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REVIEW ARTICLE

LIVER METASTASES

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Liver metastases are a very common site of distant metastases. Detection and accurate characterization of liver metastases is of importance to guide therapy. A variety of imaging modalities such as US (including contrast agents), MDCT, MRI with liver –specific contrast agents and PET/CT are available for this purpose. This review presents imaging techniques and summarizes the current knowledge, how the different imaging modalities should be used.

Key-word: Liver neoplasms, metastases.

Liver metastases are very common in oncologic patients. Early detection and accurate characterization of liver metastases is of great importance in cancer patients regarding prognosis and further patient management. In general, the presence of liver metastases indicates non-resectability of the primary tumor for oncologic reasons and chemotherapy is the treatment of choice. However, in colorectal cancer patients resection of liver metastases has been shown to improve patient survival (1). In patients with colorectal cancer with metastatic spread confined to the liver, liver resection offers the only chance of cure. The 5-year survival rate following surgery is 25-40% in comparison to 0-10% in patients treated non-surgically (1-3). However, only a minority of patients (up to 15%) with colorectal liver metastases are amenable for resection due to the number, location and size of liver metastases or the presence of extrahepatic disease. Thus, accurate staging by imaging plays a crucial role to identify patients, who may benefit from resection.

In patients with suspected liver metastases undergoing chemotherapy imaging is also crucial. It is essential to assess therapy response accurately and reproducibly. Therefore a radiologic examination in patients with suspected liver metastases should provide high sensitivity and specificity, should be non-invasive and allow detection of extrahepatic disease (4).

This review will discuss the appearance of liver metastases at various imaging modalities and their

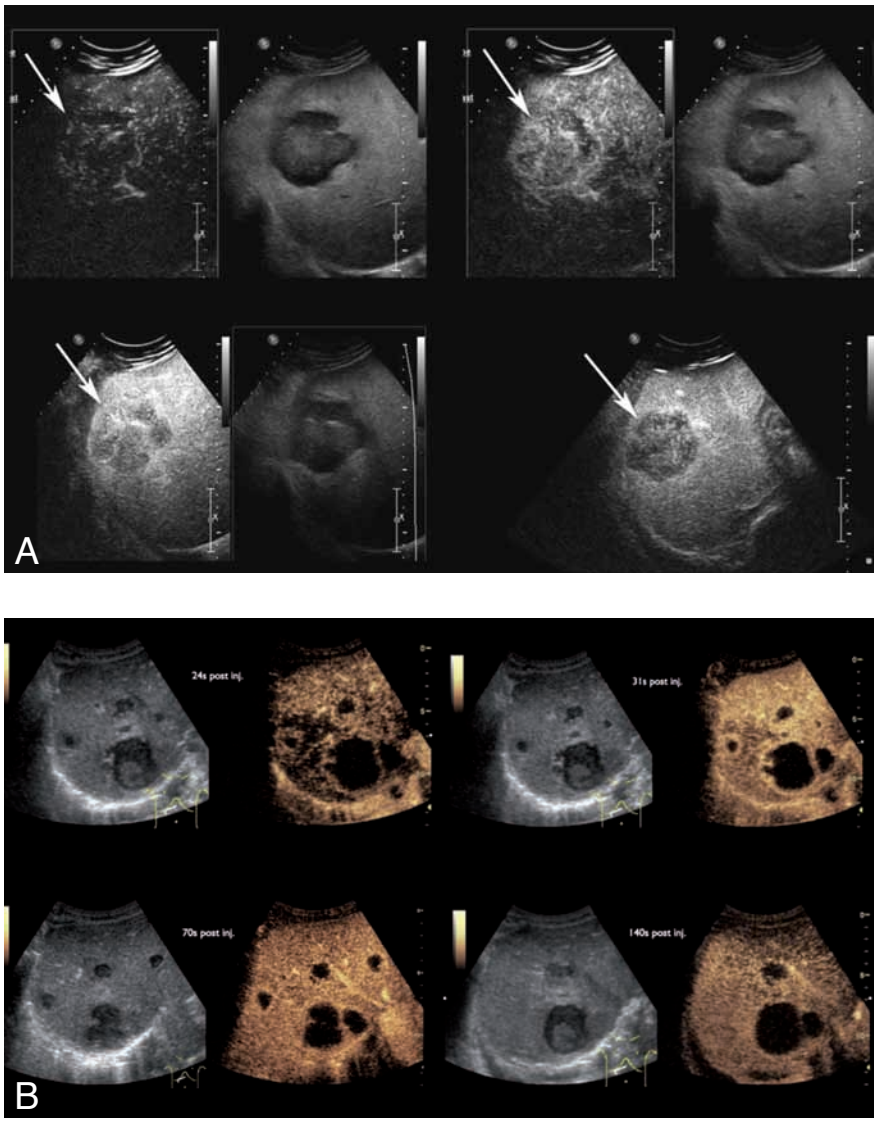

Fig. 1. — Contrast-enhanced ultrasound for characterization of liver lesions. A. Hypoechoic adenocarcinoma metastasis shows rapid enhacement after contrast agent administration with washout (arrows) in the liver-specific phase. B. Necrotic metastases from small cell lung cancer appear very hypoechoic. After contrast agent administration there is only minimal rim enhancement and no enhancement of the necrotic center.

