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KEYNOTE LECTURE

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Non-invasive diagnosis of focal liver lesions: an individualized approach

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Abstract

Modern cross-sectional imaging with multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI) often reveals small focal liver lesions, which puts pressure on the reporting radiologist to characterize these tiny lesions. On the other hand, in patients with underlying diffuse liver disease, such as cirrhosis or severe steatosis, the detection of focal liver lesions can be quite difficult. Strategies for optimal detection and characterization of focal liver lesions should be developed according to the clinical situation, the likelihood of malignant disease and the presence of underlying diffuse liver disease. The presence or absence of a clinical history of cancer determines the algorithm for further characterization: work-up with contrast-enhanced MRI, biopsy or follow-up. In patients with chronic liver disease, recent guidelines on the detection of hepatocellular carcinoma (HCC) favour the use of multiphasic MRI or MDCT, which allows confident diagnoses of HCC >1 cm. For lesions <1 cm in chronic liver disease, follow-up is recommended. In patients with moderate to severe steatosis, contrast-enhanced MDCT has low diagnostic yield for the detection of liver lesions; contrast-enhanced MRI is far superior. This review describes successful strategies for the detection and characterization of focal liver lesions in different clinical scenarios.

Keywords: *Liver; tumour; metastasis; hepatocellular carcinoma; magnetic resonance imaging; multidetector computed tomography.*

Introduction

In the meta-analysis of Kinkel et al.[1] on the diagnostic value of ultrasonography (US), computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) for liver metastases of the gastrointestinal tract, the results showed that fluorodeoxyglucose (FDG)-PET had the highest mean sensitivity of 90% for the detection of focal liver lesions, revealing a significantly greater sensitivity than US, CT, and MRI. In 2010, Niekel et al.[2] performed another meta-analysis on CT, MRI, FDG-PET, and FDG-PET/CT for the detection of colorectal liver metastases. According to their results, FDG-PET had the highest sensitivity on a per patient basis. MRI was equivalent to FDG-PET in terms of detection on a per lesion basis (sensitivity 80.3% vs 81.4%). The authors concluded that MRI is the preferred first-line modality for evaluating colorectal liver metastases, and FDG-PET can be used as the second-line modality. Following these recommendations would not only put serious strain on health care budgets in all countries, but is also in contrast with everyday experience and the results of many studies, which suggest that different imaging strategies should be used in different clinical scenarios[3].

In this review, we illustrate the role of imaging in (1) patients with focal masses detected by US, (2) liver imaging follow-up of patients with extrahepatic malignancies, (3) follow-up of patients with extrahepatic malignancies who have moderate to severe liver steatosis, (4) preoperative evaluation of patients scheduled for liver surgery, (5) surveillance of patients with known diffuse liver disease, and (6) work-up of focal lesions too small to characterize (TSTC).

