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Radiological assessment of secondary biliary tree lesions: an update

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Abstract

Objective: To conduct a systematic literature review of imaging techniques and findings in patients with peribiliary liver metastasis.

Methods: Several electronic datasets were searched from January 1990 to June 2017 to identify studies assessing the use of different imaging techniques for the detection and staging of peribiliary metastases.

Results: The search identified 44 studies, of which six met the inclusion criteria and were included in the systematic review. Multidetector computed tomography (MDCT) is the technique of choice in the preoperative setting and during the follow-up of patients with liver tumors. However, the diagnostic performance of MDCT for the assessment of biliary tree neoplasms was low compared with magnetic resonance imaging (MRI). Ultrasound (US), without and with contrast enhancement (CEUS), is commonly employed as a first-line tool for evaluating focal liver lesions; however, the sensitivity and specificity of US and CEUS for both the detection and characterization are related to operator expertise and patient suitability. MRI has thus become the gold standard technique because of its ability to provide morphologic and functional data. MRI showed the best diagnostic performance for the detection of peribiliary metastases.

Conclusions: MRI should be considered the gold standard technique for the radiological assessment of secondary biliary tree lesions.

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Background

The incidence of primary liver cancers, including hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCC), has increased in recent decades, partially because of hepatitis C virus and non-alcoholic fatty liver disease.[1] Hepatitis C virus is a major cause of chronic liver disease, affecting 170 million people worldwide (3% of the world's population), while cirrhosis can occur in 20% of these patients. Non-alcoholic fatty liver disease is the most common cause of chronic liver disease in North America, affecting up to 30% of the general population.[1] These pathological conditions increase the risk of developing liver cancer as a result of chronic damage to the hepatic parenchyma.[1] At the same time, the increasing availability of imaging modalities has allowed the diagnosis of more metastatic liver lesions,[1] and the management of patients with liver metastasis is associated with different diagnostic and treatment phases.[1] The detection of a focal liver lesion in a cancer patient does not necessarily indicate a metastasis, and lesion characterization is thus a crucial step in patient management. The detection and characterization of a lesion are followed by staging to identify lesions suitable for resection and those needing other treatments.[2] The criteria for resectability have changed in recent years, and surgeons now consider not only the number and site of the lesion, but also the quantity and quality of the non-involved liver, i.e. the functional remnant volume after surgery.[3] The correct identification of the anatomic site (intra-parenchymal or peribiliary) is an emerging requirement linked to the need to establish the resectability of a lesion, given that the location may affect the therapeutic approach.[4] Peribiliary metastases are usually considered to be infrequent, but are the most common solid biliary cancers after CCC.[5] Gastrointestinal cancers are the most common malignancies that metastasize to the biliary tree,[5] and the common hepatic duct is the most frequently involved site, with the lesion appearing as an extraluminal mass or as hepatoduodenal ligament lymph node metastasis.[5,6] However, current imaging techniques do not permit peribiliary metastases to be differentiated conclusively from CCC, and both appear as extraluminal peribiliary tissue.[4] Although fluorine-18 fluorodeoxyglucose positron emission tomography (PET) is the most accurate method for detecting peribiliary cancer, it is not specific. PET has the advantage of being able to quantify the tumor biology using fluorodeoxyglucose uptake, based on the standardized uptake value. However, the actual role of PET during the detection phase remains unclear, and it has been shown to be no better than multidetector computed tomography (MDCT) or magnetic resonance imaging (MRI).[7] Ultrasound (US) is usually recommended as the first-line tool for evaluating liver cancers, but its diagnostic accuracy is lower than that of MDCT or MRI[8] and is subject to operator expertise.[9,10] MDCT and MRI allow assessment of the liver parenchyma and biliary tree and can identify the site of the lesion and its spread.[11] International guidelines recommend the use of MDCT, because this technique is widely available and standardized, and can be used to scan the whole body in one setting.[12,13] Conversely, MRI allows a more accurate characterization of the lesions and can offer morphologic and functional data,[14,15] and the European Society of Gastrointestinal and Abdominal Radiology Working Group guidelines thus recommend the use of MRI in this clinical setting.[16,17]

This study provides an updated overview of the radiological assessment of peribiliary metastases, based on a systematic literature search and review.

