II.3

Detection and Characterisation of Liver Metastases

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Introduction

Both benign and malignant focal liver lesions are very common, and staging of the liver for metastases in cancer patients is one of the most frequent tasks of every day radiological practise.

The most common malignant liver lesions are metastases from other organs: 25 to 50% of patients with known solid malignant tumours have hepatic metastases at the time of diagnosis, with decreasing frequency of metastases in colon, gastric, pancreatic, breast and lung cancer [1]. On the other hand, the prevalence of solid benign liver tumours has been reported to be more than 20% in autopsy series [1, 2] and thus in patients with malignancy, 25-50% of lesions under 2 cm in size are benign [3, 4]. The most frequent benign lesion is haemangioma, which has a prevalence of 7-21% [2, 5], followed by focal nodular hyperplasia (FNH) with a prevalence of up to 3% [2, 6]. Adenomas are much rarer than FNH (by a factor of approximately 50) and they usually occur in female patients with a history of sex hormone medication. Other relatively rare benign lesions are pyogenic, parasitic or fungal abscesses. Areas of focal fatty change or focal fatty sparing are very common; they do not represent true lesions but may appear as pseudo-tumours on ultrasound (US) and are thus easily confused with real tumours such as metastases. Pseudo-tumours are particularly common in patients undergoing chemotherapy and their tendency to vary in extent and location over time can pose problems for serial imaging of tumour patients.

From the above, it is obvious that liver imaging of cancer patients requires an imaging modality that is not only provides highly sensitive detection, but also reliable characterisation of lesions, thus allowing differentiation of malignant from benign tumours. This is particularly important since almost all benign lesions, as well as non-end-stage metastases, are typically asymptomatic, and blood tests are non-specific.

Accurate and timely detection of hepatic metastases is very important because of their far-reaching therapeutic and prognostic implications. Especially through the recent improvements in liver resection and local ablation of metastases from colo-rectal and some other primary carcinomas, liver imaging has become more demanding. Accurate assessment of number, size and segmental location of metastases is required to identify patients that are suitable for surgical or interventional therapy, for treatment planning and for follow-up imaging under chemotherapy.

In the past, US had an important but somewhat limited role in liver imaging of cancer patients. Although commonly the first and most widespread modality used, its detection rate was inferior to that of computed tomography (CT) and magnetic resonance imaging (MRI), and its ability to differentiate metastases from other focal liver lesions was often limited. With the advent of US contrast agents (USCA) and new contrast-specific imaging techniques in the last few years, contrast-enhanced US (CEUS) has become a powerful tool, which has significantly changed the role of US for liver imaging in cancer patients.

Conventional Ultrasound

B-mode Features of Metastases

The ability of US to detect a focal liver lesion depends on a number of factors: echogenicity, size, location, and mass effect. The two most

important factors are liver-to-lesion contrast and spatial resolution: even small strongly hyper- or hypoechoic lesions are easily detected (Fig. 1a). Conversely, isoechoic masses are usually missed and must be larger in order to be detected. Mass effect is important for the detection of isoechoic lesions. It manifests as deviation or invasion of the intrahepatic vasculature and/or bulges in the liver contour.

The echo patterns of metastases are numerous (Fig. 1), but some patterns are said to be associated with certain primary tumours (Table 1). US appearances of metastases may vary within a given patient as well as over time, and particularly following chemotherapy. Most metastases are round and have well-defined margins. Hypoechoic metastases are more common (approximately 65%) than hyper- or isoechoic

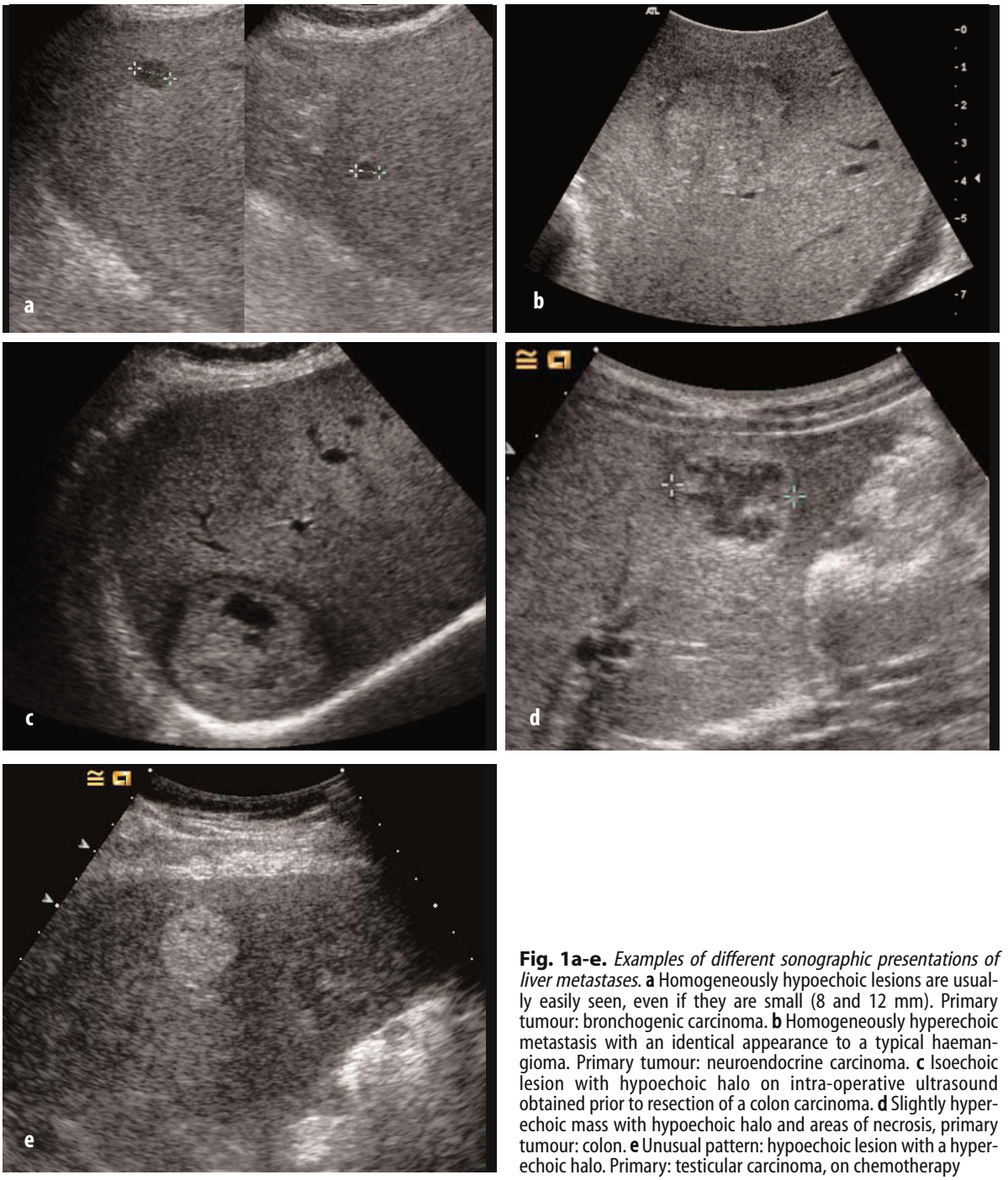


Fig. 1a-e. *Examples of different sonographic presentations of liver metastases.* **a** Homogeneously hypoechoic lesions are usually easily seen, even if they are small (8 and 12 mm). Primary tumour: bronchogenic carcinoma. **b** Homogeneously hyperechoic metastasis with an identical appearance to a typical haemangioma. Primary tumour: neuroendocrine carcinoma. **c** Isoechoic lesion with hypoechoic halo on intra-operative ultrasound obtained prior to resection of a colon carcinoma. **d** Slightly hyperechoic mass with hypoechoic halo and areas of necrosis, primary tumour: colon. **e** Unusual pattern: hypoechoic lesion with a hyperechoic halo. Primary: testicular carcinoma, on chemotherapy

Table 1. Common sonographic patterns of hepatic metastases from various primary malignancies. Note that any primary tumour may produce liver metastases with any of the patterns named

Hyporeflective (most common)
Breast
Lung
Lymphoma
Pancreas
Hyper-reflective
Colon
Neuroendocrine carcinoma
Renal cell
Choriocarcinoma
Target pattern ("halo")
Most commonly lung, colon
Occurs in all others
Calcified
Common: (treated) mucinous adenocarcinoma of colon, stomach, ovary
Rare: osteosarcoma, chondrosarcoma
Cystic
Ovary, pancreas, colon
Sarcoma
Squamous cell carcinoma
Infiltrative
Breast
Lung
Pancreas
Thyroid
Malignant melanoma

metastases. A hypoechoic halo is seen surrounding the lesions in 40% of cases [7], and is most often associated with iso- or hyperechoic metastases. The cause of the halo is controversial. It is not pathognomonic of metastases as it may also be seen in hepatocellular carcinoma (HHC), fungal abscess, adenoma and, less commonly, in FNH and haemangioma. Cystic areas indicative of necrosis may occur. Calcified metastases are sometimes seen in patients with mucinous adenocarcinoma of the gastrointestinal tract, and are more common after chemotherapy.