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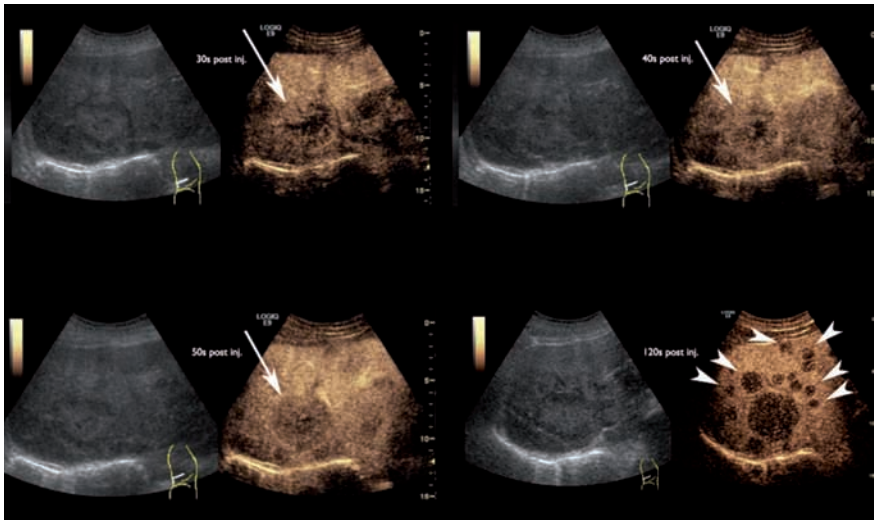


Fig. 2. — Ultrasound contrast agent for characterization and detection. Fundamental phase image shows almost isoechoic adenocarcinoma metasis with hypoechoic rim. After contrast agent there is rim enhancement of the lesion with wash-out (arrows). In the liver-specific phase, multiple additional lesions are visualized (arrowheads).

appropriate use of imaging in patients with liver metastases.

Sonography

Real-time ultrasound provides a rapid and non-invasive method to examine patients with suspected right upper quadrant disease. Hepatic metastases may be hypoechogenic, hyperechogenic, isoechogenic, even anechogenic (cystic) or of mixed echogenicity (5). The hypoechoic pattern is most common and it may be observed in any type of primary tumor. Sensitivity of grey scale US for detection of liver metastases is quite low and may even drop to 20% for lesions smaller than 1 cm (6, 7). Therefore several technical efforts have been made to increase the diagnostic power of sonography. Tissue harmonic imag-

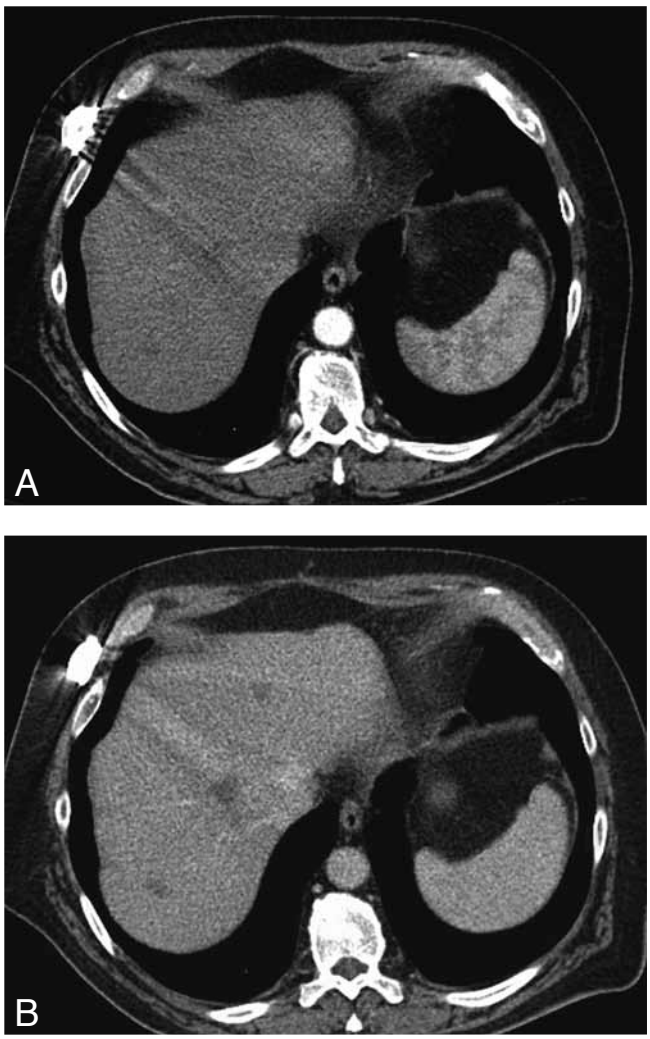


Fig. 3. — Biphasic contrast-enhanced CT scan in a patient with colo-rectal liver metastases. A. Arterial-phase scan does not show liver metastases. Artifacts are due to arterial port. B. The venous-phase image clearly demonstrates three hypoattenuating metastases.

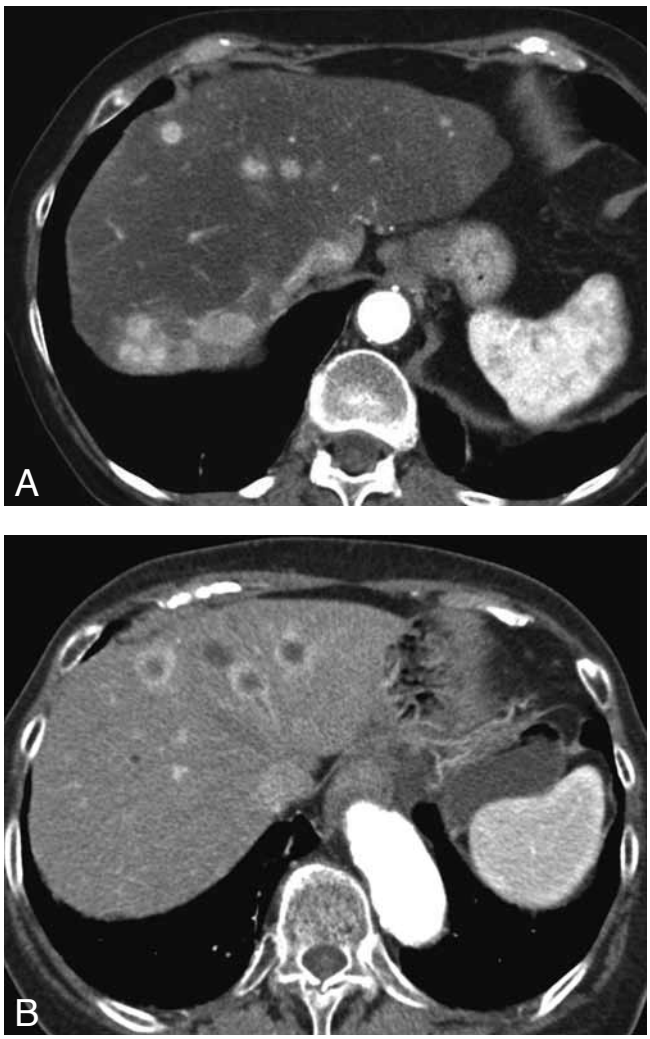


Fig. 4. — Typical enhancement features of liver metastases. A. Metastases of neuroendocrine cancer („carcinoid") are hypervascular in arterial phase. B. Adenocarcinoma metastases (e.g., of colo-rectum, pancreas, stomach, esophagus) are typically hypodense with rim enhancement.