Methods

Search criteria

A literature search was conducted to assess the use of imaging for the detection and staging of peribiliary metastases. We searched Ovid, Embase, the Cochrane database, and Medline, using PubMed as a search engine, to identify studies reporting the accuracy of MDCT, MRI, and US, with and without contrast enhancement (CEUS), to detect and stage peribiliary metastases. The databases were searched for articles published from January 1990 to June 2017. The search was conducted using the following keywords: "peribiliary metastases" AND "ultrasound" AND "detection" AND "characterization", "peribiliary metastases" AND "multidetector computed tomography" AND "detection" AND "characterization", "peribiliary metastases" AND "magnetic resonance imaging" AND "detection" AND "characterization", "peribiliary metastases" AND "diffusion weighted imaging" AND "detection" AND "characterization", "peribiliary metastases" AND "dynamic contrast enhanced magnetic resonance imaging" AND "detection" AND "characterization", "peribiliary metastases" AND "EOB-GD-DTPA contrast medium" AND "detection" AND "characterization", "peribiliary metastases" AND "multimodal imaging" AND "detection" AND "characterization". Articles were also identified using the 'related articles' function in PubMed. The references of all retrieved articles were also extensively crosschecked to identify any further studies. Relevant articles identified by reviewing titles in the reference lists were also reviewed in full.

The inclusion criteria were as follows: clinical study assessing the role of US for the detection and staging of peribiliary metastases; clinical study assessing MDCT for the detection and staging of peribiliary metastases; clinical study assessing MRI for the detection and staging of peribiliary metastases; clinical study assessing functional MRI criteria for the detection and staging of peribiliary metastases; and clinical study evaluating diffusion-weighted imaging (DWI) and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (EOB-GD-DTPA) for assessing peribiliary metastases. Articles for which the full text was not available, general overview articles, and congress abstracts were excluded. No minimum number of patients was defined as an inclusion criterion, given that peribiliary metastases are generally considered to be rare.

The authors of the studies were not contacted for further data retrieval in this study.

Results

The search results yielded 44 studies, including two studies that used diagnostic techniques other than US, MDCT, or MRI, 26 studies with a topic other than peribiliary metastasis, and 10 articles that matched more than one excluded criterion. Six articles were therefore included in the review (Figure 1, Table 1).

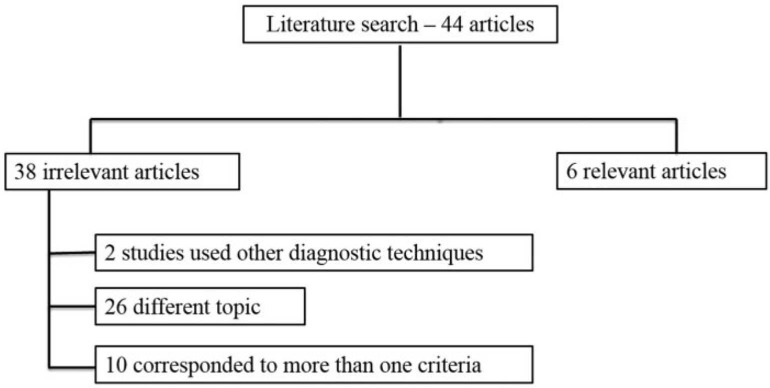

Figure 1. Included and excluded studies in systematic review.

Table 1. Reference articles used in this study.