Multiple lesions in a patient with a known primary malignancy are highly suggestive of metastases. Multiple metastases may show as several individual lesions or as diffuse infiltration, producing the "moth-eaten" appearance of a heterogeneous liver, combined with definite or questionable individual lesions (Fig. 2).

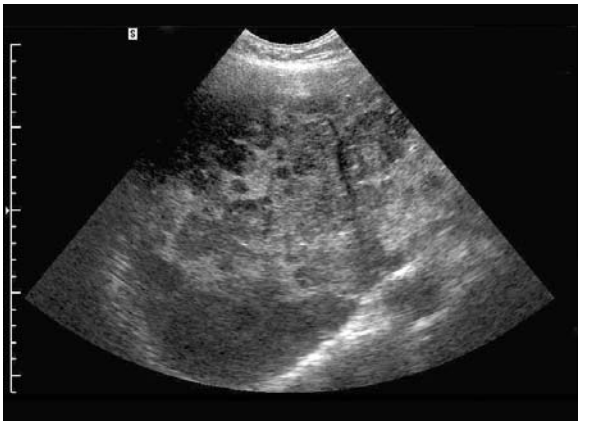


Fig. 2. Multiple/diffuse metastases giving the "moth-eaten" appearance

Doppler Imaging

For growth, liver malignancies require a neovascular supply. However, Doppler techniques are often limited in their ability to image the vascularity of metastases and other lesions since the flow signals are too low (small vessels with relatively slow flow). Power Doppler is slightly superior to conventional colour Doppler in this respect. Doppler typically shows no or some peripheral vascularity in hypovascular metastases, while hypervascular deposits may show vessels throughout the lesion (Figs. 3a, 3b). Both these patterns are also common in other focal liver lesions. The addition of Doppler is of limited value in differentiating metastases from other lesions, it has no added value for detection. Doppler can be useful to differentiate metastases from FNH (Fig. 3c) and focal fatty change/infiltration, as discussed below.

Differential Diagnosis

The differential diagnosis of metastases is wide, and includes any focal lesion that may be encountered in the liver. Generally speaking, any histologic type of lesion seen on B-mode US can mimic metastasis and vice versa. Only common lesions will be discussed here. Primary malignant lesions such as hepatocellular carcinoma and peripheral cholangiocarcinoma (CCC) cannot be differentiated from metastases based on lesion appearances alone. However, unifocal primary malignant tumours tend to present as large single tumours, which is less common in metastases. HCC usually occurs in patients with cirrhosis, and large HCC may form a tumour thrombus within the portal vein. Both of these

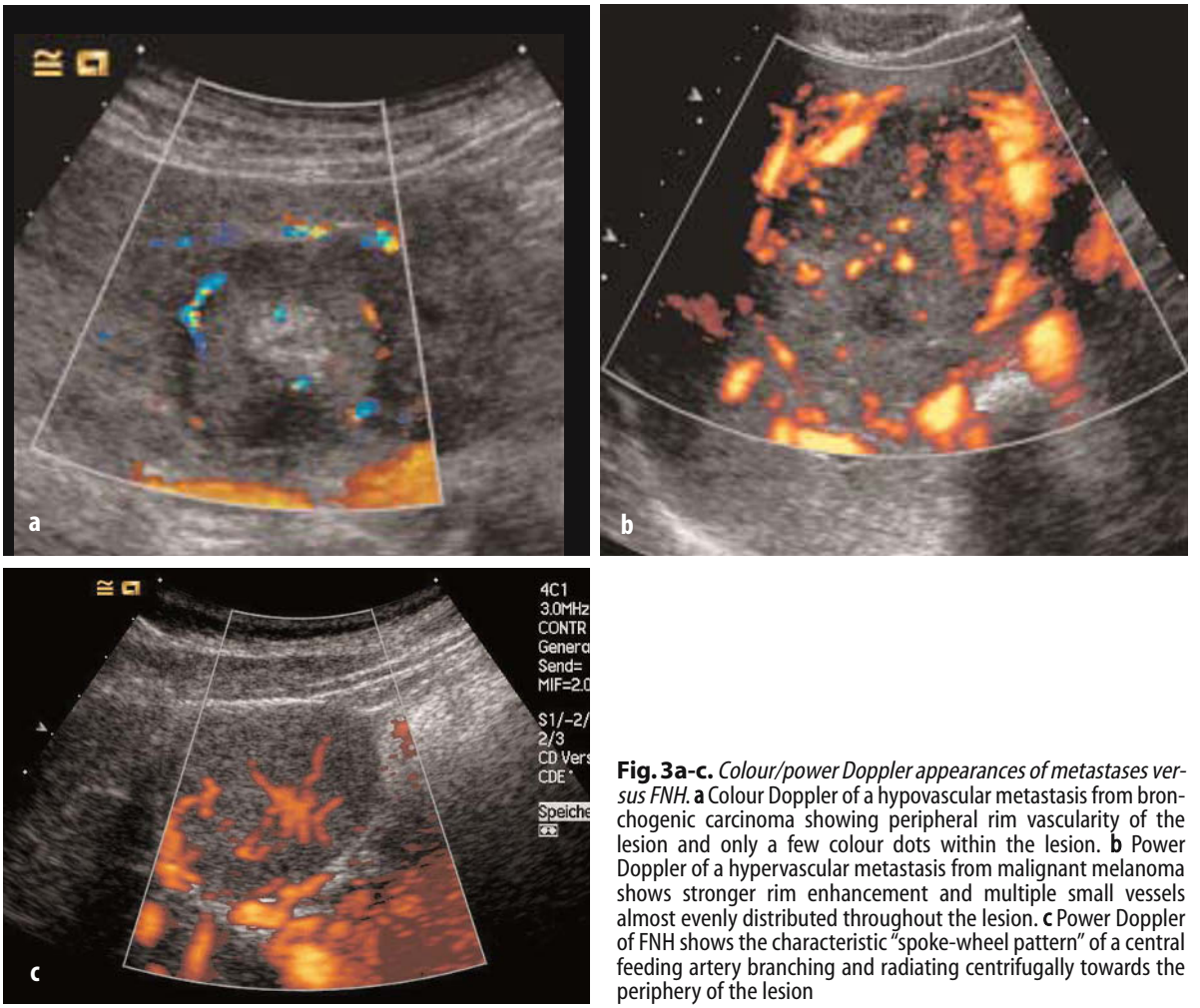


Fig. 3a-c. *Colour/power Doppler appearances of metastases versus FNH.* **a** Colour Doppler of a hypovascular metastasis from bronchogenic carcinoma showing peripheral rim vascularity of the lesion and only a few colour dots within the lesion. **b** Power Doppler of a hypervascular metastasis from malignant melanoma shows stronger rim enhancement and multiple small vessels almost evenly distributed throughout the lesion. **c** Power Doppler of FNH shows the characteristic "spoke-wheel pattern" of a central feeding artery branching and radiating centrifugally towards the periphery of the lesion

presentations are important differential diagnostic clues. (Peripheral) CCC more frequently causes (segmental) biliary obstruction than other malignant tumours. Multifocal HCC and CCC are not uncommon and may be indistinguishable from multiple metastases.