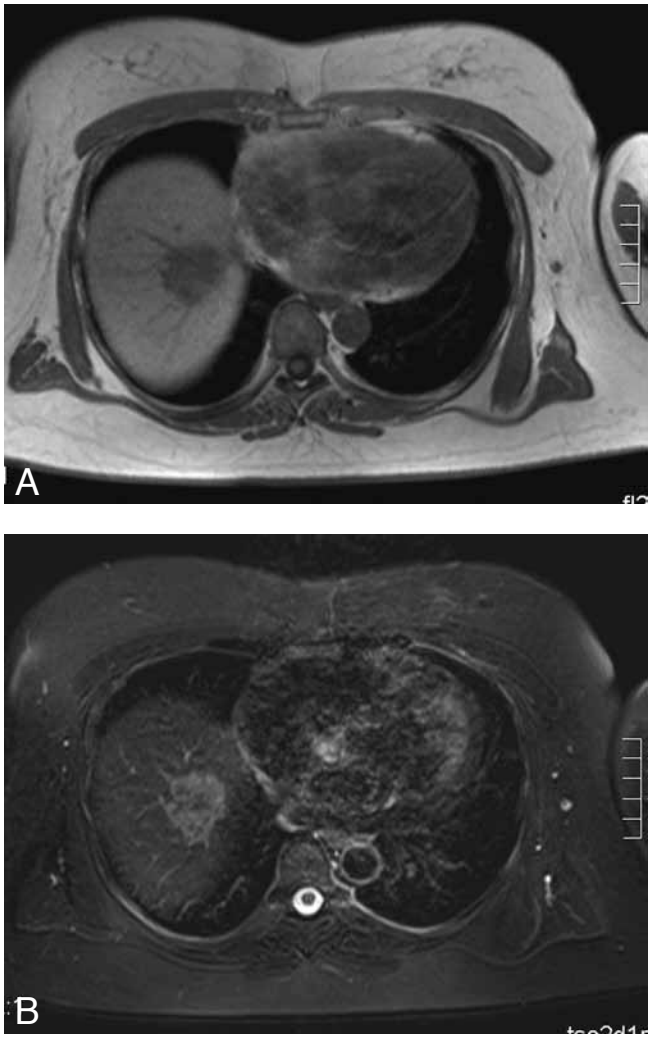


Fig. 5. — Unenhanced MRI of colon cancer metastasis. A. Lesion is hypointense on the T1-w GRE image. B. Metastasis shows moderate hyperintensity on the fat-suppressed T2w TSE image. C. The diffusion-weighted image with a high b-value of 600 mm²/s demonstrates typical high signal of metastasis due to restricted diffusion in the lesion.

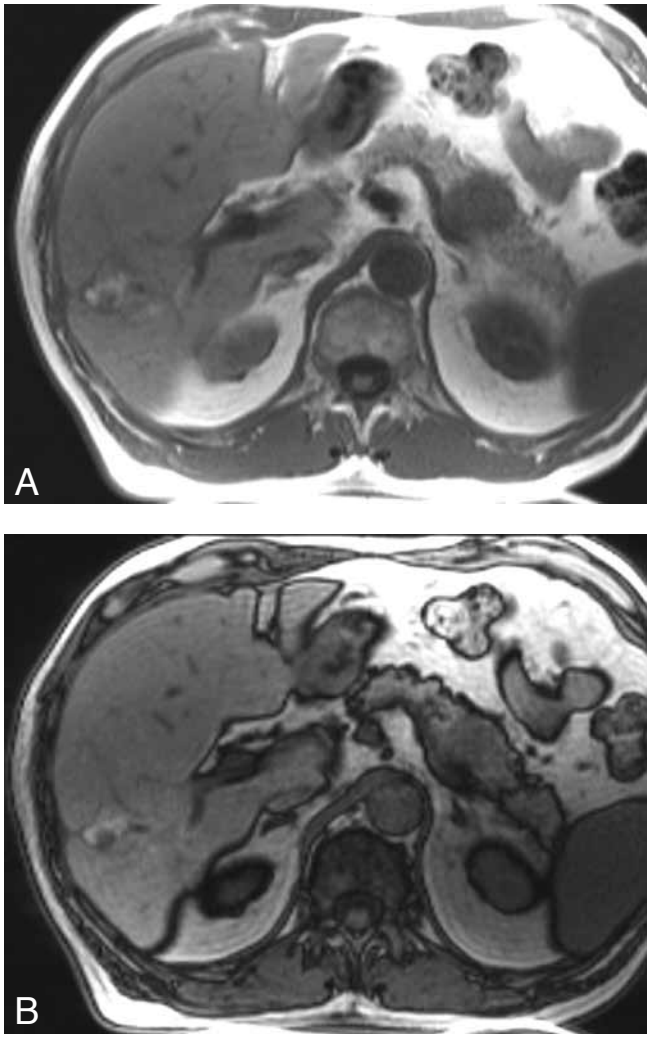
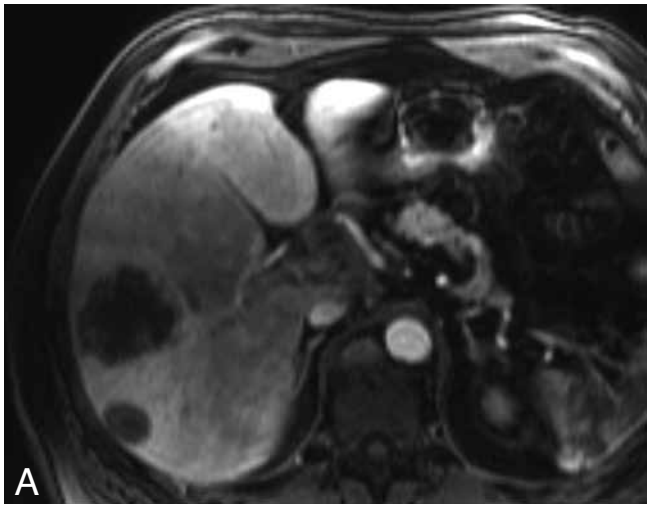
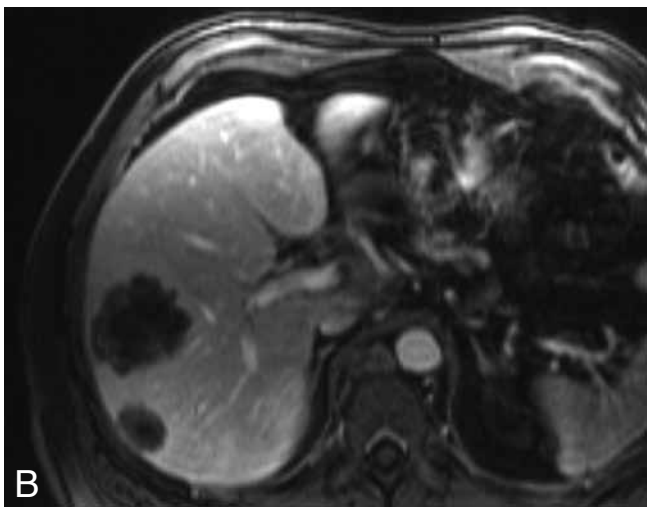


