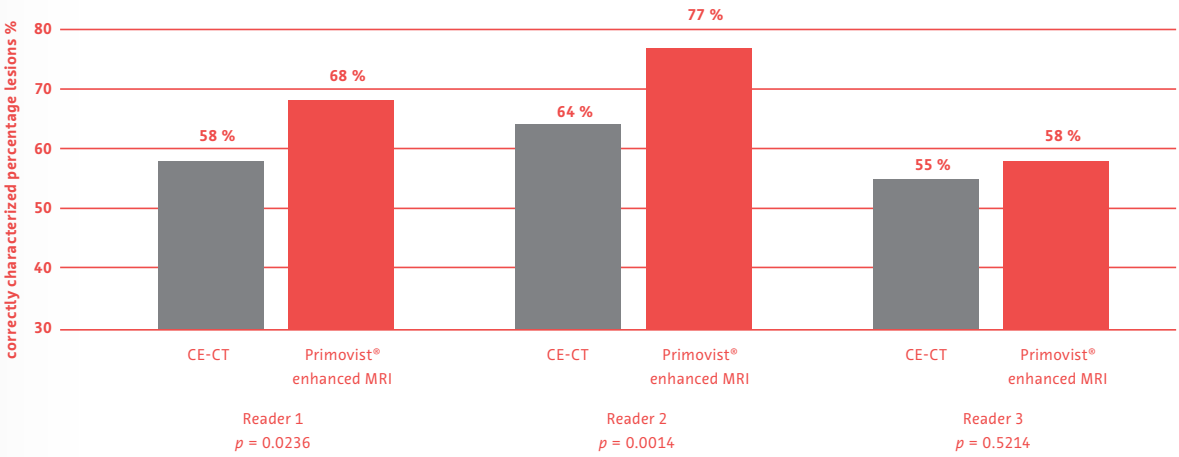
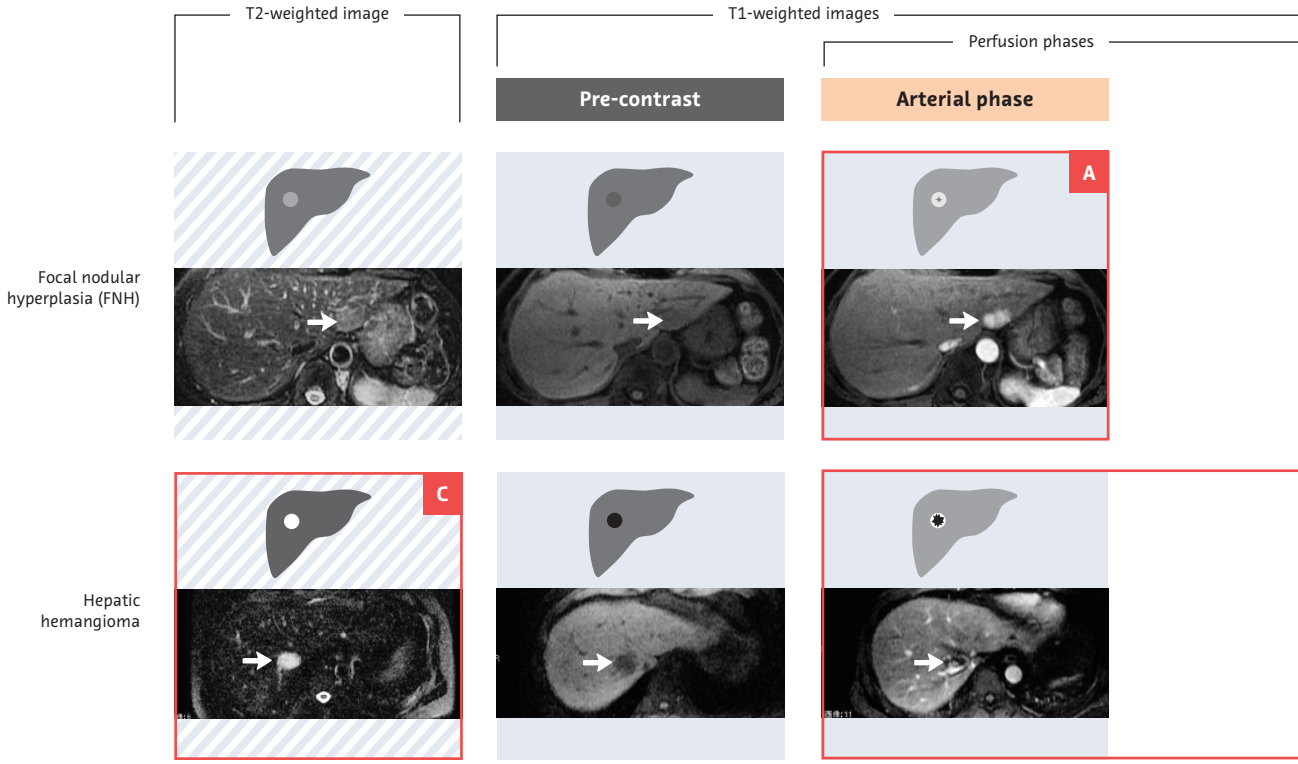


Figure 7 Correctly characterized focal liver lesions for three radiologists highly experienced in abdominal MRI [12]

* Mix of 147 benign and 105 malignant lesions. 105 malignant and 147 benign lesions (57 metastases, 41 HCC), 7 CCC, 57 hemangiomas, 59 FNH, 17 liver cysts, 2 adenomas, 6 hydatid cysts, 4 regenerative nodules, 1 focal fat, 1 abscess).