The two most common benign solid lesions – haemangioma and FNH – often have quite typical appearances, which are helpful for their diagnosis. The commonest sonographic appearance of *haemangioma* (60-70%) is a homogeneously hyperechoic lesion less than 3 cm in size. Not infrequently, these tumours show posterior acoustic enhancement, which is a very valuable differential diagnostic criterion (Fig. 4a). Atypical features are commoner in larger haemangiomas and include hypoechoic lesions (Fig. 4b), heterogeneous echogenicity with hypoechoic areas due to necrosis, haemorrhage, partial thrombosis or scarring. Calcification may also occur. A significant proportion of atypical haemangiomas have an echogenic periphery and a hypoechoic centre. Atypical haemangiomas are often indistinguishable from metastases (Fig. 4a). Despite its vascular nature, the blood flow within a haemangioma is too slow to be detected by Doppler modes.

FNH is typically homogeneously isoechoic and it is therefore often overlooked, especially when small. Its visualisation depends on mass effect, with displacement of normal vessels and a slightly different (coarser) echo pattern than the surrounding parenchyma. FNH may also be slightly hyper- or hypoechoic compared to normal liver. In large FNH (≥ 4-5 cm), a hypoechoic central scar may be visible, and colour Doppler often shows a spoke-wheel arterial pattern of vessels radiating from the centre to the periphery (Fig. 3c). While large FNHs are often easily diagnosed based on their almost isoechoic texture, the central scar, and the spoke-wheel pattern, small FNHs often lack these typical features and are easily confused with metastases, especially in young women with breast cancer (Fig. 5).

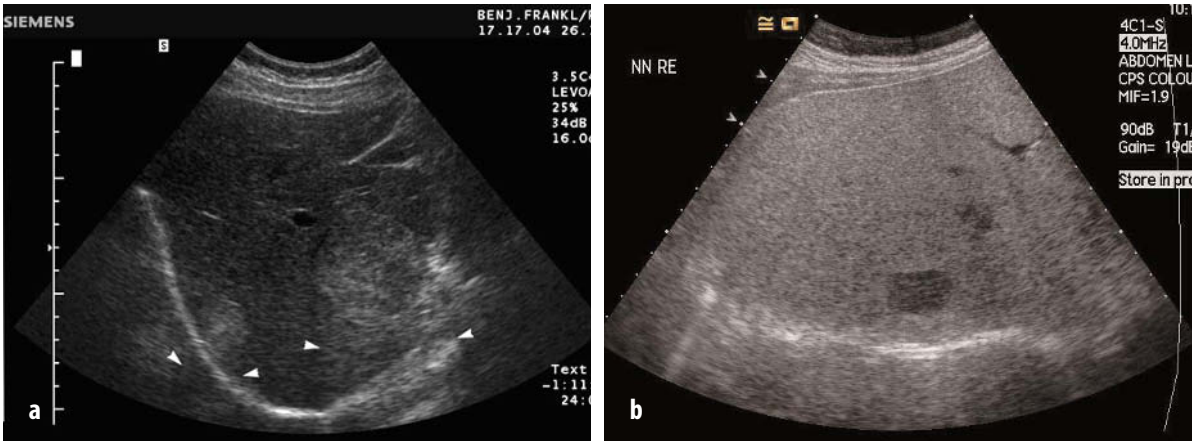


Fig. 4a, b. a Two typical homogeneously hyperechoic haemangiomas with posterior enhancement *(arrowheads)*. **b** Atypical hypoechoic haemangioma in a patient with a fatty liver and carcinoma of the prostate. The lesion is indistinguishable from a metastasis (cf. Fig. 1a)

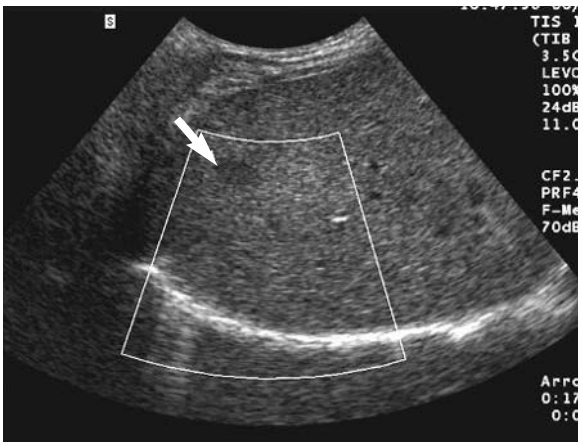


Fig. 5. Small hypoechoic FNH (*arrow*) indiscernible from metastasis

Focal fatty change presents as a hyperechoic area within the normal parenchyma and *focal fatty sparing* is a normal, relatively hypoechoic area in an otherwise hyperechoic fatty liver. Both lesion types are common in patients on chemotherapy. The size of the lesions may vary from less than a centimetre, to large areas covering several liver segments. Large areas of focal fatty change or sparing are readily diagnosed based on their characteristic 'geographical' or triangular shape without mass effect, while smaller lesions are often round or oval and are easily mistaken for metastases. A helpful differential diagnostic feature is their preponderance to occur at typical anatomical sites such as in segment IV at the insertion of the falciform ligament or in segment V near the main portal vein or the gallbladder fossa. On Doppler imaging, focal fatty change and sparing shows no abnormal vascularity and normal hepatic vessels crossing the lesion without displacement may be seen.

Multiple (fungal) *abscesses* sometimes occur in patients on chemotherapy (especially children) and they represent an important differential diagnosis of multiple lesions in patients on chemotherapy. Abscesses often do not have a typical cystic appearance, since their liquid portion contains corpuscular echogenic material. Their appearance can be identical to that of metastases, including the presence of a hypoechoic halo in fungal disease. Clinical signs and symptoms of infection may point towards the presence of an abscess.

Fatty Infiltration of the Liver and Metastases

Diffuse fatty infiltration of the liver, which often occurs during chemotherapy, can have substantial impact on US of focal liver lesions. On the one hand, it increases the reflectivity of the hepatic parenchyma and thus aids detection of lesions that would be isoechoic in a normal liver, and of hypoechoic lesions, since liver-to-lesion contrast is increased – one could call fatty infiltration a 'natural contrast agent'. On the other hand, severe fatty infiltration increases attenuation of sound by the liver and thus reduces penetration, which can obscure lesions in deeper liver areas. Further problems can occur when a small benign isoechoic lesion such as FNH or haemangioma, which remained undetected before chemotherapy, becomes visible as a 'new' hypoechoic lesion on follow-up. Such lesions are commonly misinterpreted as metastases (Fig. 4b).

Current Role and Limitations of Conventional US in Clinical Practice

As discussed above, there are no pathognomonic features of metastases on B-mode or colour Doppler and the differentiation of a single metastasis from other lesions is usually not possible. Such lesions are usually investigated further through the use of US contrast agents, other imaging modalities or sometimes biopsy. In a patient with a known primary malignancy, any focal liver lesion seen on unenhanced US must be regarded as suspicious of metastasis until proven otherwise. However, many lesions (25-50% of lesions ≤ 2 cm [3, 4]) will eventually prove to be benign, once contrast-enhanced US, other imaging tests or biopsy are used further to characterise the lesion.

The accuracy of unenhanced US for the assessment of hepatic metastases is lower than that of CEUS, CT and MRI. In series with true gold standard (intra-operative US or resection), its sensitivity ranges between 50% and 76% [8-12] (Table 2), which is considerably lower than that of CT and especially MRI. Problems of US for the detection of metastases are that the subdiaphragmatic areas of segments IVa and VIII are sometimes difficult to access and that there is poor liver-to-lesion contrast of almost isoechoic metastases, especially when small. For lesions smaller than 1 cm, the false negative rate is as high as 80% [9]. The false positive rate of US is in the order of 5-10% on a by patient basis and considerably higher on a lesion-by-lesion basis. For these reasons, CEUS, CT or MRI will be added to conventional US in most cancer patients for definitive liver staging, unless multiple metastases are clearly shown.