Authors	Granata et al.[4]	Granata et al.[18]
Patients (number)	34	35
MR (number detected lesions)	34	35
T2-W Diagnostic performance (confidence scale: 1–4)	4	
DW Diagnostic performance (confidence scale: 1–4)	4	
Arterial phase Diagnostic performance (confidence scale: 1–4)	3.4	
Portal phase Diagnostic performance (confidence scale: 1–4)	3	
EOB-phase Diagnostic performance (confidence scale: 1–4)	3.6	
US (number detected lesions)		1
MDCT (number detected lesions)		8

MR: magnetic resonance, DW: diffusion-weighted, EOB: ethoxybenzyl, US: ultrasound, MDCT: multidetector computed tomography.

Discussion

Peribiliary metastasis is usually considered to be a rare occurrence.[4] However, Granata et al.[18] assessed 35 oncology patients with peribiliary metastases and showed that the incidence of peribiliary metastases was miscalculated. The authors suggested that the incidence of this condition was related to the choice of MDCT as a diagnostic test in the preoperative setting and during follow-up of patients with liver cancers. The development of MDCT technology has drastically changed liver imaging, with the possibilities of shorter acquisition times, obtaining thinner sections in a single-breath hold, and allowing lesion display and higher quality vascular reconstructions. Multiphase image acquisition allows data to be obtained during a true arterial, venous, delayed, or other chosen phase. Furthermore, the introduction of several image noise-reduction algorithms has resulted in preserved image quality and reduced radiation dose. The acquisition of imaging data with isotropic voxels allows high-quality three-dimensional reconstructions with precise vascular mapping and parenchymal definition, so enabling accurate segmental lesion localization to support surgical and non-surgical treatment planning.[19] MDCT has thus replaced conventional angiography for defining vascular anatomy.[20] Moreover, the accurate evaluation of liver volume is essential to ensure acceptable remnant liver parenchymal function in patients undergoing resection. Developments in MDCT imaging enable more precise evaluation of liver size and aid assessment of the volume of the regenerated liver after pre-surgical portal vein embolization.[21,22] Its accessibility, speed, and lower cost compared with MR scanning mean that MDCT has become the optimal imaging technique for evaluating liver nodules, with significant diagnostic accuracy in terms of their detection and characterization.[19] MDCT is therefore now the technique of choice in both the preoperative setting and during follow-up of oncological patients. However, the diagnostic performance of MDCT for the detection and characterization of biliary tree cancers is lower than that of MRI. Granata et al.[18] found that MDCT only identified 23% of peribiliary metastases, in agreement with several previous reports[23–25] that demonstrated the inadequate performance of MDCT for detecting biliary tumors (Figure 2). Several studies reported that MDCT only detected 69% of lesions, and accurately evaluated resectability in only 54% of cases. The sensitivity and specificity of MDCT for discriminating between malignant and non-malignant biliary tree nodules ranged from 82%–90% and 65%–80%, respectively.[23–25] Granata et al. suggested that the low diagnostic performance of MDCT in this subset of liver metastases was due to progressive contrast enhancement of the metastases, such that small lesions were undetected by MDCT imaging because their attenuation was similar to that of the surrounding liver parenchyma.[18] In contrast to Granata et al.,[18] several studies have suggested that MDCT allows better definition of the relationship between

Figure 2. MDCT scan during portal phase of contrast study. Peribiliary metastasis shown as a hypoattenuated area in liver segment II, not correctly identified.

the tumor and the neighboring vasculature and biliary structures in patients with biliary malignancies.[26–28] However, the lower detection rate similar to MRI (Figures 3–5), and the fact that unobserved lesions might affect the choice of therapeutic approach, indicate the need for radiologists to assess the occurrence of ancillary signs, such as biliary duct dilatation, and suspected peribiliary metastases should be evaluated by MRI.[18] Granata et al.[18] also showed that US and CEUS had lower diagnostic performances than MRI for assessing secondary peribiliary lesions (Figure 6). To the best of our knowledge, this article by Granata et al. is the only one to date evaluating the diagnostic performance of CEUS for peribiliary lesions, and reported that US and CEUS only detected the intraparenchymal part of the metastasis. US has usually been employed as the first-line imaging technique for the assessment of liver lesions because it is relatively cheap, noninvasive, and easily accessible. However, the sensitivity and specificity of US for both the detection and characterization of lesions are related to the operator's