Fig. 6. — Melanoma metastasis. A. the T1w GRE in-phase image show s hyperintense lesion. High signal intensity can be due to hemorrhage, melanin or fat. B. On the T1w GRE opposed phase the lesion stays hyperintense, which excludes the presence of fat. High signal intensity is due to melanin content in melanoma metastasis.

ing detects the reflected harmonic response of a transmitted pulse and improves signal-to-noise ratio, and better spatial resolution due to the higher receiver frequency.

US contrast agents, which consist of gas-filled microbubbles typically smaller than 8μm surrounded by a stabilizing layer and dissolved in water, were developed to increase the diagnostic accuracy of US for tumor detection and characterization. After IV injection of these blood-pool agents, depending on the sound pressure, different mechanisms produce augmentation of signal in the vascular system for several minutes as the microbubbles do not leave the intravascular space. Contrast-enhanced US (CEUS) allows dynamic imaging with a very high temporal resolution, not only as a





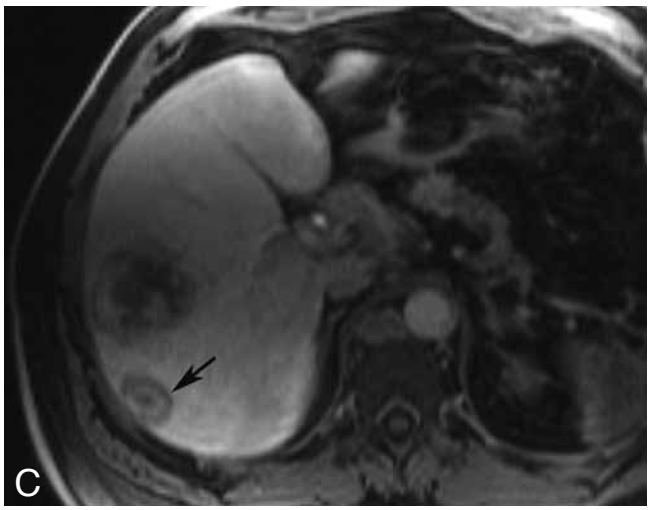
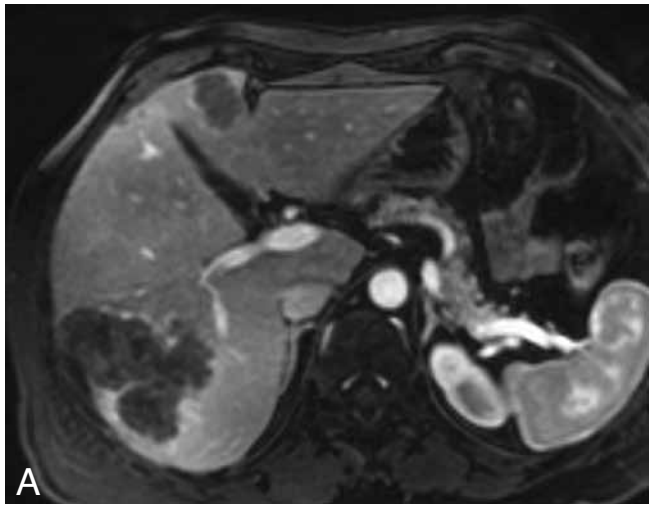


Fig. 7. — Dynamic gadolinium-enhanced MRI of colon cancer metastasis. A-C Dynamic contrast-enhanced MRI in the arterial (A), venous (B), and equilibrium-phase (C) shows rim enhancement in the venous phase and peripheral wash-out (arrow), which is quite specific for malignancy.