The role of US for follow-up of patients with hepatic metastases during chemotherapy is controversial. Its operator-dependant nature, and problems with reproducible image documentation limit its ability to clearly show small changes over time. In most cancer centres, CT or MRI are therefore preferred for follow-up imaging.

Contrast-Enhanced Ultrasound

Contrast Agents and Imaging Techniques

Two contrast agents are currently licensed for liver imaging in Europe: Levovist (Schering, Germany) and SonoVue (Bracco, Italy). The imaging technique varies according to the contrast agent chosen. Contrast-specific imaging modes exploiting non-linear bubble behaviour must be used with both agents to achieve clinically useful signal enhancement. Such imaging modes are now available on most medium and high end US systems.

Levovist, which was the first agent to be commercially available, has liver-specific properties during its late phase; this is advantageous for detection of metastases. High mechanical index (MI) imaging (MI > 0.7) must be applied when using Levovist. It provides signal enhancement due to strong non-linear signals from disrupting microbubbles. The disadvantage of this technique is the highly transient nature of the signals, which persist only for a few frames after insonation of an individual area, until the bubbles in the imaging plane are destroyed. To exploit the enhancement for clinical use, special scanning techniques such as rapid sweeping through the liver to image intact bubbles with each new frame or intermittent imaging have to be employed. Such scanning techniques are somewhat cumbersome and multiple sweeps through the liver are only possible with repeated injections. For these reasons, Levovist is no longer used on a large scale despite some very good results for detection and characterisation of focal liver lesions.

SonoVue, a more recent agent, provides strong and persistent signal enhancement due to its strong harmonic resonance at low (≤ 0.2) and very low (< 0.1) MI, where minimal or no bubble destruction occurs. This allows for continuous real-time imaging of a lesion during its vascular phase, as well as comprehensive surveying of the

Table 2. Sensitivity of conventional and contrast-enhanced US in detection of hepatic metastases; studies with true gold standard (IOUS ± resection) only

Author year	Contrast agent	No. patients	Sensitivity baseline	Sensitivity post-contrast
Clarke 1989 [8]	Only unenhanced	54	76%	-
Wernecke 1991 [9]	Only unenhanced	75	53%	-
Ohlson 1993 [10]	Only unenhanced	71	50%	-
Albrecht 2000 [11]	Levovist	35	70%	82%
Konopke 2005 [12]	SonoVue	56	53%	86%

liver in multiple planes during the delayed phase. Low MI imaging with SonoVue is now preferred in most instances, although it has weaker liver-specific properties than Levovist.

Several experimental agents such as Sonazoid (NC100100; Amersham Medical, UK) or BR14 (Bracco, Italy) combine the advantages of good enhancement at low MI with strong liver-specific properties. Early clinical studies have demonstrated the potential of such agents for detection of metastases. Unfortuna-tely, for commercial reasons, manufacturers are currently hesitant to continue the clinical development of such agents.

With real-time low MI imaging, the dynamic enhancement pattern and the vascular morphology of a lesion is assessed during the arterial (starting 10-20 seconds, and ending 25-53 seconds after injection) and portal-venous (starting 30-45 seconds and ending 120 seconds after injection) phases [13]. The delayed phase (> 2 minutes after injection) is particularly useful for detection of metastases as they show as non-enhancing defects. Characterisation is also improved by the late phase as the great majority of benign lesions show contrast up-take in this phase (see below).

Features of Metastases on Contrast-Enhanced Ultrasound

Metastases show characteristic dynamic features in all three phases after contrast injection (Figs. 6-8). All metastases have a predominantly arterial blood supply as opposed to a portal-venous one, but the degree of arterial perfusion is variable. Their appearance during the arterial phase of contrast-enhancement depends on the extent of arterial perfusion. Hypovascular metastases with relatively low arterial supply are common and typically occur in patients with adenocarcinoma or squamous cell carcinoma from gastrointestinal and other primaries. These lesions typically show rim enhancement of varying extents in the arterial phase. Hypervascular metastases are less common overall, they occur in patients with renal cell, thyroid or neuroendocrine carcinomas as well as with malignant melanoma and sarcoma and in about 25% of patients with breast cancer. During the arterial phase, hypervascular metastatic deposits show as homogeneously and strongly enhancing hyper-reflective and lesions, sometimes with non-enhancing necrotic areas. At the beginning of the portal-venous phase, the (rim) enhancement fades and the entire lesion becomes increasingly hyporeflective. In the delayed phase, both hypo- and hypervascular metastases almost invariably show as dark enhancement defects while the enhancement persists in normal liver parenchyma [7], independent of the contrast agent and imaging technique used. During the delayed phase metastases are often very well-defined, often with sharp, "punched out" borders (Figs. 7-10). Both portal-venous and delayed phase imaging markedly increase the contrast between the enhancing normal liver and the non-enhancing metastases and thus improve detection (Figs. 9, 10), see below for details.

Differential Diagnosis on Contrast-Enhanced US

As discussed above, unenhanced US is usually not able to reliably differentiate metastases from other lesions. Conversely, the use of contrast agents achieves this goal in most cases, since all

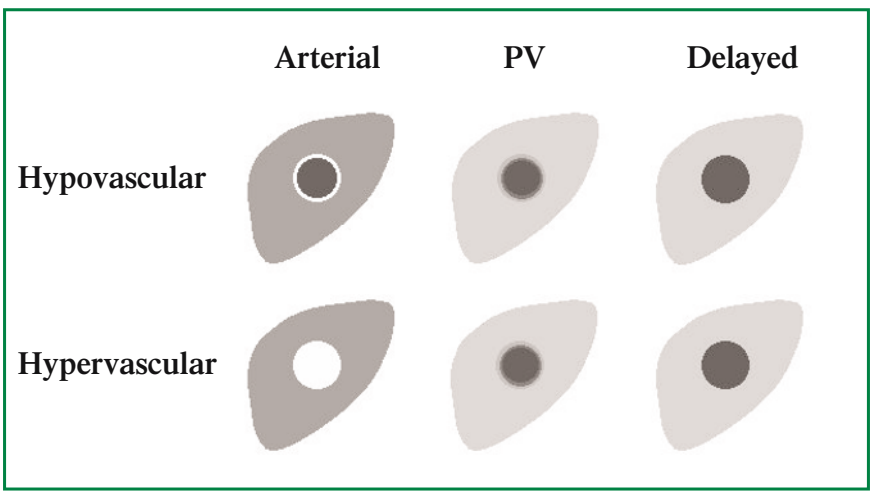
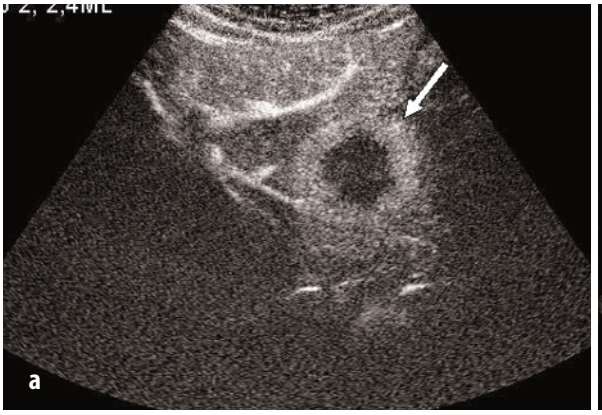
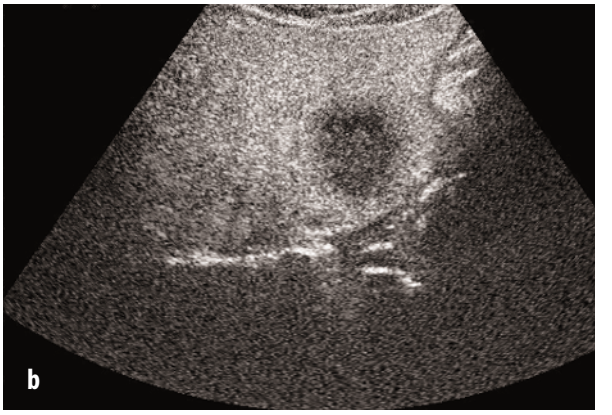