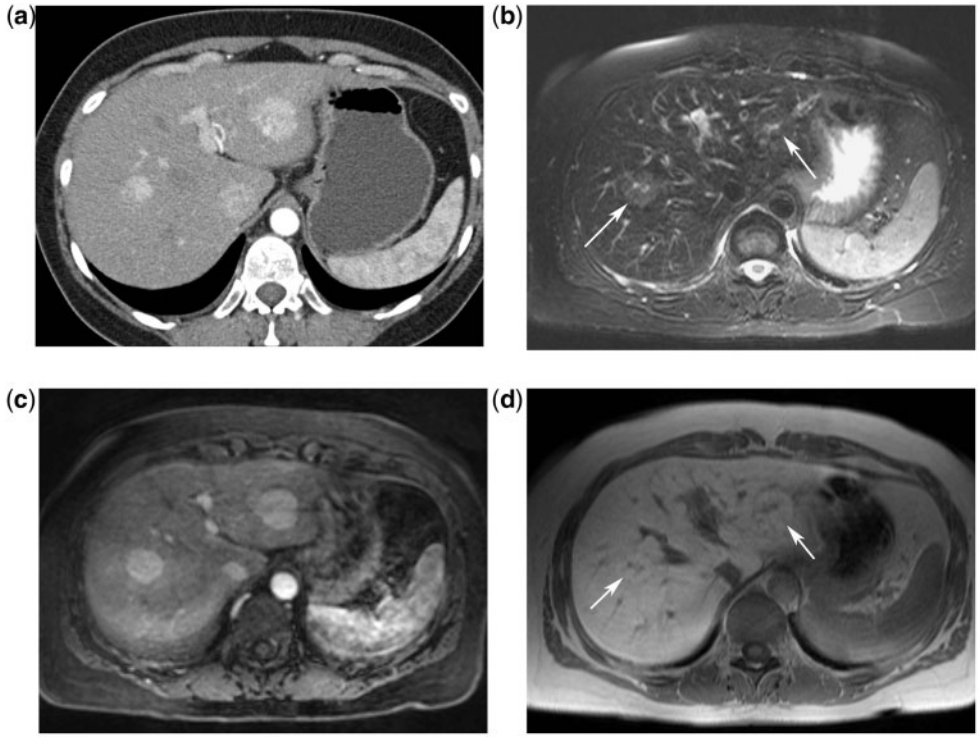

Figure 1 **Incidentally detected focal liver lesion. Contrast-enhanced CT in the arterial phase (a) demonstrates 2 hypervascular lesions, which cannot be characterized with certainty. Axial T2-weighted MR image (b) shows the lesion to be isointense with hyperintense central scars (arrows). On the T1-weighted gradient recalled echo (GRE) image in the hepatobiliary phase (d), the lesions are isointense due to hepatocellular uptake of contrast material (arrows). Findings are indicative of FNH.**

Focal masses detected by ultrasound

In patients with focal liver lesions, detected incidentally or due to clinical symptoms, non-invasive characterization is important. If malignancy is suspected, exact assessment of the tumour burden by detection of all liver lesions is needed. It has been shown that MRI with liver-specific contrast agents is superior to contrast-enhanced CT in terms of lesion characterization[4–6]. In particular, MRI with liver-specific agents is superior to CT for differentiation between hepatocellular and non-hepatocellular lesions, with an accuracy of 90% versus 64%[6]. Differentiation between metastases and benign hepatocellular lesions (e.g. focal nodular hyperplasia (FNH)) is achieved with high accuracy[7] (Fig. 1). Thus, contrast-enhanced MRI is the technique of choice to characterize equivocal lesions detected at US without wasting time and resources with multiphase CT.

Preoperative evaluation of patients scheduled for liver surgery

Several studies have shown that contrast-enhanced MRI is superior to helical and MDCT in the detection of liver metastases[8–10]. In the subgroup of patients with small liver metastases (up to 1 cm), MRI proved to be particularly superior to CT[10,11] (Fig. 2). MRI even outperforms PET/CT in patients with colorectal cancer metastases[12,13]. It has been shown that contrast-enhanced MRI is more cost effective than contrast-enhanced CT in the evaluation of patients scheduled for liver segment or lobe resection, as additional information provided by MRI may prevent surgical intervention in 33%[14]. However, best results can be achieved in preoperative staging if contrast-enhanced MDCT of the chest and the abdomen is combined with contrast-enhanced MRI (preferably with liver-specific contrast agents) for exact assessment of intrahepatic tumour burden. Nowadays, adequate preoperative staging combining MDCT and MRI rarely leads to a change in intraoperative strategy in patients undergoing resection of colorectal cancer liver metastases. In a recent study, additional lesions were detected intraoperatively by intraoperative ultrasound (IOUS) and manual palpation in only 8.2%; most of them were small (<1 cm) and subcapsular[15].