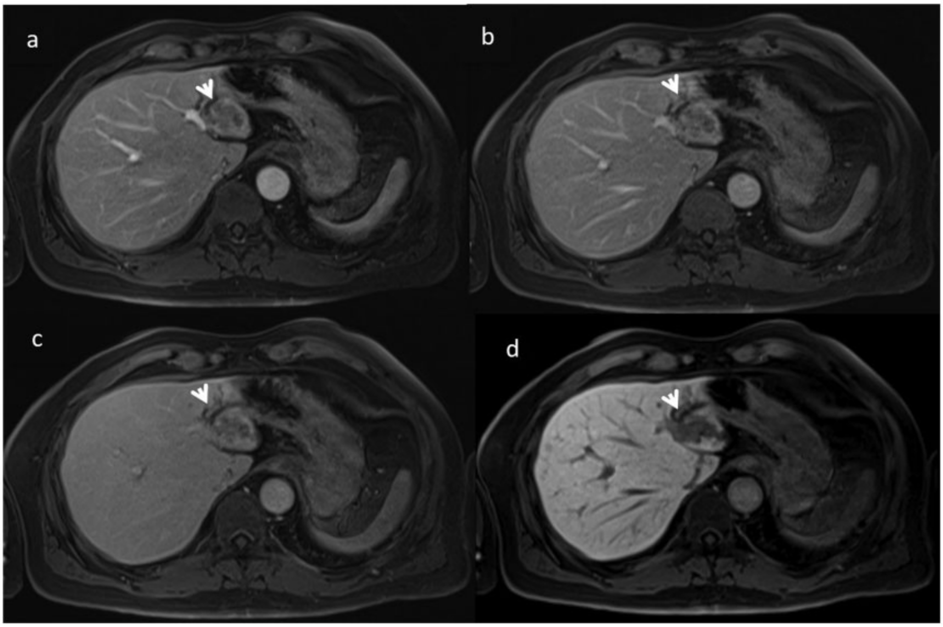

Figure 3. Same patient as in Figure 2. Volumetric interpolated breath-hold sequence T1-W with fat saturation in axial plane. Typical progressive enhancement during contrast study underestimated the real extension in (a) arterial phase, (b) portal phase, and (c) delayed phase. (d) The lesion appeared as soft tissue in the peribiliary area in the hepatobiliary phase.