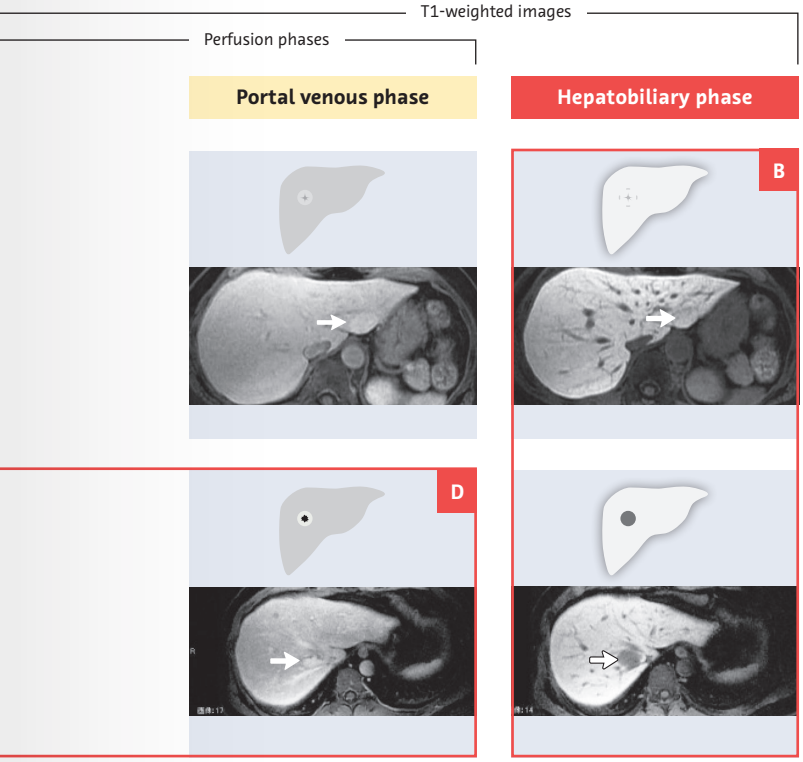
12. Halavaara J, Breuer J, Ayuso C, et al. J Comput Assist Tomogr 2006;30:345–354.
23. Purysko AS, Remer EM, Veniero JC. Clin Radiol 2011;66:673–684.
24. Huppertz A, Haraida S, Kraus A, et al. Radiology 2005;234:468–478.

Improved[12] characterization of benign focal lesions with Primovist®



12. Halavaara J, Breuer J, Ayuso C, et al. J Comput Assist Tomogr 2006;30:345–354.

Characterization of benign focal liver lesions with Primovist® enhanced MRI: The diagnosis is based on the evaluation of signal characteristics of unenhanced T2- and T1-weighted imaging, perfusion imaging (arterial, portal venous phase) and the hepatobiliary phase provided by Primovist®. As demonstrated below, this additional phase provides essential information for lesion characterization.