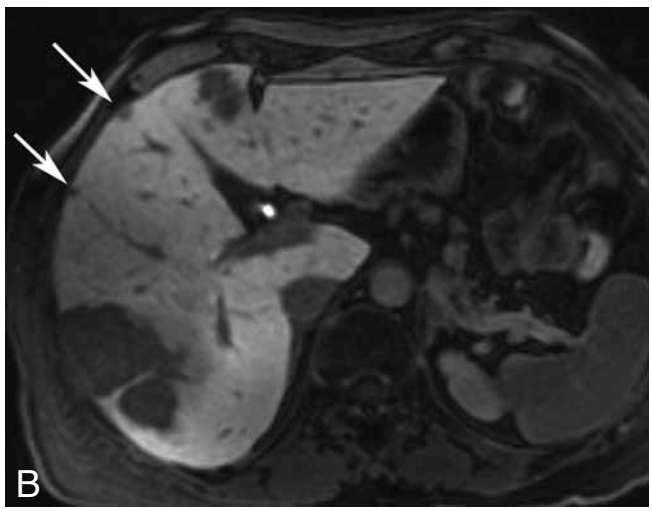


Fig. 8. — The value of liver-specific contrast agents. A. Gadoxetic acid-enhanced MRI in the venous phase shows 2 liver metastases. B. The delayed-phase image shows two adddditional small subcapsular lesions (arrrows) not well seen in the venous phase.

single acquisition in the arterial, portal-venous, and delayed phase, as in CT. Different focal liver lesions show quite distinct enhancement features, due to the high temporal resolution of CEUS. Metastases are either hypoechogenic or hyperechogenic in the arterial phase and usually hypoechogenic in the portal venous and the delayed vascular phase due to contrast agent washout (8) (Fig. 1). In contrast, hemangiomas typically show peripheral and centripetal enhancement with sustained enhancement in the delayed phase due to vascular pooling.

Compared to standard grey-scale US, CEUS allows better detection and characterization of focal liver lesions. In the study of von Herbay et al. the use of CEUS improved the sensitivity and specificity of US in the differentiation of malignant vs.

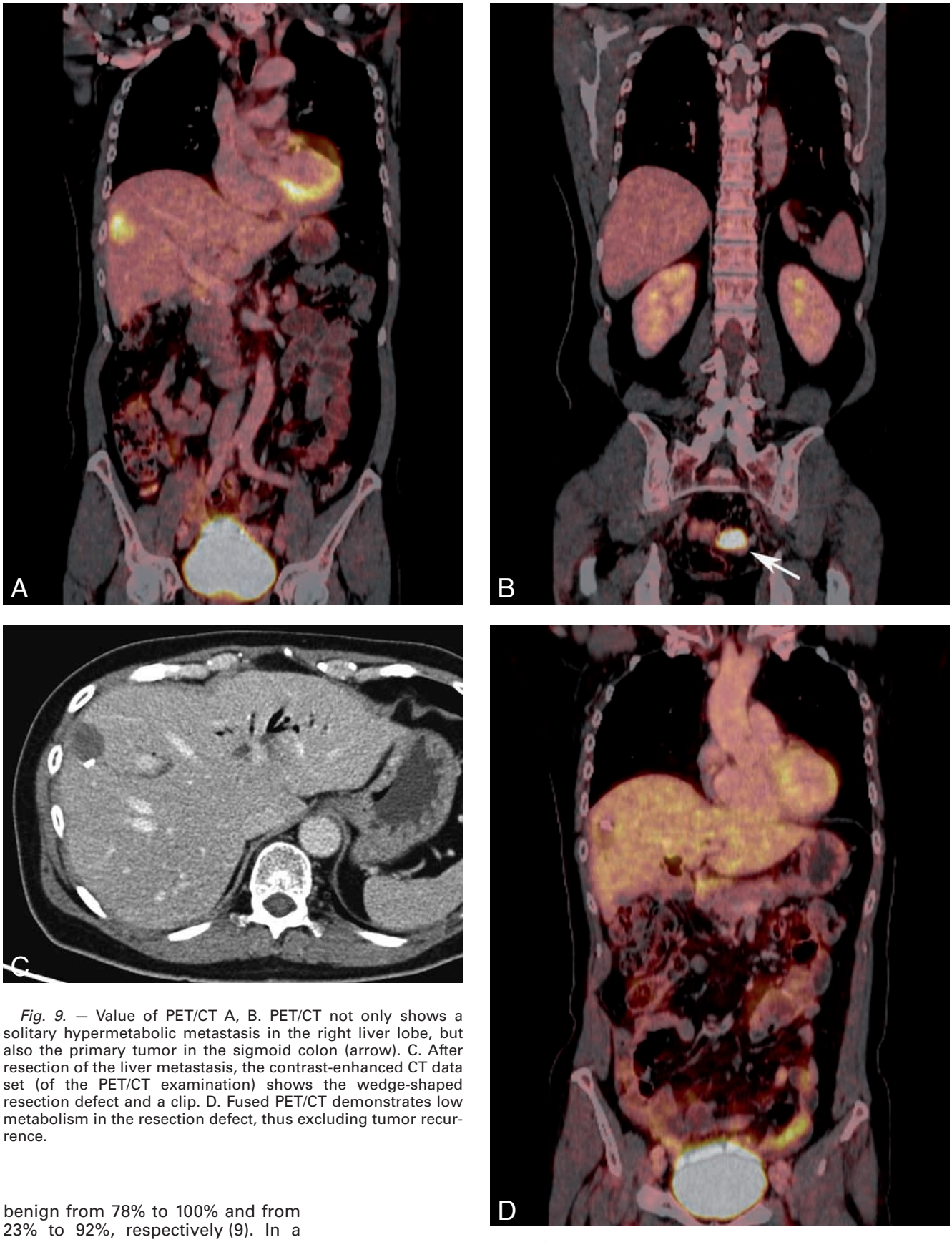


Fig. 9. — Value of PET/CT A, B. PET/CT not only shows a solitary hypermetabolic metastasis in the right liver lobe, but also the primary tumor in the sigmoid colon (arrow). C. After resection of the liver metastasis, the contrast-enhanced CT data set (of the PET/CT examination) shows the wedge-shaped resection defect and a clip. D. Fused PET/CT demonstrates low metabolism in the resection defect, thus excluding tumor recurrence.

benign from 78% to 100% and from 23% to 92%, respectively (9). In a large multicenter trial the addition of contrast-enhanced ultrasound increased the sensitivity of detection of metastases on a per-lesion basis from 71% (standard US) to 87% (Fig. 2). Thus the guidelines of EFSUMB for the use of contrast agents in ultrasound recommend the use of US contrast agents in oncologic patients to clarify a questionable lesion detected at baseline examination (10).