Follow-up of patients with extrahepatic malignancies

For the follow-up of patients with extrahepatic primary tumours, different strategies have been endorsed,

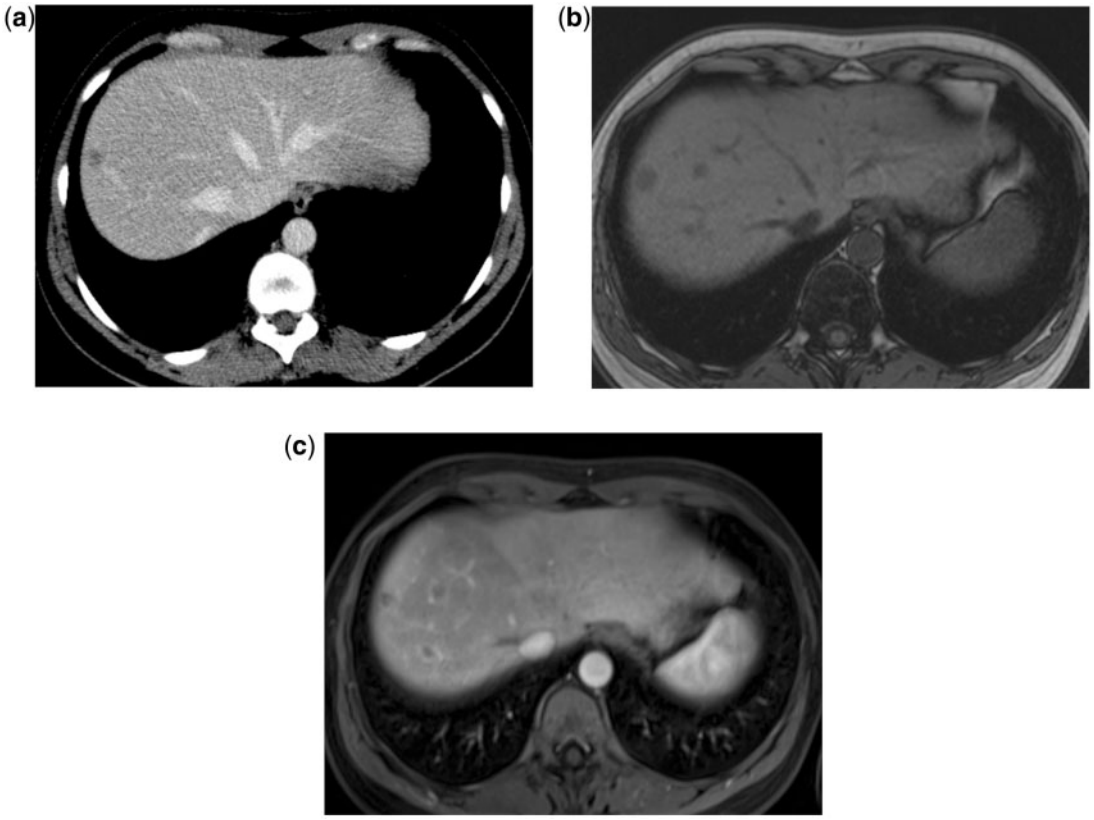

Figure 2 **Preoperative assessment of colorectal liver metastases. At the contrast-enhanced MDCT, one small lesion is faintly seen in the right lobe. Unenhanced T1-weighted GRE (b) and gadolinium-enhanced MR images in the venous phase (c) reveal 3 lesions in the right lobe with rim enhancement, suggestive of metastases.**

depending on the tumour histology and location, tumour grading, staging, etc. These strategies may include PET/CT, contrast-enhanced CT of the chest, abdominal, and pelvis, abdominal sonography or even no imaging follow-up at all. For several gastrointestinal tract malignancies, CT of the chest and abdominal pelvis has been established as the modality of choice. The guidelines of the European Society of Medical Oncology (ESMO) recommend CT follow-up of patients with colon cancer, rectal cancer and pancreatic cancer[16–18], mainly at intervals of 6–12 months. There is no evidence that CT follow-up of patients with oesophageal or gastric cancer improves outcome[19,20]. There are no published data to indicate the optimal imaging follow-up strategy of patients with surgically treated gastrointestinal stromal tumour (GIST). According to the ESMO guidelines[21], low risk GISTs should be followed with CT every 6 months (for 5 years), whereas intermediate- to high-risk tumours need close follow-up with CT every 3–4 months for 3 years, then every 6 months until 5 years[21]. If CT follow-up of cancer patients reveals newly established liver lesions, further work-up depends on the treatment options. If palliative chemotherapy is indicated, treatment success will be assessed by CT. If curative resection of liver metastases is an option (e.g. patients with colorectal cancer), the exact definition of the tumour burden with liver MRI may be indicated (see paragraph on preoperative evaluation).In the case of increasing tumour marker levels, according to the primary malignancy and negative MDCT of the chest and abdomen, PET/CT should be sought.