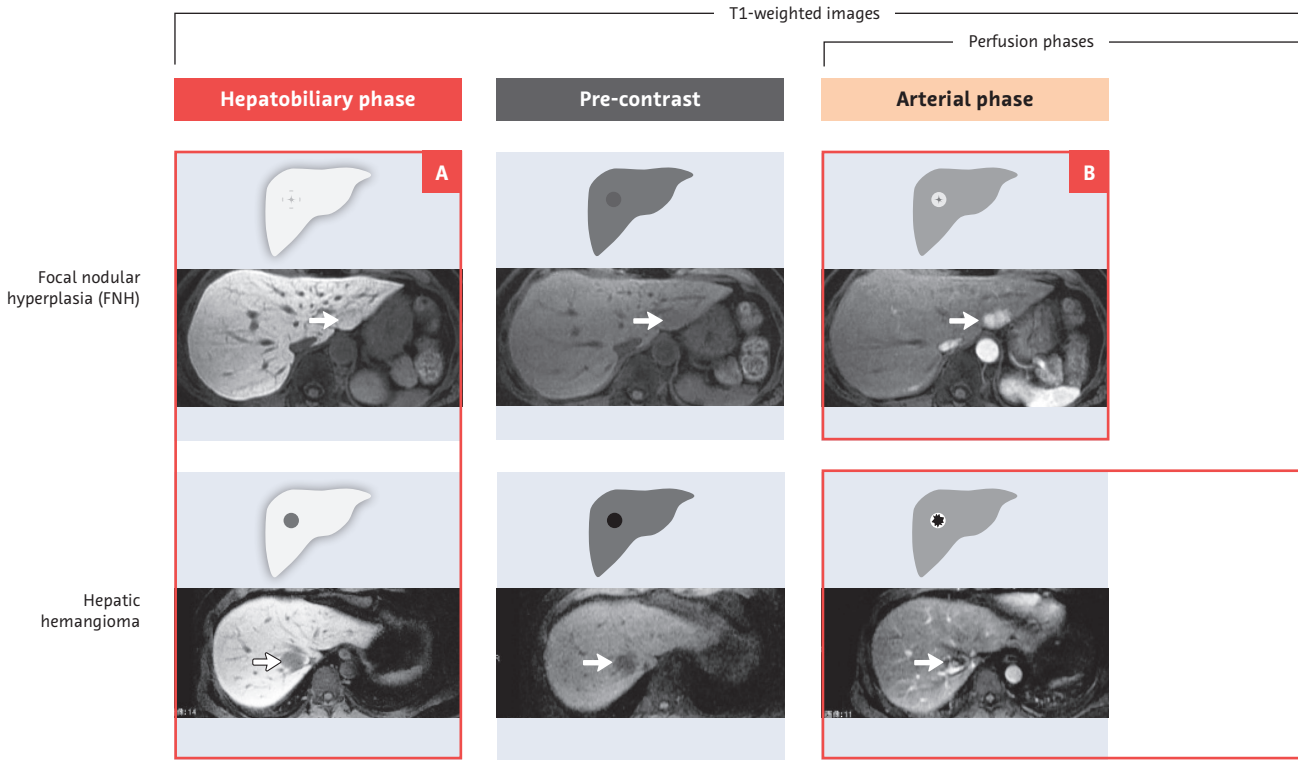
Characteristic Signal Behavior of Hepatic Lesions in Primovist® enhanced MRI

Figure 8 FNH **(A)** shows central scar and fibrous septum, clearly depicted in the arterial phase. Hemangioma **(C)** exhibits very high signal intensity in T2w. Hemangioma **(D)** shows a characteristic centripedal (inward) enhancement and **(B)** no hepatocyte selective uptake, whereas hepatocytic lesion FNH reveals hepatocyte selective uptake.

Signal patterns of actual lesions do not always show the same results as indicated in this material (one example shown for each type of lesion). Dashed lines in pictograms indicate the presence of a lesion and do not indicate capsules.

Images courtesy of Katsuyoshi Ito; MD, PhD (Department of Radiology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan)

Improved[12] characterization of benign focal lesions with Primovist®



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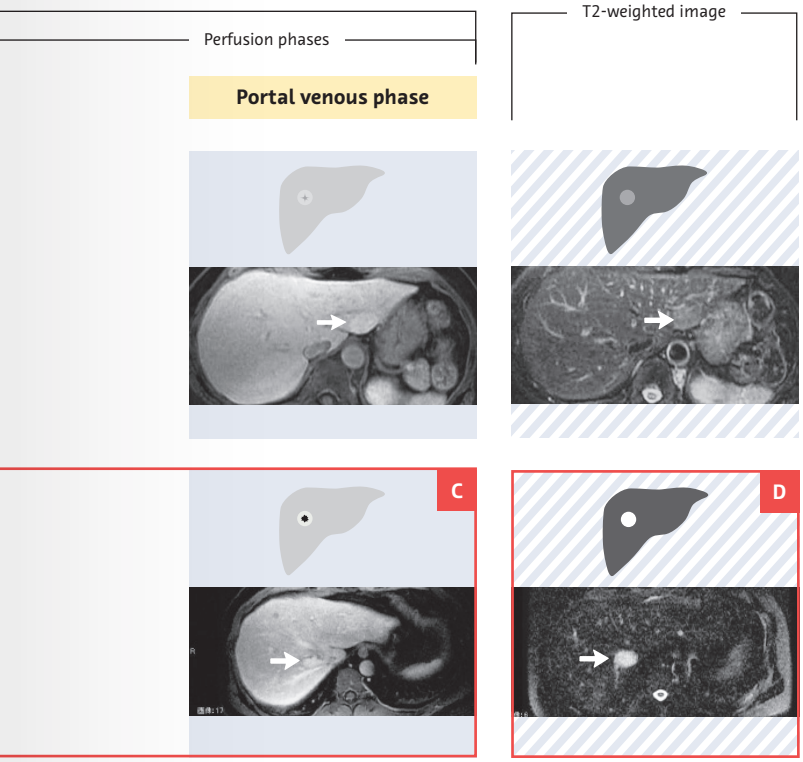

Characteristic Signal Behavior of Hepatic Lesions in Primovist® enhanced MRI

Figure 8 FNH is a hepatocytic lesion and reveals hepatocyte selective uptake **(A)**, whereas hemangioma cannot show uptake as it does not contain any functioning hepatocytes. FNH shows a central scar and fibrous septum, clearly depicted in the arterial phase **(B)**. Hemangioma exhibits a characteristic centripedal (inward) enhancement **(C)** and very high signal intensity in T2w **(D)**.