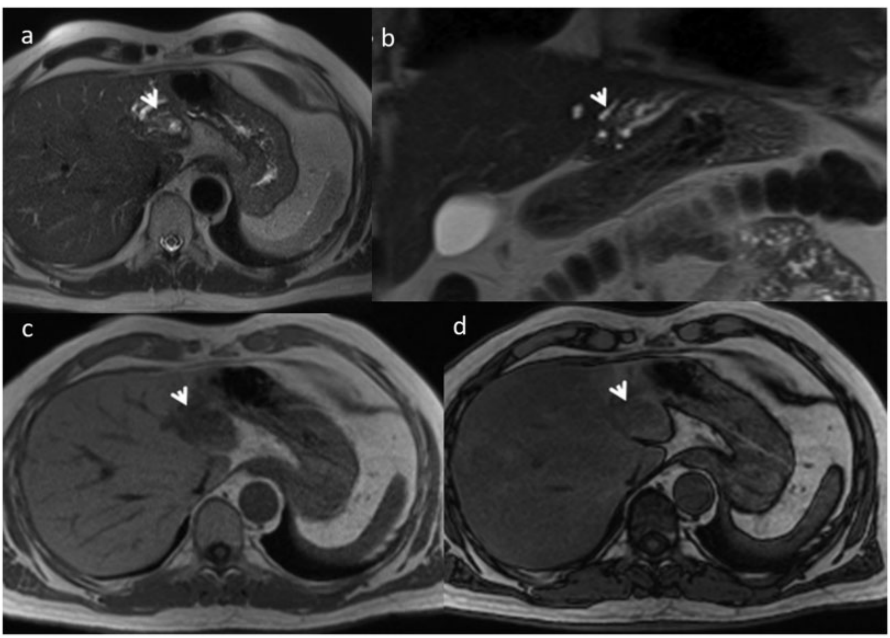

Figure 4. Same patient as in Figures 2 and 3. Peribiliary metastasis visible as a hyperintense signal (arrow) in T2-W sequences. (a) Half-Fourier acquisition single-shot turbo spin-echo (HASTE) T2-W in axial plane, (b) HASTE T2-W in coronal plane and hypointense signal in T1-W, (c) Fast low-angle-shot two-dimensional (FL 2D) T1-W in phase, and (d) FL 2D T1-W out phase sequence.

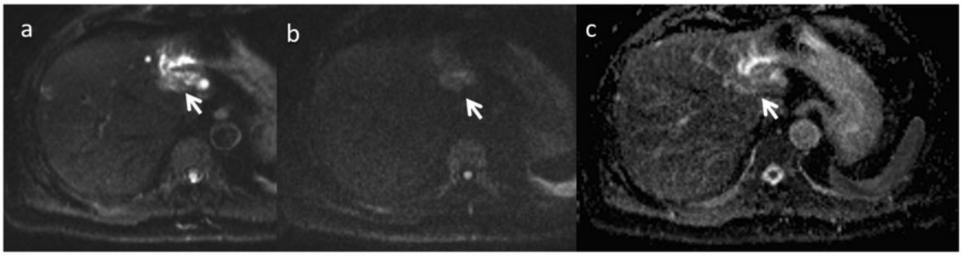

Figure 5. Same patient as in Figures 2–4. DWI sequences: (a) b value = 50 s/mm^2, (b) b value = 800 s/mm^2, and (c) ADC map. The lesion showed a restricted signal (arrow) with hypointense signal on ADC map (arrow).