Follow-up of patients with extrahepatic malignancies with liver steatosis

Patients with colorectal cancer metastases now receive neoadjuvant chemotherapy before liver resection, because it has been shown that the outcome can be improved[22]. However, different therapeutic agents, including irinotecan or oxaliplatin, induce steatosis and steatohepatitis[23], which is a major risk factor for post-operative complications after hepatectomy[24]. Moreover, severe steatosis of the liver may interfere with imaging assessment (Fig. 3).MDCT is quite accurate for defining patients with more than 30% steatosis of the liver[25]. In these patients with moderate to severe liver steatosis, contrast-enhanced MDCT has been shown to have only limited accuracy in the detection of small metastases. In a recent study by Kuleman et al.[26], MRI detected significantly more liver metastases than MDCT (88% vs 65%).

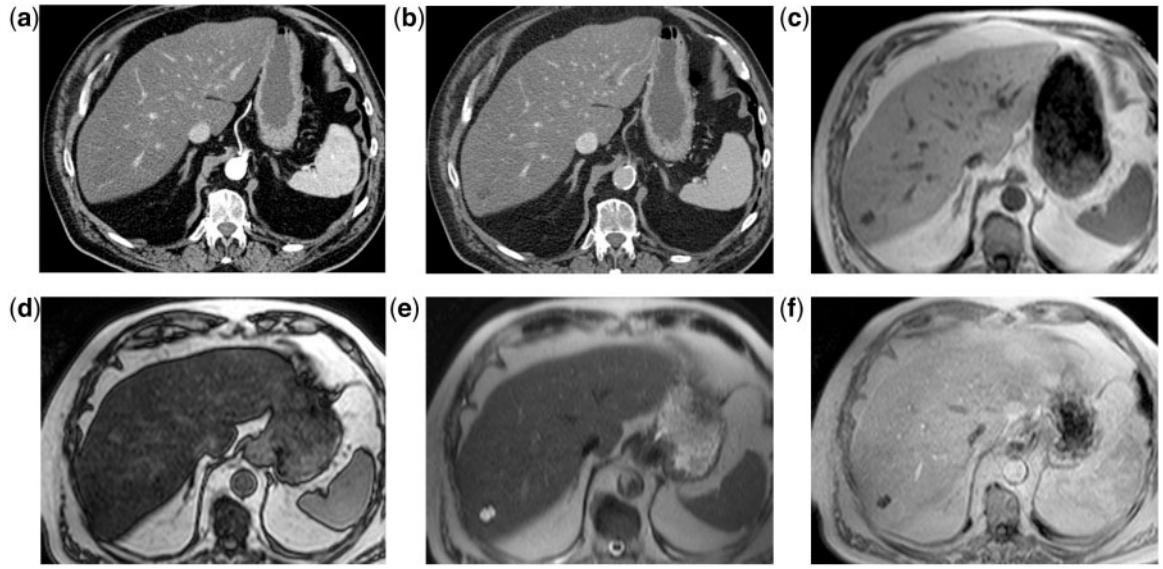

Figure 3 **Focal lesion in a patient with severe steatosis. Contrast-enhanced MDCT in the arterial (a) and venous (b) phases shows a small lesion in the right lobe, which seems to be solid. No further characterization is possible with CT. Unenhanced T1-weighted MR in-phase (c) and opposed-phase (d) show a hypointense lesion in the right lobe and severe signal intensity drop due to steatosis. On the T2-weighted image (e), the lesion is very hyperintense. Gadolinium-enhanced T1-weighted GRE image in the equilibrium phase shows minimal nodular enhancement, suggestive of a slow-flow haemangioma.**