Signal patterns of actual lesions do not always show the same results as indicated in this material (one example shown for each type of lesion). Dashed lines in pictograms indicate the presence of a lesion and do not indicate capsules.

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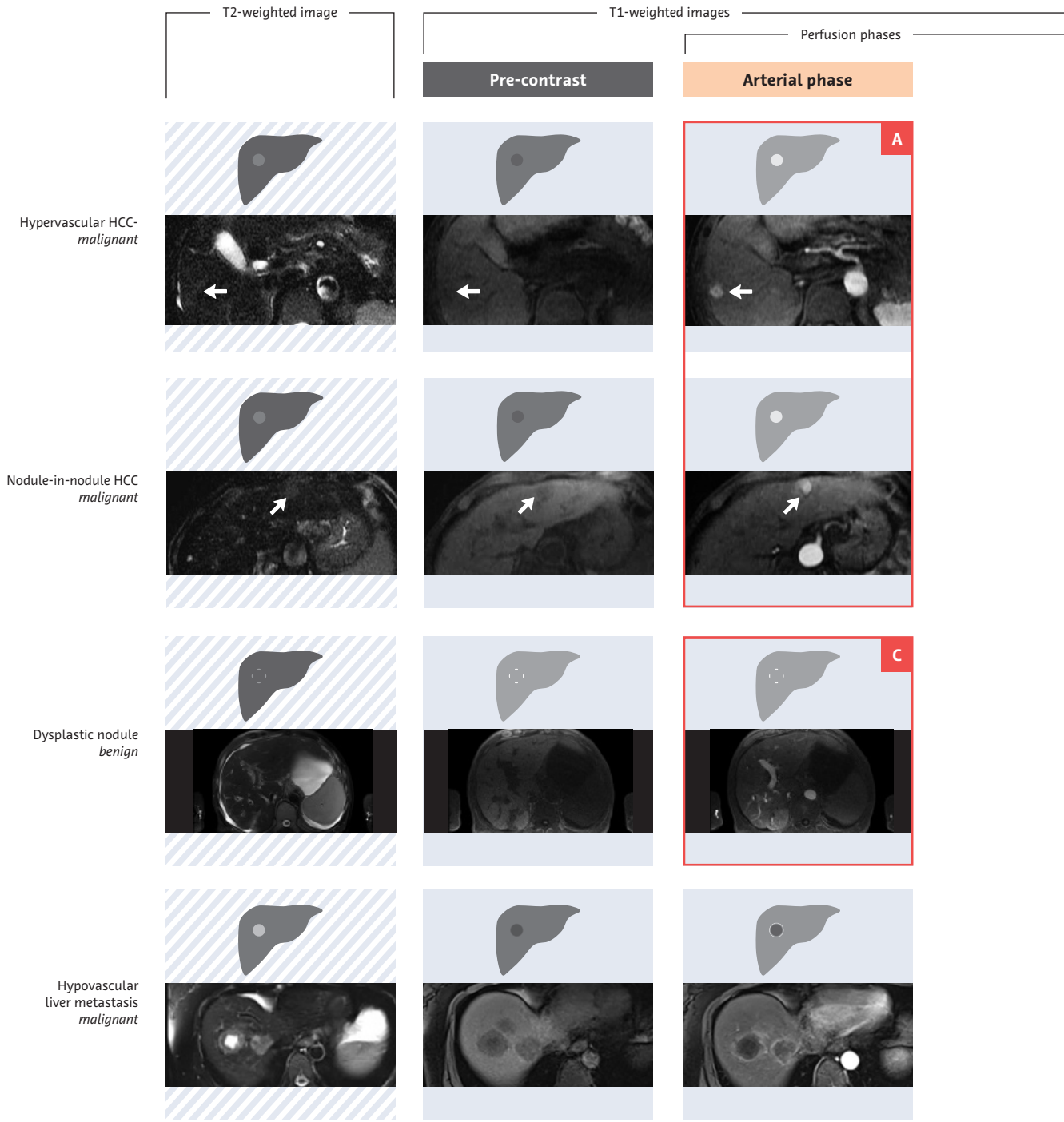
Primovist® improves the differentiation between benign and malignant focal lesions