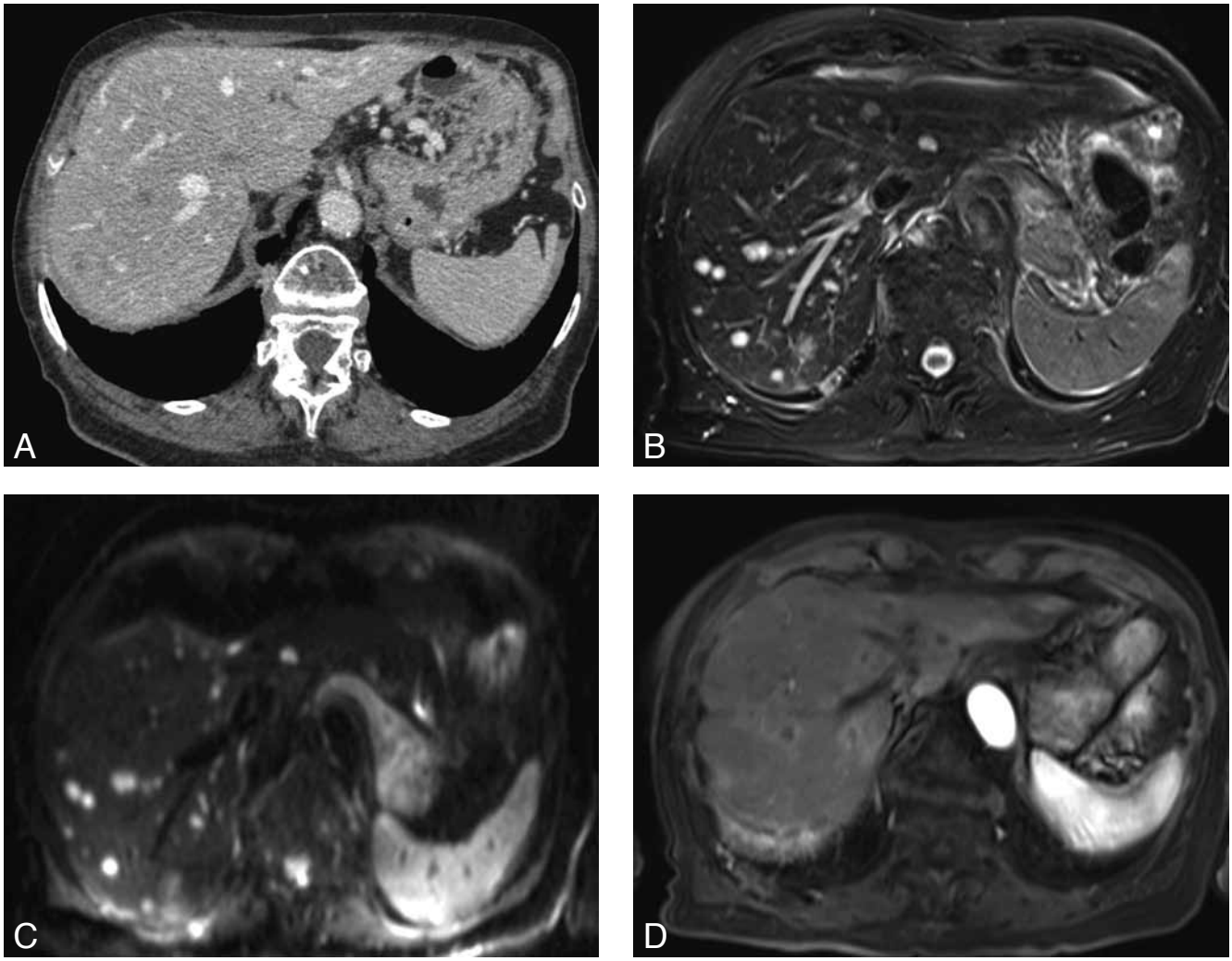


Fig. 10. — DWI and gadolinium-enhanced MRI at 3.0T is superior to MDCT. A. At MDCT three small metastases are visualized, with low contrast. B. T2w MRI at 3.0T shows many more hyperintense metastases. C. At DWI the lesions are displayed with excellent conspicuity. D. Gadolinium-enhanced MRI shows typical rim enhancement of metastases.

Multidetector-row CT (MDCT)

Computed tomography (CT) is the most widely used imaging modality for detection and characterization of hepatic metastases. With the advent of MDCT scanners thin-slice imaging of the entire liver within one breathhold has become possible. The new 256+-row detector scanners allow imaging of the liver in 1-2 seconds, which renders appropriate timing and contrast material administration and scanning crucial.

An unenhanced scan may be helpful for assessment of diffuse liver steatosis and characterization of small focal lesions. However, recent studies have shown that a virtual scan in patients, who undergo dual energy CT, will be able to replace true unenhanced scans (11). A biphasic scan after contrast material administration in the arterial and the venous phases is recommended to optimize metastasis detection and characterization (12) (Fig. 3). Some primary tumors will seed hypervascular liver metastases (e.g., neuroendocrine tumor, renal cancer, sarcomas, etc.), whereas most liver metastases will be hypovascular (adenocarcinoma in colorectal, pancreatic, gastric or esophageal primaries) (Fig. 4).

For follow-up studies in patients with primary tumors known to seed hypovascular metastases (e.g., colorectal cancer) a single scan in the venous phases may suffice as radiation exposure is an important issue in patients undergoing several follow-up studies. Weg et al. showed that the use of 2.5 mm thick slices results in a 86% increase in the detection rate of small (< 1 cm) liver lesions compared to 10 mm thick sections (13). These results have been corroborated by Kopka et al., who found that a slice thickness of 3.75 mm was superior to 5 mm in terms of lesion detection (14). Further decrease of slice thickness to 1 mm will only increase image noise. Therefore overlapping slices with a thickness of 2-4 mm is recommended for axial viewing. Multiplanar reconstructions (MPR) in coronal plane improve subcapsular lesion detection.