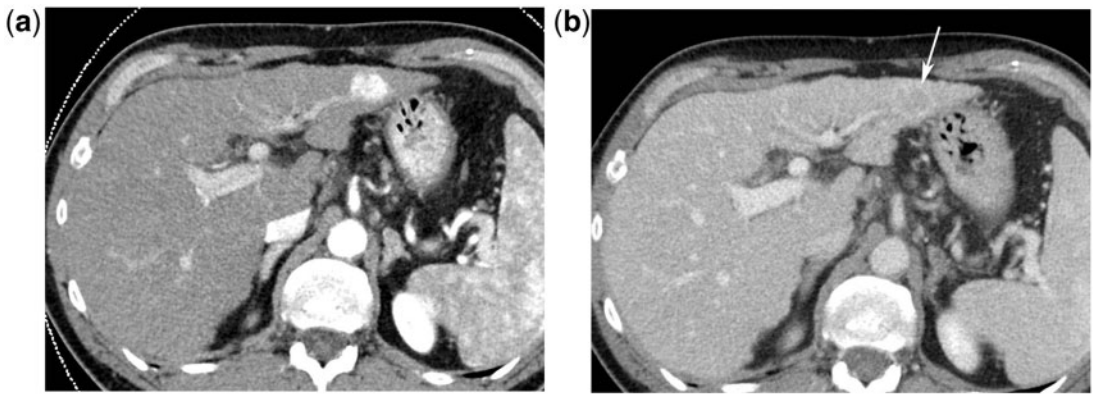

Figure 4 **HCC: arterial hypervascularity and wash-out sign at MDCT. Contrast-enhanced MDCT in the arterial (a) and venous (b) phases demonstrates a small hypervascular tumour in a patient with cirrhosis, which shows wash-out to hypoattenuation in the venous phase. These imaging features are pathognomonic in a patient with liver cirrhosis.**

For the subgroup with metastases up to 1 cm, MDCT showed only 11% and MRI 66%. Thus, evaluation of the exact number and location of liver metastases in patients with steatosis is the domain of contrast-enhanced MRI, which should be added in the case of an equivocal lesion at CT.

Detection and staging of HCC

HCC is a major health problem worldwide due to its high incidence and adverse outcome. The presence of chronic liver disease is the most important risk factor for the development of HCC. Thus, surveillance of patients with chronic liver disease makes early detection of HCC possible. Different surveillance strategies have been proposed[27–30]: the serum tumour marker alpha-fetoprotein (AFP) has been found to be not useful, with an unacceptably low sensitivity and specificity. Moreover, even in AFP-positive patients, early detection of HCC is not possible. It has been found that US surveillance of patients with chronic liver disease at 6- to 12-month intervals is feasible and significantly improves