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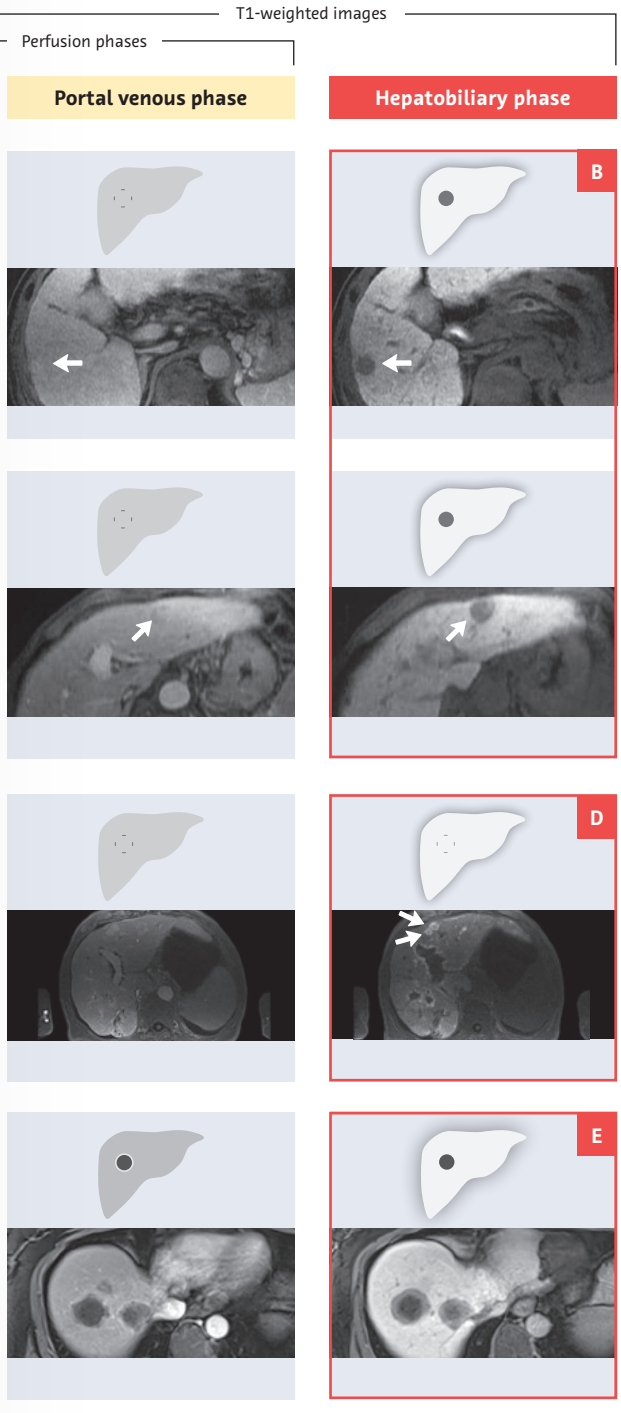

Characteristic Signal Behavior of Hepatic Lesions in Primovist® enhanced MRI

Figure 8 Classic hypervascular HCC, nodule-in-nodule HCC, dysplastic nodules (DN) and hypovascular liver metastasis. The HCCs **(B)** reveal no hepatocyte selective uptake (dark in the hepatobiliary phase), whereas the DNs **(D)** show uptake (arrows – higher signal intensity than the liver parenchyma). The HCCs are hypervascular **(A)** during the arterial phase, while the DNs are not **(C)**. The metastasis shows no uptake in the hepatobiliary phase **(E)**.

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Hypervascular HCC, Nodule-in-nodule HCC:
Images courtesy of Katsuyoshi Ito; MD, PhD (Department of Radiology, Yamaguchi University Graduate School of Medicine, Yamaguchi, Japan)

Dysplastic nodule, liver metastasis:
Images courtesy of Alexander Huppertz; MD, PhD (Klinik-Gruppe Ernst von Bergmann, Potsdam, Germany)