Magnetic Resonance Imaging (MRI)

With its inherent high soft tissue contrast MRI has been found to be the most sensitive technique for detection of liver metastases. One of the major challenges of liver MR imaging is to overcome motion arti-

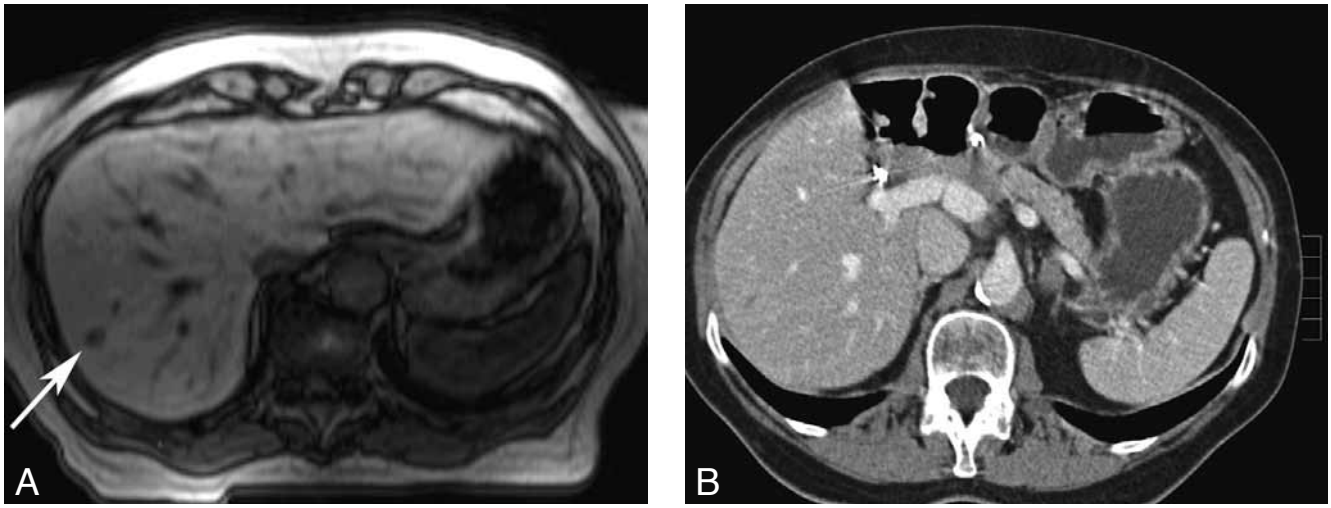


Fig. 11. — Mangafodipir-enhanced MRI is superior to contrast-enhanced MDCT for lesion detection. A. The mangafodipir-enhanced T1w GRE images shows a small lesion in the right lobe (arrow). B. The lesion is only faintly seen at MDCT.

facts due to breathing, gastric peristalsis, and cardiac or aortic pulsation. Multi-channel torso coils are now standard in body MR imaging and a field strength of 3.0 T is preferable. The standard MRI protocol should always include unenhanced T1- and T2-weighted, diffusion-weighted images (DWI), and contrast-enhanced sequences (Fig. 5). To assess liver or lesion fat content unenhanced T1 weighted in- and opposed-phased GRE sequences are necessary. Turbo-spin echo (TSE) (synonym: fast spin echo, FSE) with fat saturation are preferred for T2-weighted imaging.

Typically liver metastases are hypointense on T1-weighted images with the exception of melanoma or hemorrhagic metastases, which may be hyperintense due to melanin or methemoglobin content, respectively (Fig. 6). Most metastases are moderately hyperintense on T2-weighted images (15). However, the signal intensities of hepatic metastases can vary. In cystic metastases (e.g., ovarian cancer) or when liquefactive necrosis or mucin is present, signal intensity on T2-weighted images increases. In these cases only dynamic gadolinium-enhanced imaging will help in the differentiation of small metastases from cysts or hemangiomas (16).

Due to increased cellularity water molecule diffusion is restricted in most types of liver metastases, which can be utilised by diffusion-weighted MR imaging. Due to restricted diffusion of water molecules, metastases appear hyperintense on DWI images using a high b-value of 500-1000 mm/s (17-19) (Fig. 5). Several studies showed that the use of DWI improves the detection of focal liver lesions (17, 18). Even as an adjunct to MRI with liver-specific contrast agents, DWI may improve lesion detection (19). Recent studies suggest that DWI may also help in the characterization of focal hepatic lesions using the apparent diffusion coefficient (ADC), although further studies are needed to corroborate these findings (20). DWI of the liver is prone to motion and susceptibility artefacts in the left lobe, which often impairs image quality at 3.0T. Image quality is therefore more predictable at 1.5T.

Contrast-enhanced MRI

After intravenous bolus injection non-specific gadolinium chelates (extracellular contrast agents) are distributed in blood vessels and rapidly diffuse into the extracellular space. Liver lesions show MRI enhancement patterns similar to those obtained with contrast-enhanced CT. Several agents are available, being injected IV as a bolus at a standard dosage 0.1 mmol/kg body weight. Routinely dynamic axial T1-w GRE images are obtained at least in the arterial, the venous, and the equilibrium phases (at 3-5 min post injection). Most liver metastases are hypovascular (e.g., from colorectal, gastric, pancreatic and esophageal cancer) and similar to CT can be delineated best in the venous phase. Some metastases, especially from renal or neuroendocrine cancer, are hypervascular and therefore best depicted in the arterial phase. The equilibrium phase is important for lesion characterization. Hemangiomas typically show persistent gadolinium pooling at this time point, whereas most metastases appear hypointense or centrally isointense with peripheral washout sign (21) (Fig. 7). Cystic metastases will show a blurred edge in the equilibrium phase compared to the non-enhanced images, because contrast material diffuses into the tumor periphery, which helps in the differentiation from simple cysts. The two most common patterns of enhancement of hypo- and hypervascular lesions in the arterial phase both are peripheral ring enhancement (72%) and heterogeneous enhancement (17%) (22) (Fig. 7). Homogeneous hyperintense enhancement in the arterial phase is typically found in small (< 1.5 cm) hypervascular metastases whereas larger lesions (> 3 cm) tend to be heterogeneous. Perilesional enhancement is often found in hypovascular metastases with a wedge-shaped pattern probably resulting from portal venous obstruction or venous shunting. However, this pattern is also observed in hemangiomas, which limits its value for lesion characterization.