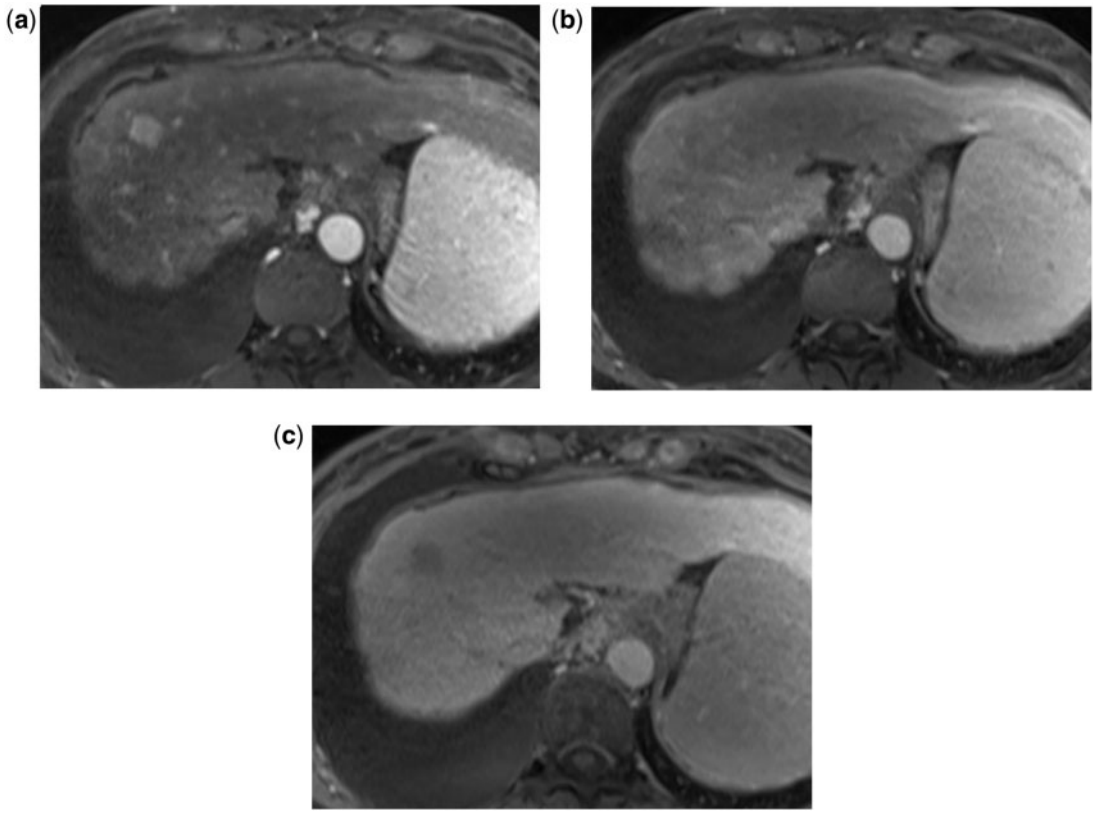

Figure 5 **HCC: arterial hypervascularity and wash-out sign at MRI. HCC in the right lobe is hypervascular in the arterial phase (a), isointense in the venous phase (b) and shows wash-out to hypointensity in the equilibrium phase after 5 min (c). These imaging features are also pathognomonic for HCC. In principle, wash-out of HCC to hypointensity/ hypoattenuation can be seen in the venous and/or equilibrium phases.**

early detection of small HCC and, thus, survival[28,29]. Shortening these intervals to 3 months does not improve survival further[31]. It is an important task to characterize those lesions found at US and to assess tumour burden. Recent guidelines by the American Association for the Study of Liver Diseases[30] recommend that multiphasic CT or MRI should be used for characterization of nodules in liver cirrhosis. In nodules >1 cm, arterial hypervascularity and the wash-out sign in the venous or equilibrium phases allow a confident diagnosis of HCC without histological evidence (Figs. 4 and 5). The most recent guideline of the European Association for the Study of the Liver takes a more conservative approach; it states that reliance on a single imaging modality is "only recommended in centres of excellence with high-end radiological equipment"[32]. If the results of contrast-enhanced CT (or MRI) are equivocal, both guidelines recommend that the respective other examination should be performed. If both examinations do not allow a confident diagnosis, than percutaneous biopsy should be sought. In nodules <1 cm in diameter, US follow-up at 3 months should be performed to assess lesion growth.