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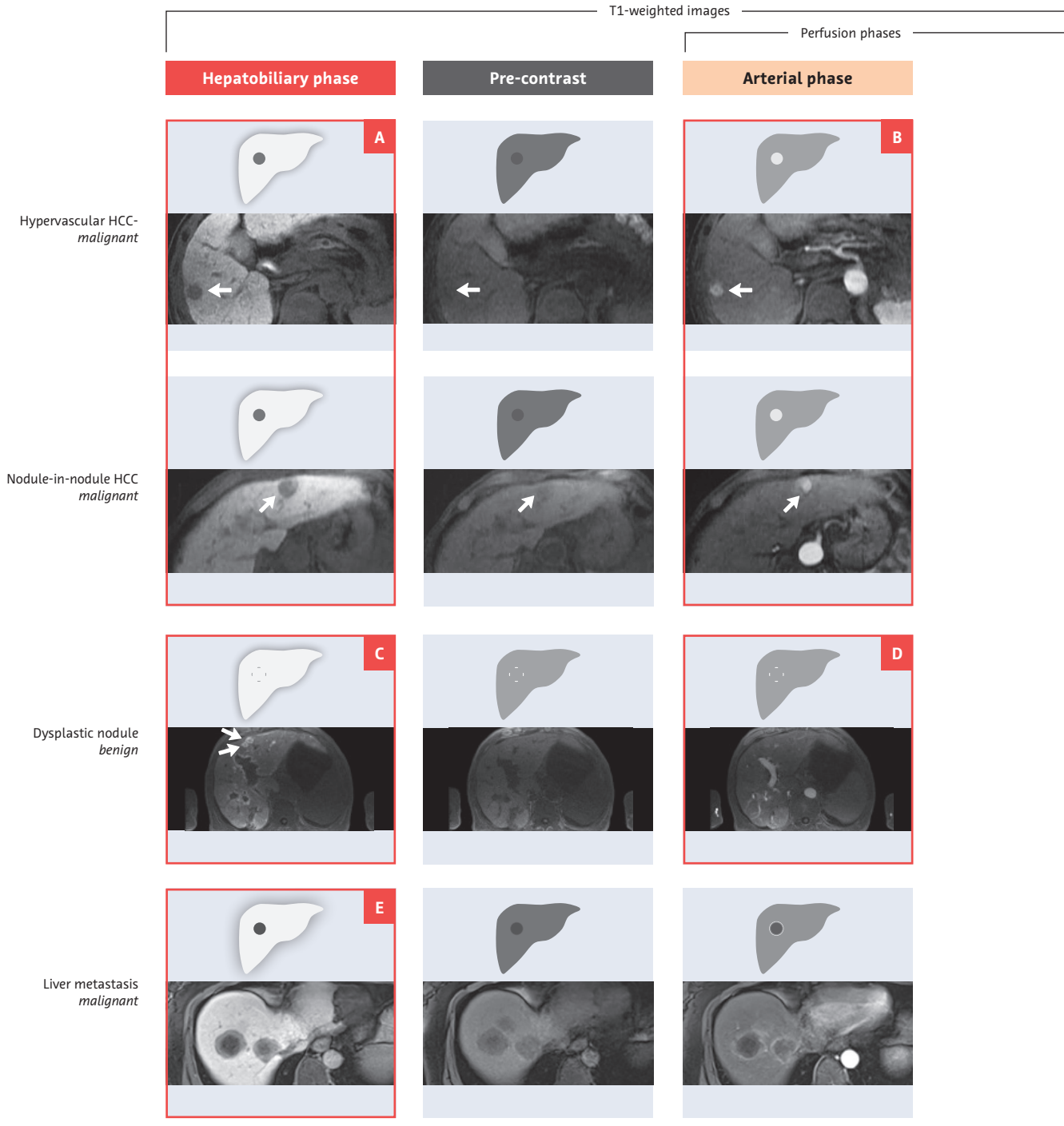

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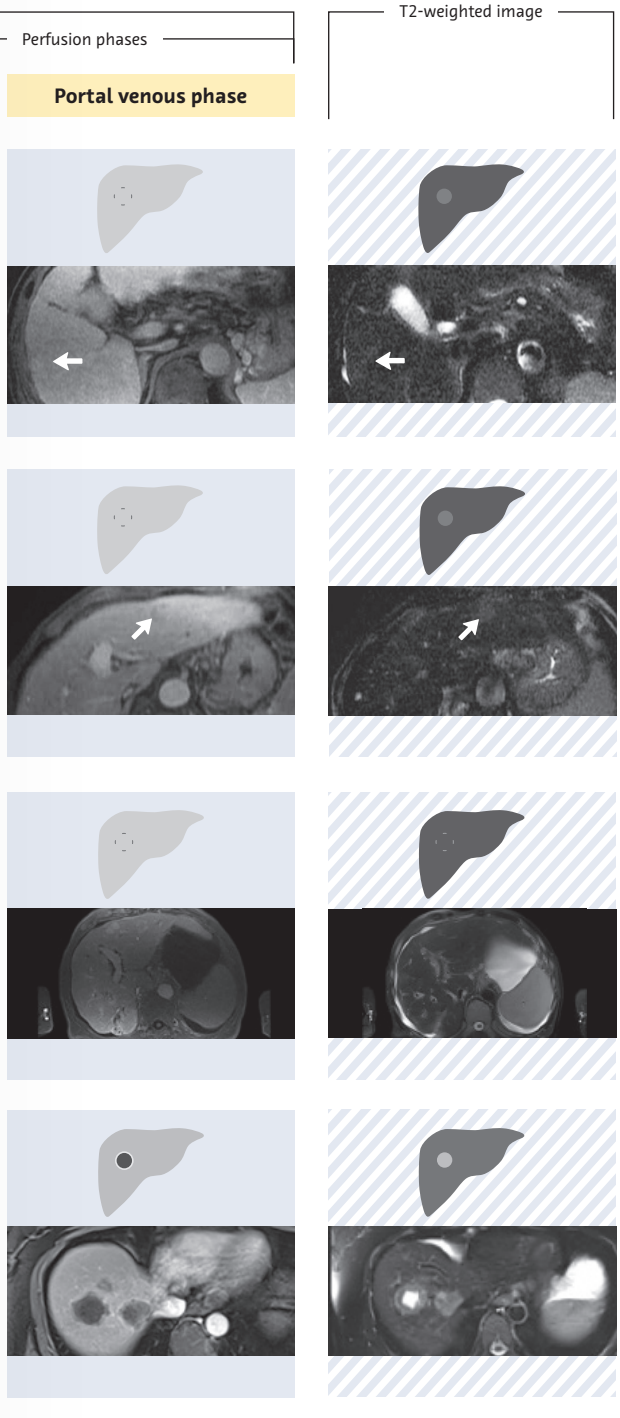

Characteristic Signal Behavior of Hepatic Lesions in Primovist® enhanced MRI

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Dysplastic nodule, liver metastasis:
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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;101:613–621.