Fig. 6. Schematic display of the dynamic enhancement of hypo- and hypervascular metastases post-contrast injection during the arterial, portal-venous (PV) and delayed phase





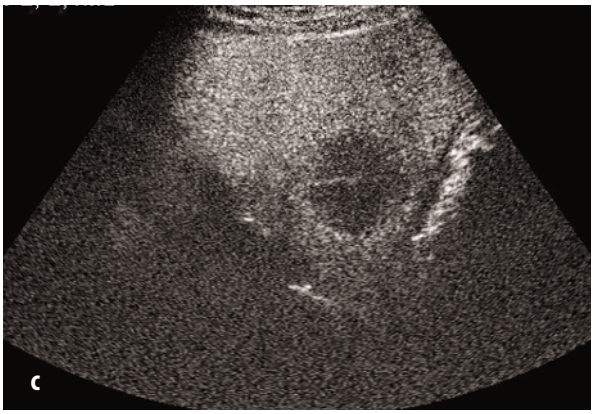
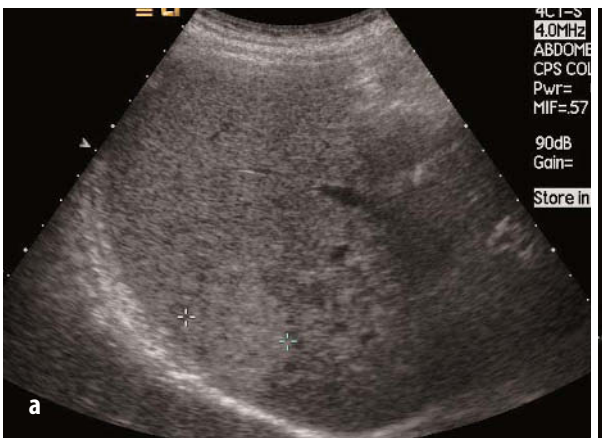
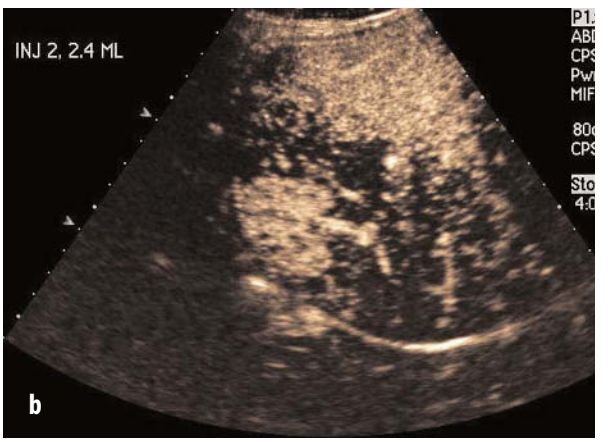
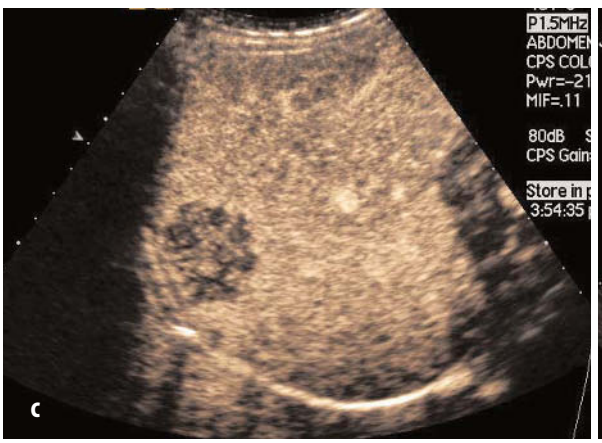


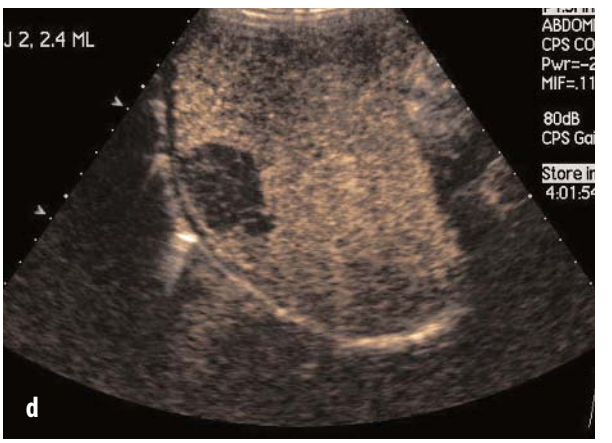
Fig. 7a-c. *Dynamic features of a "hypovascular" hepatic metastasis from a breast primary after contrast injection (SonoVue).* **a** In the arterial phase the lesion displays strong peripheral rim enhancement (*arrow*). **b** Portal-venous phase imaging shows fading of the rim. **c** In the delayed phase, the lesion shows as a hypoechoic enhancement defect

Fig. 8a-d. *Dynamic features of a "hypervascular" metastasis from a bronchogenic carcinoma after contrast injection (SonoVue).* **a** Conventional greyscale image shows a hyperechoic lesion. **b** During the arterial phase 18 seconds post injection, the lesion enhances homogenously while there is little contrast up-take by the liver parenchyma. **c** Portal-venous phase image (46 seconds post-injection) shows enhancement of normal liver and partial contrast wash-out from the lesion. **d** Delayed phase image (3:07 minutes post-injection) with persistent enhancement of the normal liver and complete contrast wash-out from the metastasis









common solid benign liver lesions have characteristic dynamic imaging features on contrast-enhanced US and their diagnosis is thus often unproblematic [7, 14-16]. Most of these features are analogous to those on dynamic CT and MRI.

Haemangiomas show a characteristic peripheral nodular arterial phase enhancement followed by gradual centripetal filling during the later phases (Fig. 11). The filling may be partial or complete. The speed of filling is size dependent: while small haemangiomas often fill within less than a minute, large lesions may take 5 minutes or more. The portal-venous and delayed enhancement of haemangiomas has been referred to as "lake-like". Many large haemangiomas will not fill completely and approximately 5-10% of smaller haemangiomas will show only minor peripheral filling (Fig. 12).