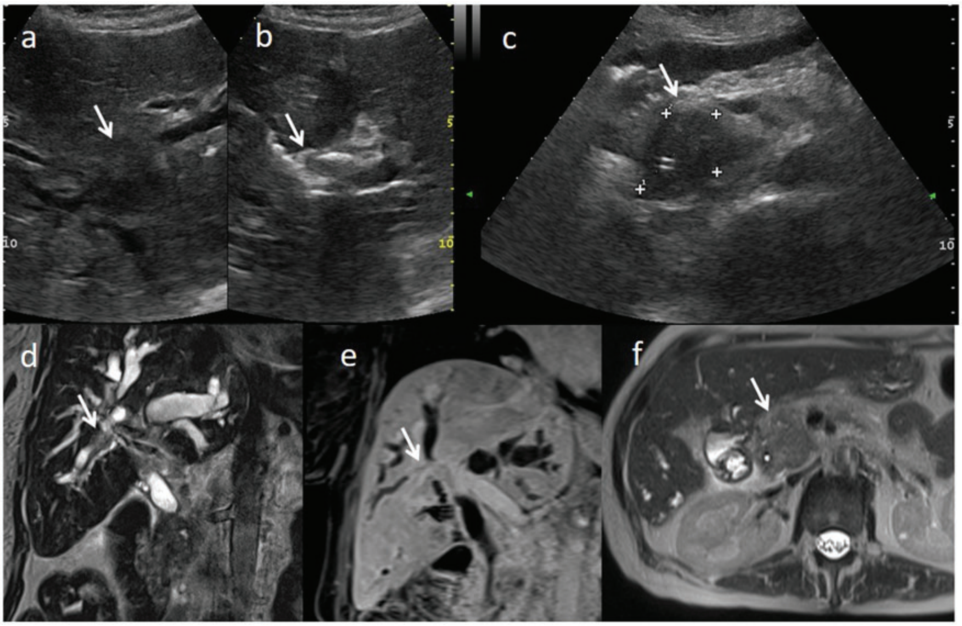

Figure 6. A 54-year-old man with pancreatic cancer. (a–c) US study. The metastasis was not defined and appeared as an isoechoic-hypoechoic lesion causing biliary tree dilatation. (c) The pancreatic cancer appeared as a hypoechoic lesion. (d) Half-Fourier acquisition single-shot turbo spin-echo (HASTE) T2-W in coronal plane. Metastasis shown as a hypointense signal in the peribiliary space, better defined than by US (arrow). (e) Volumetric interpolated breath-hold sequence T1-W in portal phase of contrast-enhanced MR study. The lesion appeared isointense relative to the surrounding liver parenchyma. (f) HASTE T2-W in axial plane, showing evident (arrow) pancreatic cancer.

expertise and to the patient's body habitus.[29,30] CEUS evaluates the dynamic parameters of the nodule, and several studies have found no significant difference in terms of diagnostic accuracy among CEUS, MDCT, and MRI for the detection of liver cancers.[29–32] However, CEUS has the same limitations as conventional US.[29–32] Similar to MDCT, Granata et al.[18] found that US identified biliary tree dilatation in all cases. MR should therefore be performed in all patients with biliary tree dilatation in whom no nodules were detected by CEUS. MRI has become the gold standard for oncological examinations based on its ability to reveal morphological and functional parameters, which in turn allow the assessment of important prognostic features and may guide patient treatment.[33–45] According to Granata et al., MRI exhibited the best diagnostic performance for detecting peribiliary metastases compared with MDCT, US, and CEUS,[18] with MRI identifying all the lesions. T2-W sequences (Figure 7) and DWI sequences (Figure 8) performed better[4,18] than post-contrast T1-W sequences. The authors suggested that the lower diagnostic accuracy of T1-W sequences post-contrast agent was related to the typical pharmacokinetics of these lesions, with progressive contrast enhancement (Figure 9) resulting in a lower signal/lesion ratio compared with T2 sequences and T1 sequences without contrast agent or in hepatospecific phase.[4,18]

The European Society of Gastrointestinal and Abdominal Radiology Working Group recommended the use of MRI to increase the detection and assessment of liver lesions, using morphological and functional sequences (DWI, dynamic contrast enhanced-MRI, and cholangio-pancreatography images).[16] However, Granata et al.[4,18] found that cholangiography sequences performed less