2 **Omata M, Cheng AL, Kokudo N, et al.** Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11:317–370.

3 **Kudo M, Matsui O, Izumi N, et al.** JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014;3: 458–68.

4 **Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC).** 2018 Korean Liver Cancer Association–National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma Korean J Radiol. 2019;20(7):1042–1113.

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6 **Bayer plc UK, SmPC Primovist. (2019).** https://www.medicines.org.uk/emc/product/3904/smpc Accessed 11 May 2020

7 **Bluemke DA, Sahani D, Amendola M, et al.** Efficacy and safety of MR imaging with liver-specific contrast agent: U.S. multicenter phase III study. Radiology 2005; 237:89–98.

8 **Huppertz A, Balzer T, Blakeborough 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.

9 **Asato N, Tsurusaki M, Sofue K, et al.** Comparison of gadoxetic acid-enhanced dynamic MR imaging and contrast-enhanced computed tomography for preoperative evaluation of colorectal liver metastases. Jpn J Radiol 2017;35:197–205.

10 **Raman SS, Leary C, Bluemke DA, et al.** Improved characterization of focal liver lesions with liver-specific gadoxetic acid disodium-enhanced magnetic resonance imaging: a multicenter phase 3 clinical trial. J Comput Assist Tomogr 2010;34:163–72.

11 **Chung YE, Kim MJ, Kim YE, et al.** Characterization of incidental liver lesions: comparison of multidetector CT versus Gd-EOB-DTPA-enhanced MR imaging. PLoS ONE 2013;8(6):e66141.

12 **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.

13 **Bray F, Ferlay J, Soerjomataram I, et al.** Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

14 **Chen W, Zheng R, Baade PD, et al.** Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–32.

15 **Hackl C, Neumann P, Gerken M, et al.** Treatment of colorectal liver metastases in Germany: a ten-year population-based analysis of 5772 cases of primary colorectal adenocarcinoma. BMC Cancer. 2014;14:810.

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17 **Marrero JA, Kulik LM, Sirlin CB, et al.** Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723–750.

18 **Hamm B, Staks T, Mühler A, et al.** Phase I clinical evaluation of Gd-EOB-DTPA as a hepatobiliary MR contrast agent: safety, pharmacokinetics, and MR imaging. Radiology. 1995;195(3):785–792.

19 **Bracco UK Limited, SmPC Multihance. (2018).** https://www.medicines.org.uk/emc/medicine/6132 Accessed 15 Jan 2018

20 **Jhaveri KS, Fischer SE, Hosseini-Nik H, et al.** Prospective comparison of gadoxetic acid-enhanced liver MRI and contrast-enhanced CT with histopathological correlation for preoperative detection of colorectal liver metastases following chemotherapy and potential impact on surgical plan. HPB (Oxford). 2017;19:992–1000.

21 **Hanna RF, Miloushev VZ, Tang A.** Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. Abdom Radiol (NY). 2016;41:71–90.

22 **Kim HD, Lim YS, Han S, et al.** Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. Gastroenterology. 2015;148:1371–1382.

23 **Purysko AS, Remer EM, Veniero JC.** Focal liver lesion detection and characterization with GD-EOB-DTPA. Clin Radiol 2011;66:673–684.

24 **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.

Abbreviations

APASL	Asian Pacific Association for the Study of the Liver
CE-CT	Contrast-enhanced computed tomography
CT	Computed tomography
CRC	Colorectal cancer
CRLM	Colorectal liver metastases
DN	Dysplastic nodule
EOB	Ethoxybenzyl
ESMO	European Society for Medical Oncology
FNH	Focal nodular hyperplasia
GBCA	Gadolinium-based contrast agent
Gd	Gadolinium
HCC	Hepatocellular carcinoma
MR	Magnetic resonance
MRI	Magnetic resonance imaging
PPV	Positive predictive value
T	Tesla