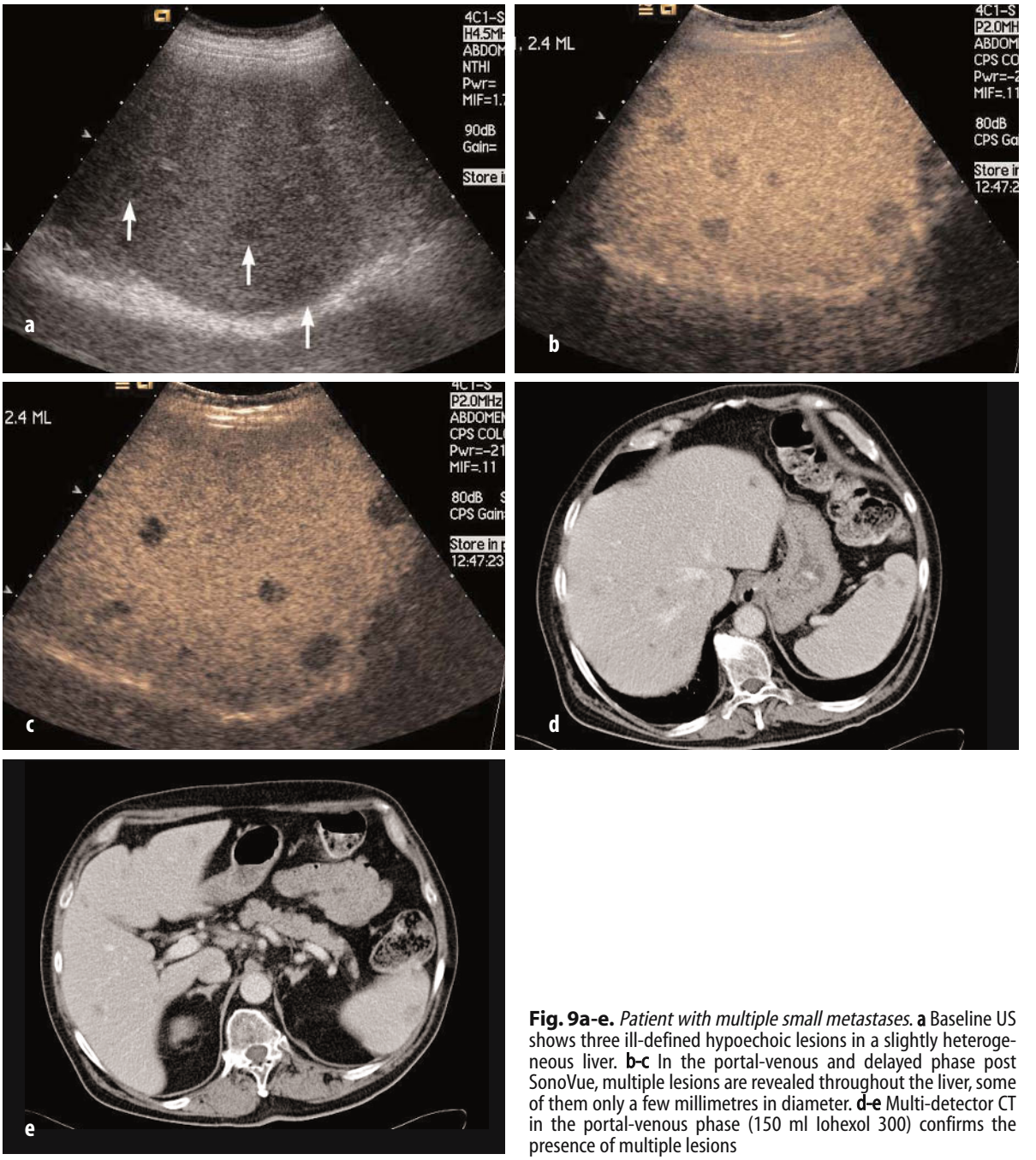


Fig. 9a-e. *Patient with multiple small metastases.* **a** Baseline US shows three ill-defined hypoechoic lesions in a slightly heterogeneous liver. **b-c** In the portal-venous and delayed phase post SonoVue, multiple lesions are revealed throughout the liver, some of them only a few millimetres in diameter. **d-e** Multi-detector CT in the portal-venous phase (150 ml Iohexol 300) confirms the presence of multiple lesions

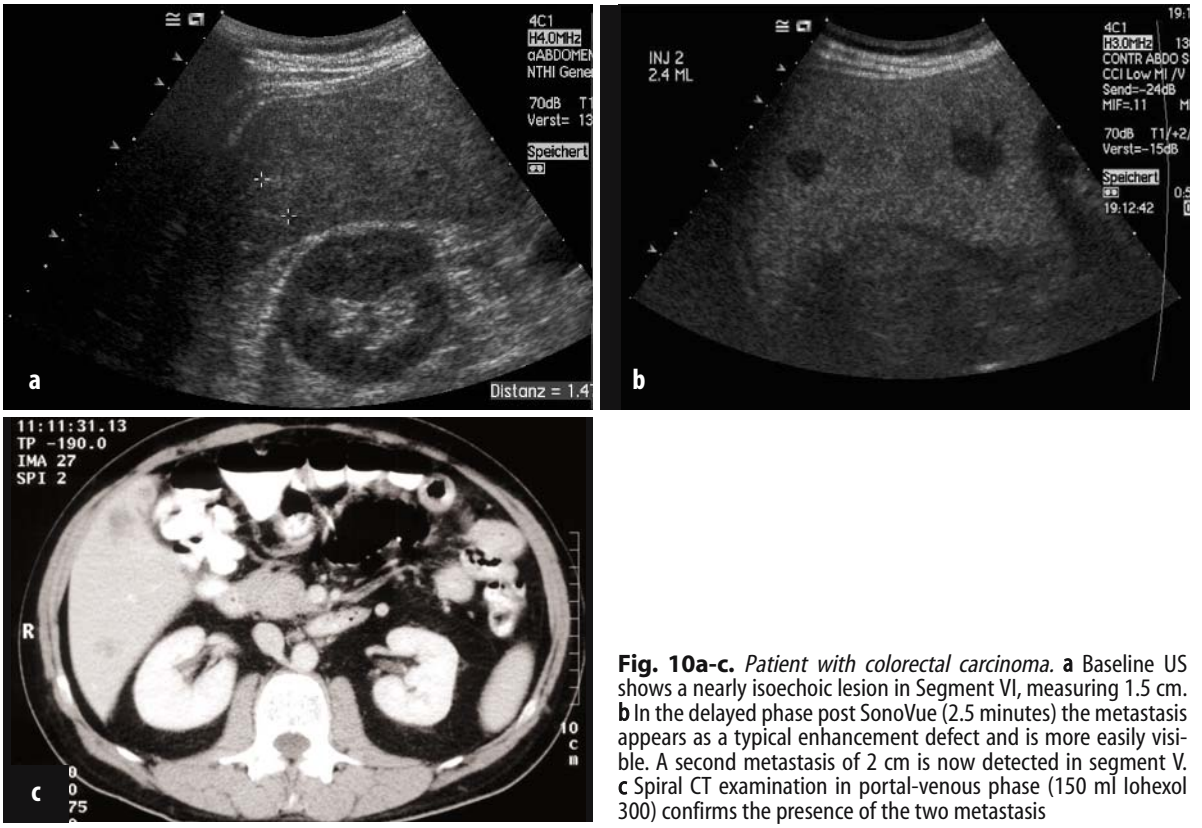


Fig. 10a-c. *Patient with colorectal carcinoma.* **a** Baseline US shows a nearly isoechoic lesion in Segment VI, measuring 1.5 cm. **b** In the delayed phase post SonoVue (2.5 minutes) the metastasis appears as a typical enhancement defect and is more easily visible. A second metastasis of 2 cm is now detected in segment V. **c** Spiral CT examination in portal-venous phase (150 ml Iohexol 300) confirms the presence of the two metastasis