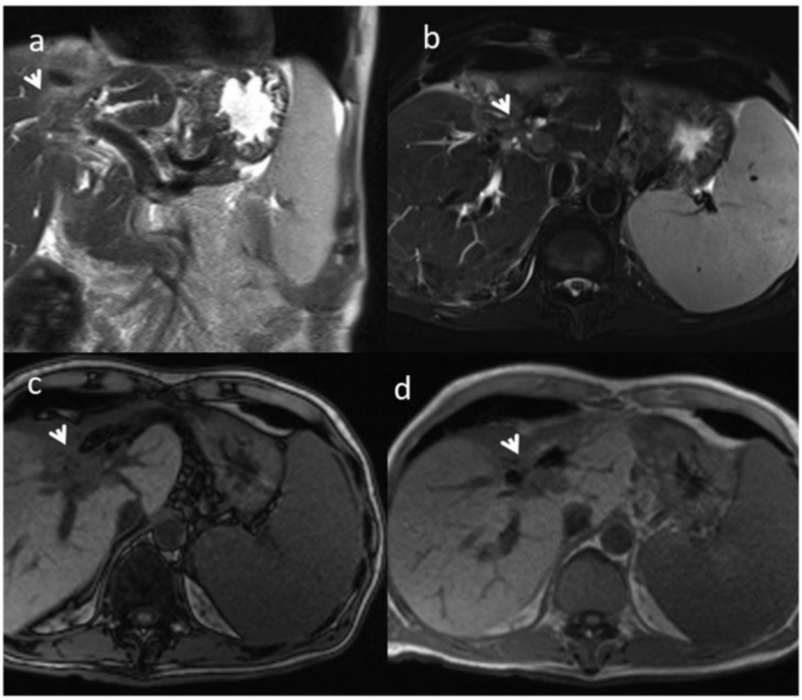

Figure 7. Post-surgical follow-up. Recurrence of peribiliary metastasis appearing hyperintense (arrow) in (a) Half-Fourier acquisition single-shot turbo spin-echo (HASTE) T2-W in coronal plane and (b) SPACE T2-W FS in axial plane, and hypointense (arrow) in (c) T1-W fast low-angle-shot two-dimensional (FL 2D) out of phase and (d) T1-W FL 2D in phase. T2-W sequences showed the best diagnostic performance for defining the lesion.

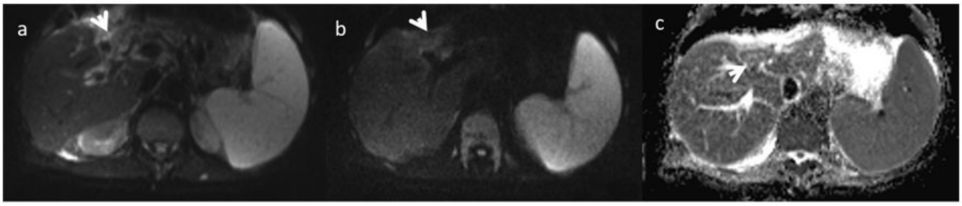

Figure 8. Same patient as in Figure 7. DWI sequences: (a) b value = 50 s/mm^2, (b) b value = 800 s/mm^2, and (c) ADC map. The lesion showed a restricted signal (arrow) with isointense signal on ADC map (arrow).