In contrast to non-specific gadolinium chelates, which are distributed into the extracellular space, liver-specific contrast agents are taken up intracellularly either by hepatocytes (hepatobiliary contrast agents) or by Kupffer cells, e.g. cells of the reticuloendothelial system of the liver. Unfortunately, the reticulo-

endothelial liver-specific contrast agents and the hepato-biliary contrast agent mangafodipir (Teslascan®, GE Healthcare) have been withdrawn from the market recently, leaving two contrast agents available, which combine extracellular and hepatobiliary properties (hybrid contrast agents).

Gadobenate dimeglumine (MultiHance®, Bracco, formerly known as Gd-BOPTA), and gadoxetic acid (Primovist®, Bayer, formerly known as Gd-EOB-DTPA), are hybrid gadolinium based contrast agents, which carry a lipophilic ligand (23). After IV bolus injection these agents show rapid biphasic liver enhancement with the first phase similar to that of non-specific gadolinium chelates. Due to their ligand a fraction of the injected dose is taken up by the hepatocytes, which leads to a SI increase on T1-weighted images. The contrast agent component is washed out from the extracellular compartment, which results in improved contrast between liver and metastases on delayed-phase images (gadoxetic acid: 20 min, gadobenate 60 min post injection) (23, 24) (Fig. 8).

PET and PET-CT

By far the most commonly used tracer for PET imaging of liver metastases is 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG). Tumor imaging with this tracer is based on the principle that cancer typically has an increased glucose uptake and an altered intracellular glucose metabolism, which traps ^{18}F-FDG in the cells. The PET scanner detects the positrons emitted by the decaying ^{18}F and represents this visually. Metabolic activity of tumors can be assessed by calculating the standardized uptake value (SUV). However, ^{18}F-FDG also accumulates in normal liver tissue, resulting in high background, which limits the detection of hypermetabolic liver metastases. FDG-PET is a valuable tool in the detection of hepatic metastases (25, 26). Especially in patients with equivocal CT and MR findings and for detection of tumor recurrence FDG-PET has been helpful (27). PET-CT scanners combine the functional information obtained from a PET scan with the anatomic information of a MDCT scan. If adequate contrast-enhanced CT scanning protocols are used, it is the imaging modality of choice to detect extrahepatic disease (28) (Fig. 9).

Which is the best modality?

There is an ongoing debate, which imaging modality offers the best and cost-effective assessment of liver metastases (4). A recent meta-analysis of Niekel et al. has compared the diagnostic value of CT, MRI, PET, and PET/CT in the evaluation of colorectal liver metastases derived from studies published between 1990 and 2010 (29). The authors found that MRI was the most sensitive method for detection of metastases. Especially for detection of small metastases it was superior to contrast-enhanced CT. There were too few studies on PET/CT to be included in the analysis to draw further conclusions (29). Interestingly, this meta-analysis did not find any benefit of contrast-enhanced MRI over unenhanced MRI (including DWI).

Generally MDCT scanning is used as a screening examination of the liver in most institutions as it is a robust, widely available and valuable imaging technique and moreover allows the assessment of extrahepatic disease (chest, abdomen, and pelvis). PET scanning is not used routinely in the initial assessment of oncologic patients because of its cost, poor spatial resolution and lack of anatomic information. Moreover it is not superior to MDCT in the initial staging of primary colorectal cancer.

Depending on local availability and user experience contrast-enhanced ultrasound may be an option for initial liver assessment with sensitivity for liver metastasis detection comparable to that of MDCT. Unenhanced ultrasound of the liver, however, is now obsolete in oncologic patients due to its low sensitivity for lesion detection. Only a few studies compared MDCT and MRI regarding liver evaluation. It was demonstrated that MRI, either gadolinium-enhanced or with liver-specific SPIO contrast agents, demonstrates a higher diagnostic accuracy than MDCT for detection and characterization of focal liver lesions (30) (Figs. 10, 11). Compared to helical CT multiple studies have shown that MRI with different contrast agents is superior regarding lesion detection and characterization (31, 32). MRI is routinely used in patients with unequivocal CT scans or with contraindications to a CT examination. It should also be used in patients with severe liver steatosis as this condition markedly decreases the diagnostic performance of US and CT in liver evaluation. Moreover it plays a major role in the assessment of patients who are eligible for resection of liver metastases.

Diagnostic value of preoperative MDCT and MRI

Preoperative imaging capabilities with CT and MRI in patients with colorectal liver metastases have dramatically improved in the last decade. It has been shown that with the use of state-of-the-art MDCT and/or MRI combined with a multidisciplinary preoperative evaluation additional liver metastases will only be found in 8% of patients during surgery (33). MRI with non-specific gadolinium chelates or liver-specific agents has been shown to be superior to MDCT for detection of liver metastases. Because of the higher sensitivity of MRI regarding liver metastases detection and the better characterization of small lesions a preoperative MR study with liver-specific contrast agent is recommended in all patients (4).

Conclusion

In conclusion, contrast-enhanced chest and abdomen MDCT and liver MRI (with liver-specific contrast agents if available) are recommended for an optimal preoperative evaluation of patients undergoing liver metastasis resection. It has to be shown if PET/CT will prove its diagnostic efficacy to replace CECT in this indication.

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