It may be difficult to characterize small arterially enhancing nodules in cirrhosis, differentiating between HCC, dysplastic nodules and transient hepatic attenuation differences (THADs). In the absence of a wash-out sign, small HCC or dysplastic nodules are difficult to differentiate from THADs. Assessment of shape and location is helpful: wedge-shaped, geographic or triangular lesions disappeared or shrank in 67–73% of lesions, indicating benignity (Fig. 6). On the other hand, round or oval hypervascular nodules disappeared or got smaller in only 52% and were considered definite pseudolesions[33]. Round or oval lesions were classified as HCC in 28%, based on lesion growth or histology. Location is also an important factor, as subcapsular lesions are benign in 84%, whereas nodules with central intraparenchymal location were found to be benign in only 70%[34]. At multivariate analysis, several risk factors for the development of small arterially enhancing nodules into an HCC could be identified[35]: the presence of HCC treatment history, the presence of coexistent HCC and the absence of a coexistent identifiable arterioportal shunt. MRI with diffusion-weighted imaging has also been shown to be a reliable technique to differentiate between arterio-portal shunts and HCC[36]. In general, multiphasic contrast-enhanced CT is an excellent technique for the detection of HCC, but MRI has been shown to be superior, especially for the detection of small tumours[37–39].

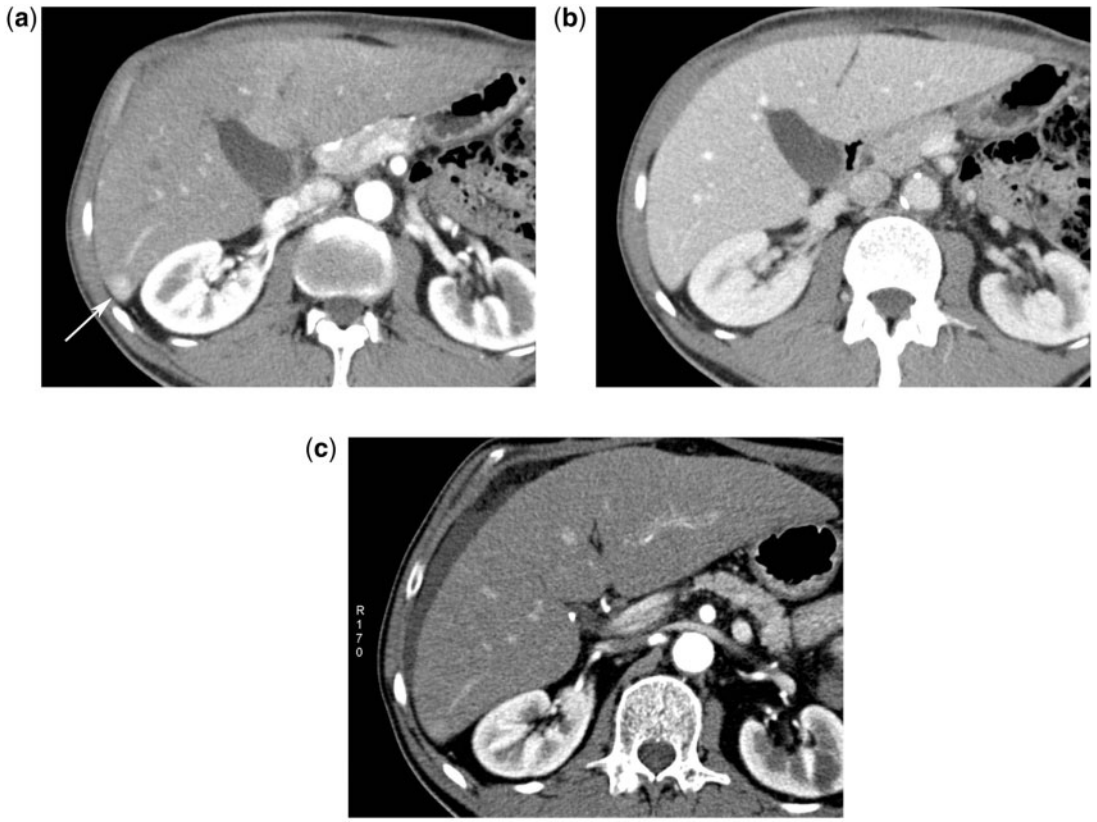

Figure 6 **THAD in a patient with liver cirrhosis. Contrast-enhanced MDCT in the arterial phase (a) shows a small peripheral zone of hyperattenuation (arrow), which is isodense in the venous phase (b). Follow-up was recommended. At the follow-up study 10 months later (c), the THAD is only faintly seen.**