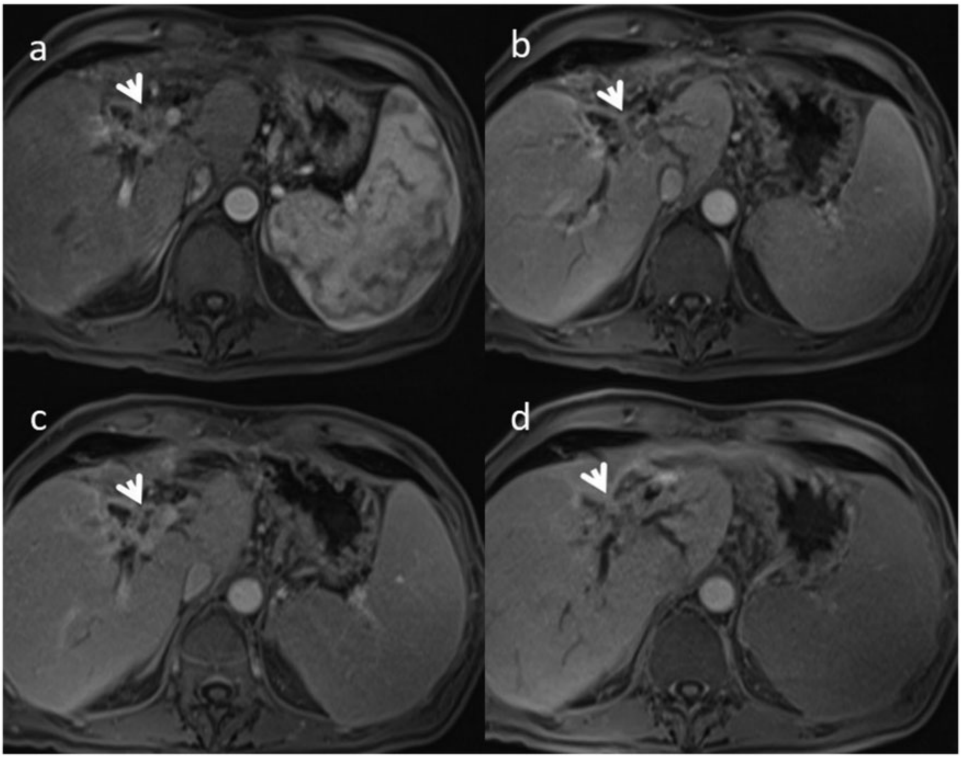

Figure 9. Same patient as in Figures 7 and 8. Volumetric interpolated breath-hold sequence T1-W with fat saturation in axial plane. Typical progressive enhancement was evident during contrast study in (a) arterial phase, (b) portal phase, and (c, d) delayed phase. Post-contrast study showed a poorer diagnostic performance compared with T2-W sequences (Figures 7 and 8).

well than T2-W, DWI, and post-contrast T1-W sequences. They suggested that this lower performance was due to the peribiliary position of the lesions, resulting in biliary compression such that cholangiography sequences could only provide indirect data and could not detect small lesions.[4,18] Conversely, T2-W and DWI, with the highest diagnostic performances, can detect lesions and define their location and spread. T2-W and DWI sequences during MR examination are therefore essential for the accurate staging of peribiliary lesions. However, because of overlap between the signal and ADC values among these lesions, DWI and apparent diffusion coefficient (ADC) values do not allow their proper characterization, and DWI does not allow histological differentiation between metastases of different origins or between metastasis and CCC.[4,18] Similarly, Park et al. evaluated the incremental advantage of adding DWI sequences to gadoxetic acid-enhanced MRI and MR cholangiopancreatography for the assessment of CCC, and showed that DWI improved assessment of the tumor extent along the bile duct.[45] In contrast to Granata et al.,[4] Choi and co-workers showed that DWI was not helpful for detecting involvement of the secondary biliary confluence, and did not improve the diagnostic performance in terms of the characterization of perihilar lesions.[46]

EOB-GD-DTPA MRI is considered to show the best diagnostic accuracy for the detection and mapping of liver metastases,[47–55] and accurate recording is essential for choosing the best surgical[53] or non-surgical therapeutic approach.[56] However, Granata et al.[4,18] showed that T1-W sequences during hepatospecific phase had a lower diagnostic performance for detecting peribiliary metastases than T2-W sequences, because the lesions were not intra-parenchymal and, in contrast to parenchymal lesions, the peribiliary lesions did not appear hypointense. Indeed, peribiliary metastases appeared isointense/hypointense in hepatobiliary-phase images. Although EOB-GD-DTPA did not increase the number of detected metastases, Granata et al.[4,18] showed that this contrast medium provided useful functional information, and the biliary ducts neighboring the lesions did not expel the contrast agent during the hepatobiliary phase. However, the main limit of MRI was its inability to classify histological types of lesions, even in relation to CCC, with no significant differences among all metastases and among secondary lesions and CCC in all the study sequences.[4,18]

Conclusions

Peribiliary metastasis is usually considered to be sporadic, but its true incidence may have been underestimated because of the use of MDCT as the first-line technique during cancer patient staging and follow-up. The diagnostic performance of MDCT for detecting and characterizing biliary metastasis is lower than that of MRI, with a detection rate only of 41. MRI has the best diagnostic performance for detecting peribiliary metastases compared with MDCT and US/CEUS. However, both MDCT and US can identify secondary signs, such as biliary tree dilatation, and patients with these signs should then be assessed with MRI. The progressive contrast enhancement of lesions means that post-contrast sequences have a lower diagnostic performance and lower signal/lesion ratio compared with T2-W and DWI. Furthermore, examination in the hepatospecific phase is less effective because peribiliary metastases are basically isointense or only mildly hypointense during this phase. MRI should thus be considered the gold standard technique for the radiological assessment of secondary biliary tree lesions.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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