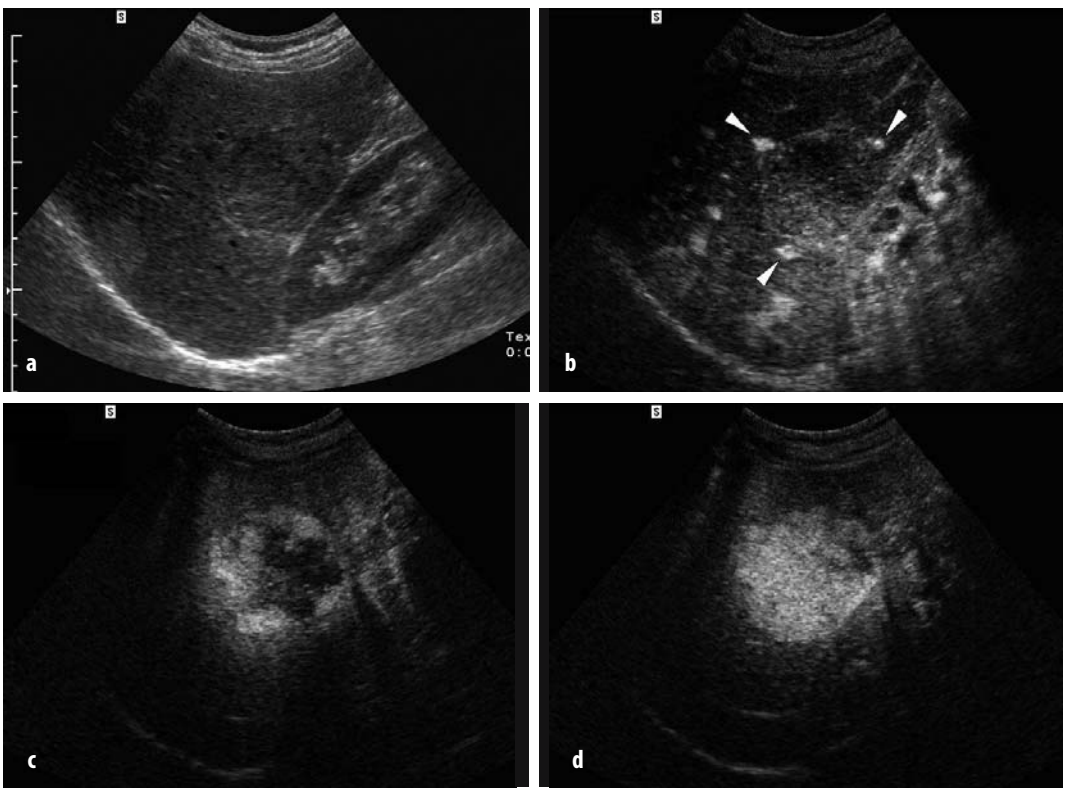


Fig. 11a-d. T*ypical dynamic enhancement of a haemangioma using Sonazoid.* **a** Atypical baseline appearances: isoechoic lesion suspicious of metastases in a patient with colon carcinoma. **b** Arterial phase with peripheral nodular enhancement (*arrowheads*). **c** Partial centripedal fill-in in the portal-venous phase (45 seconds post injection). **d** Complete filling of the haemangioma in the delayed

This can lead to misinterpreted identification as metastases. In such instances it is important to carefully assess the arterial phase for peripheral nodular enhancement (haemangioma) versus rim enhancement (metastasis), although these can be confused in small lesions.

FNH appear as lesions with homogeneous enhancement in the arterial phase. In about 50% of FNH this is preceded by a typical spoke-wheel arterial pattern with centrifugal filling early in the arterial phase through a dominant feeding artery, lasting for a few seconds (Fig. 13). In the subsequent phases, the lesions show a similar degree of enhancement to the normal liver, due to the fact that they consist of a liver-like tissue. A non-enhancing central scar is frequently seen in larger FNH during the delayed phase (Fig. 13c). Delayed phase imaging is particularly useful for FNH, as they invariably show as isoechoic or hyperechoic lesions, often with a non-enhancing central scar that was previously invisible. They are thus easily differentiated from metastases. Small FNH especially may become completely occult in the delayed phase due to their liver-like contrast behaviour.

Focal fatty change and focal fatty sparing show the same contrast behaviour as normal liver parenchyma in all phases, since they contain no abnormal vessels and essentially consist of normal parenchyma. Normal vessels that cross the lesions without displacement are much more commonly seen than on conventional Doppler imaging, since much smaller vessels can be imaged. Again, these lesions usually disappear after contrast injection (Fig. 14).

Liver *abscesses* can be confused with metastases on CEUS since they also show rim enhancement in the arterial phase and produce enhancement defects in the subsequent phases. An important differential diagnostic clue is the complete absence of vessels and enhancement in the central liquid portion of an abscess, while even hypovascular metastases will display some weak but visible central enhancement due to small vessels, provided they are not necrotic.

Detection of Hepatic Metastases with CEUS

As with other imaging modalities, the use of contrast agents substantially improves the ability of US to detect liver metastases. As described above, metastases are seen as non-enhancing defects in an otherwise homogeneously enhancing liver in the portal-venous, and particularly in the delayed phase, after contrast injection. The impact on detection is most marked for small lesions below 1 cm in diameter (Fig. 9) and for lesions that are isoechoic on baseline US. On the other hand, small metastases are less readily detected than larger lesions even with the use of contrast agents and may still be missed.

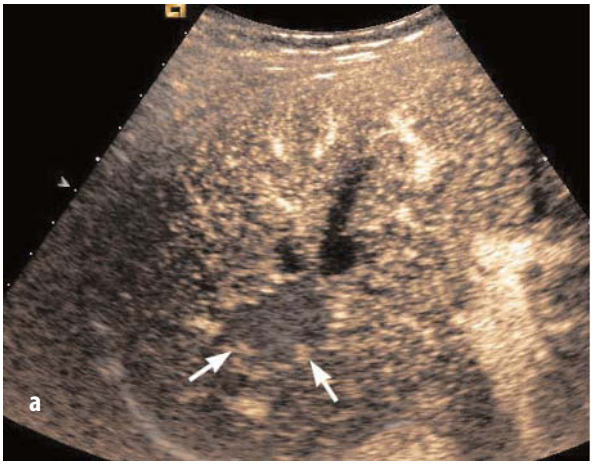
The use of contrast agents improves the sensitivity of US in detection of individual lesions by about 20% in comparison to baseline, independent of the type of contrast agent used [11, 12, 17-20]. To the authors knowledge, only two studies with a real gold standard (intra-operative US ± resection) have been published [11, 12]: they showed a sensitivity of 82-86%, which is comparable to contrast-enhanced CT and MRI with non-specific Gadolinium chelates [21-24]. One of these studies compared CEUS and spiral CT and found that the detection rate of CEUS was almost identical to that of dual phase spiral CT (82% versus 80%) [11].

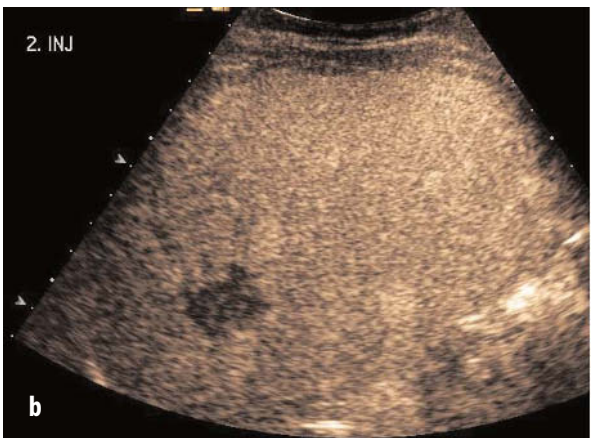
Specificity in diagnosing metastatic liver disease is also improved with USCA by up to 28% [18], since benign lesions show late phase enhancement similar to normal liver – independent of their arterial behaviour – and they are thus usually not confused with metastases. Furthermore, equivocal findings such as focal areas of heterogeneous parenchyma on baseline US, which raise the possibility of metastases, can be assessed further with contrast agents. If homogeneous enhancement is seen, metastases can be ruled out.

Limitations of CEUS

Some of the limitations of baseline US also apply to CEUS. If sonographic visualisation of some parts of the liver is poor due to obesity or otherwise unfavourable anatomy, this will not improve with the use of contrast agents. This is particularly true for subcapsular regions near the dome of the diaphragm.

Penetration of contrast-specific imaging modes is usually limited to 12-15 cm. This may not be insufficient for full visualisation of the deep parts of the liver in larger patients, even if low frequencies are used. Scanning the patient on the left side is very helpful in order to overcome this limitation, as the liver moves forward towards the transducer at the anterior abdominal wall in this position. Fatty change of the liver aggravates the problem of limited penetration and in severe fatty infiltration, large parts of the liver may not be assessable by CEUS. Other imaging modalities should be used in such patients.