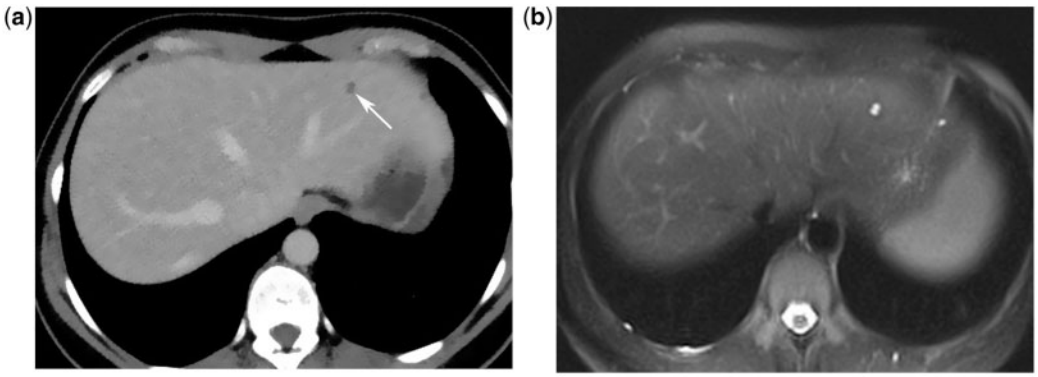

Figure 7 **Lesion TSTC. Contrast-enhanced MDCT (a) shows a small lesion in the left lobe, which cannot be characterized. In a patient with a history of malignant disease, further work-up is recommended. The T2-weighted MR image (b) shows the tiny lesion to be very hyperintense, suggestive of a small cyst. Another tiny cyst is shown in the left lateral segment.**

Thus, the choice between MDCT or MRI depends on local expertise and availability of equipment.

TSTC lesions

Focal liver lesions are quite often found with thin-section CT or MRI. Jones et al.[40] found hepatic lesions 15 mm or smaller in 17% of patients undergoing abdominal CT. In a study on patients with a history of malignant disease, Schwartz et al.[41] detected small lesions up to 10 mm in diameter in 12.7% of patients. In patients with breast cancer, the prevalence of TSTC lesions was even higher (29.4%) at CT[42]. Most of these lesions are benign. Only 22%[40] of lesions up to 15 mm and 11.6% of lesions up

to 10 mm[41] demonstrated interval growth and were therefore considered malignant. The likelihood of metastatic disease correlated with the type of primary malignancy; small lesions were metastatic in 4% in lymphoma, 14% in colorectal cancer and 22% in breast cancer[41]. With the use of multirow thin-section MDCT, the prevalence of TSTC lesions is even higher than in the helical or non-helical area[40–42]. However, this relates to an increased detection rate of small benign findings (i.e. cysts) and, thus, a decreased proportion of metastatic lesions[42]. In a study of patients with breast cancer[43], one or more small hyperattenuating lesions were seen in 35%, but these patients were not at an increased risk of developing liver metastases subsequently.

What should the work-up of these small lesions be? It has been found that, in patients without a history of malignant disease[40] and a single small lesion, the risk of malignant disease is virtually zero. Thus, no further work-up can be recommended. On the other hand, in patients with malignant disease, careful analysis of the imaging features is important. Benign lesions have very discrete margins and are of markedly low attenuation[44]. If a definitive diagnosis is warranted, contrast-enhanced MRI with or without diffusion-weighted pulse sequences is likely to help in differentiating between small cysts and haemangiomas versus malignant disease (Fig. 7)[45,46]. It has been shown that MRI characterization of small lesions is very accurate in routine clinical practice[47]. In most patients, close follow-up CT (preferably 3 months) allows early detection of metastatic growth, without adversely affecting the prognosis.

Conclusion

An individualized approach to detection and characterization is necessary, based on the clinical history and the likelihood of malignant disease, the presence of diffuse liver disease and lesion size.

Conflict of interest

The authors have no conflicts of interest to declare.

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