Abbreviated Prescribing Information

Contents 1 ml solution for injection contains 181.43 mg (0.25 mmol) gadoxetic acid, disodium (Gd-EOB-DTPA) as active ingredient. **Indications** Primovist is a gadolinium-based contrast agent for T1-weighted magnetic resonance imaging (MRI) of the liver. In dynamic and delayed imaging, Primovist improves the detection of focal hepatic lesions and provides additional information regarding characterization and classification of focal liver lesions, thus increasing diagnostic confidence. It is for diagnostic use by intravenous administration only. Dosage Primovist is a ready-to-use aqueous solution to be administered undiluted as an intravenous bolus injection at a flow rate of about 2 ml/sec through a large-bore needle or indwelling catheter (18-20 gauge is recommended). After the injection of the contrast medium the intravenous cannula should be flushed using physiological saline solution. Recommended dose of Primovist: Adults: 0.1 ml/kg body weight Primovist (equivalent to 25µmol/kg body weight) Imaging: After bolus injection of Primovist, dynamic imaging during arterial, portovenous, and equilibrium phases utilizes the different temporal enhancement pattern of different liver lesion types to obtain information about their classification (benign/malignant) and the specific characterization. It further improves visualization of hypervascular liver lesions. The delayed (hepatocyte) phase starts at about 10 minutes post injection (in confirmatory studies most of the data were obtained at 20 minutes post injection) with an imaging window lasting at least 120 minutes. The imaging window is reduced to 60 minutes in patients requiring hemodialysis and in patients with elevated bilirubin values (> 3 mg/dl). The enhancement of liver parenchyma during the hepatocyte phase assists in the identification of the number, segmental distribution, visualization, and delineation of liver lesions, thus improving lesion detection. The different enhancement/washout patterns of liver lesions contribute to the information from the dynamic phase. Hepatic excretion of Primovist results in enhancement of biliary structures. Newborns, infants, children and adolescents: No clinical experience is yet available for patients under 18 years of age. **Administration** The usual safety rules for magnetic resonance imaging must be observed, e.g. exclusion of cardiac pacemakers and ferromagnetic implants. The patient should refrain from eating for two hours prior to examination to reduce the risk of aspiration. 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. **Contraindications** Hypersensitivity to the active substance or to any of the excipients. **Special Precautions • Hypersensitivity** As with other intravenous contrast agents, Primovist can be associated with anaphylactoid/hypersensitivity or other idiosynchratic reactions characterized by cardiovascular, respiratory and cutaneous manifestations, and ranging to severe reactions including shock. Patients with a history of allergic/allergoid reactions to any allergen as well as patients with bronchial asthma might be at higher risk for severe reactions. Most of these reactions occur within half an hour of administration. However, in rare cases delayed reactions (after hours up to several days) may occur. As with other contrast enhanced diagnostic procedures, post-procedure observation of the patient is recommended. Medication for the treatment of hypersensitivity reactions as well as preparedness for institution of emergency measures are necessary. The risk of hypersensitivity reactions is higher in case of: - previous reaction to contrast media - history of bronchial asthma - history of allergic disorders. Patients taking beta blockers who experience such reactions may be resistant to treatment with beta agonists. • **Cardiovascular disease** Caution should be exercised when Primovist is administered to patients with severe cardiovascular problems because only limited data are available so far. • **Impaired renal function** There have been reports of nephrogenic systemic fibrosis (NSF) associated with the use of some gadolinium-containing contrast agents in patients with - acute or chronic severe renal impairment (GFR < 30 ml/min/1.73m2) and - acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. Although the systemic body exposure with gadolinium is low based on the diagnostic dosage of Primovist as well as its dual elimination pathways (renal and hepatobiliary), there is a possibility that NSF may occur with Primovist. Therefore, Primovist should only be used in these patients after careful risk/benefit assessment. Prior to administration of Primovist all patients should be screened for renal dysfunction by obtaining a history and/or laboratory tests. Primovist can be removed from the body by hemodialysis. For patients already receiving hemodialysis at the time of Primovist administration, prompt initiation of hemodialysis following the administration of Primovist should be considered, in order to enhance the contrast agent's elimination. • **Local intolerance** Intramuscular administration should be strictly avoided, because it may cause local intolerance reactions including focal necrosis. **Adverse Drug Reactions** Most of the undesirable effects were of mild to moderate intensity. ***Uncommon*** **Nervous system disorders** headache, dizziness, dysgeusia, paresthesia, parosmia **Vascular disorders** Blood pressure increased, flushing **Respiratory, thoracic and mediastinal disorders** respiratory disorders (dyspnea, respiratory distress) **Gastrointestinal disorders** vomiting, nausea **Skin and subcutaneous tissue disorders** rash, pruritus **General disorders and administration site conditions** chest pain, injection site reactions, feeling hot ***Rare*** **Nervous system disorders** vertigo, akathisia, tremor **Cardiac disorders** bundle branch block, palpitation **Gastrointestinal disorders** dry mouth, oral discomfort, salivary hypersecretion **Skin and subcutaneous tissue disorders** maculopapular rash, hyperhidrosis Musculoskeletal and connective tissue disorders back pain **General disorders and administration site conditions** chills, discomfort, fatigue, malaise, feeling abnormal. In very rare cases anaphylactoid reactions ranging to shock may occur. Slightly elevated serum iron and serum bilirubin values have been observed in less than 1% of patients after administration of Primovist. ***Postmarketing spontaneous reporting*** Tachycardia and restlessness have been reported in rare cases. **Drug Interactions** • Compounds belonging to the class of rifamycins block the hepatic uptake of Gd-EOB-DTPA thus reducing the hepatic contrast effect. • Elevated levels of bilirubin or ferritin can reduce the hepatic contrast effect of Primovist. • Serum iron determination using complexometric methods may result in false values for up to 24 hours after the examination with Primovist. For detailed information, please refer to full prescribing information. Effective date: May 2014

The patient data that appears in this document is actual health information but all personal identifiers have been removed or otherwise anonymized. No personally identifiable information is shown.

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