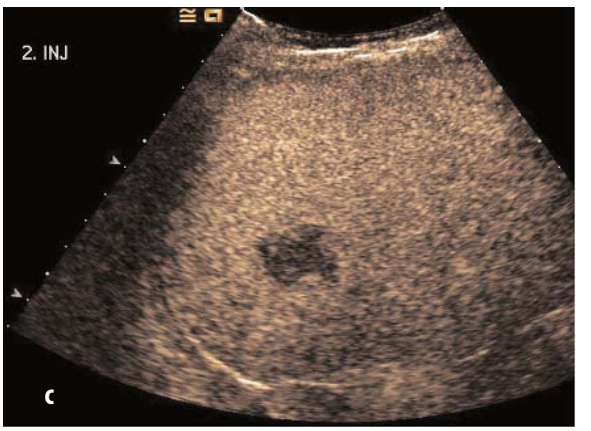
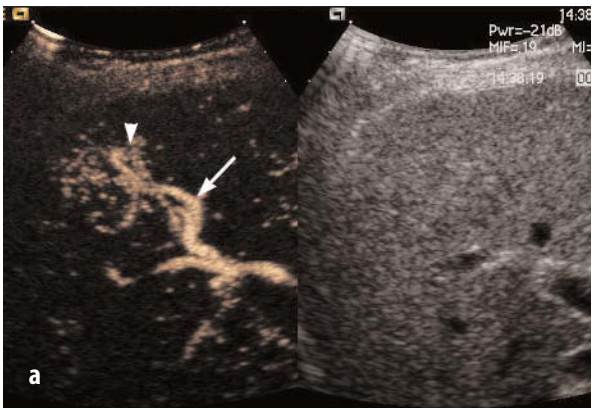
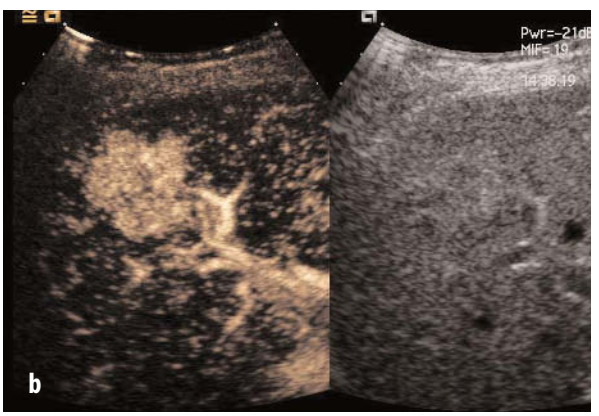


Fig. 12a-c. *Haemangioma with atypical partial filling after injection of SonoVue*. **a** Typical peripheral nodular enhancement (*arrows*) in the arterial phase. **b** Partial centripedal fill-in during the portal-venous phase. **c** No further filling of the haemangioma in the delayed phase. The centre of the lesion remains without contrast-enhancement throughout the entire examination. This can easily lead to confusion with metastases. The important differential diagnostic criterion is the arterial peripheral nodular enhancement typical of the haemangioma (versus rim enhancement, which is commonly seen in metastases)





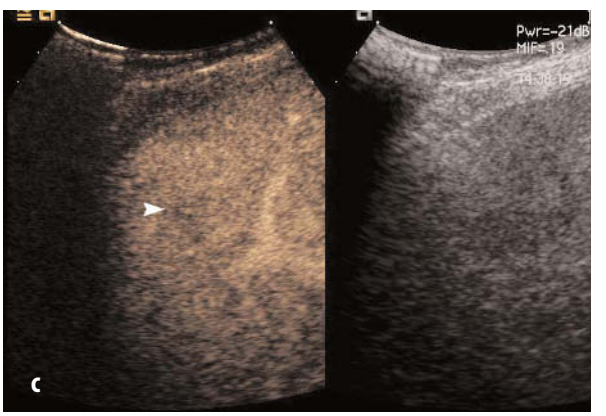


Fig. 13a-c. *Focal nodular hyperplasia post SonoVue*. **a** Large feeding artery (*arrow*) and spoke-wheel vascular pattern in the lesion (*arrowheads*) during the early arterial phase (14 seconds post injection). **b** Two seconds later the lesion is completely filled with contrast and appears hyperenhancing to normal liver. **c** In the portal-venous/delayed phase (2 minutes post injection) the lesion is isoenhancing to normal liver with the exception of a small hypoenhancing central scar (*arrowhead*)

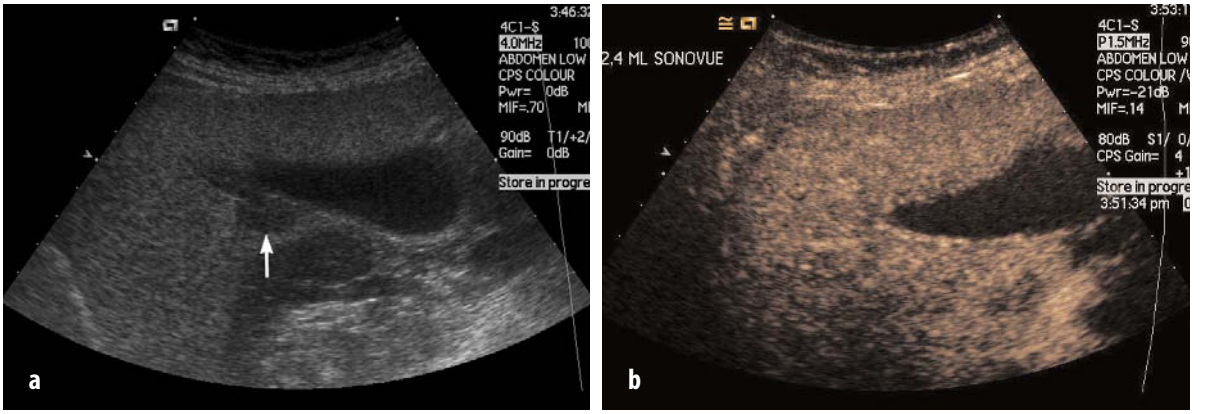


Fig. 14a, b. *Focal fatty sparing near the gallbladder in a patient with pharyngeal carcinoma.* **a** Unenhanced US shows a round hypoechoic lesion suggestive of a metastasis (*arrow*). **b** Homogeneous enhancement of the lesion in the delayed phase post SonoVue. The lesion is iso-enhancing to normal liver and becomes invisible

Current Role of CEUS in Clinical Practice

Contrast agents have greatly enhanced the role of US for liver imaging in oncology patients. There are two main indications for the use of contrast agents in this patient group: detection of metastases and characterisation of uncertain lesions.

Detection

According to the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) for the use of contrast agents in US [13], contrast agents should be used in 'all liver ultrasound scans to rule out metastases, unless conventional ultrasound shows clear evidence of these lesions'. This recommendation reflects the substantial improvement in sensitivity and the fact that the sensitivity of unenhanced US is too low to rule out metastases. Conventional US without contrast agents now has to be regarded as inadequate for ruling out metastases. The use of contrast agents is also recommended by the EFSUMB guidelines 'in selected cases, when clinically relevant for treatment planning, to assess the number and location of liver metastases as a complement to CT and/or MRI', since CEUS may show lesions that were missed by other imaging modalities. This obviously has important implications for planning of liver resection or local ablation. It is important to remember that CEUS is complementary to CT and/or MRI in such patients, and that it cannot replace the other modalities in the pre-operative or pre-interventional work-up, since CT and MRI give more comprehensive information about the liver and all other abdominal organs, including lymph nodes and peritoneum. The maximum information should be sought in these patients by combining several modalities. CT and/or MRI can, however, be replaced by CEUS for liver staging in patients with extra-abdominal tumours such as breast carcinoma, who usually do not require comprehensive abdominal imaging beyond the liver.

Characterisation

As discussed above, CEUS is ideally suited to characterise liver tumours in cancer patients, in whom 50-75% of lesions ≤ 2 cm represent metastases, while the remainder is benign. CEUS should be the first-line modality for the evaluation of lesions seen on baseline US. It should be performed as part of the initial US examination and, in most cases, it will provide a definitive lesion diagnosis. This approach avoids further imaging such as MRI or CT in many patients, especially when dealing with a benign lesion. It spares the patient from psychological stress while waiting for another examination. It is also cost-effective and makes the best use of the resources of a health care system, since the added cost of USCA is lower than that of an additional CT and especially of an MRI examination. CEUS can also be very useful in patients with a lesion that cannot be characterised on CT or even MRI. Not infrequently, such lesions can be characterised on CEUS, sparing the patient a biopsy. This approach is also recommended by the EFSUMB guidelines.

Key Points

- Conventional US without contrast agents is limited in its ability to detect metastases and to differentiate metastases from benign lesions.
- USCA substantially improves the ability of US to visualise metastases and thus increases the sensitivity of US for the detection of metastases, to a level that is comparable to spiral CT.
- CEUS provides reliable differentiation between metastases and benign lesions in most cases.
- USCA should be used in all oncology patients undergoing sonographic liver staging, unless metastases are clearly demonstrated by unenhanced US.

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