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# Contrast-Enhanced Ultrasound in the Follow-Up of Choroidal Melanoma Patients: Features of Liver Metastasis Arising Several Years after Treatment of the Primary Tumor

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## Key Words

Contrast-enhanced ultrasound · Choroidal melanoma · Metastasis

## Abstract

Choroidal melanoma is an insidious tumor frequently causing late liver metastases which are associated with a poor outcome. Since metastatic liver lesions are potentially resectable with curative intention, tight follow-up schedules after treatment of primary tumors for the early detection of liver metastasis have been proposed. The methods employed so far, however, have proven to be of limited sensitivity, and it is likely that a combined approach comprising the use of both imaging techniques and biohumoral markers will, in the future, improve the efficacy of methods directed to the early detection of liver metastases. Contrast-enhanced ultrasound (CEUS) is increasingly used in the clinic due to its advantage over conventional sonography for the early detection of tumor lesions and thus represents a promising accurate and cost-effective diagnostic tool. To our knowledge, its use has not been proposed yet for the early diagnosis of metastatic choroidal cancer. Here, we describe for the first time the CEUS features of a large liver metastasis originating from choroidal cancer occurring 13 years after diagnosis in comparison to MRI and conventional sonography and propose CEUS as routine follow-up method for the early detection of liver metastases of patients affected by choroidal melanoma.

## Introduction

Choroidal melanoma is a primary intraocular malignant tumor frequently causing liver metastases several years after the first diagnosis. Liver metastases may occur in the absence of specific complaints and were reported to present with signs of impaired liver function such as coagulation disorders or obstructive jaundice, reflecting the presence of large lesions which had remained undetected over several years. Early detection of liver metastatic disease and eligibility for surgery have a determinant prognostic relevance, with patients not eligible for operation having a median survival of 6 months. Therefore, several tight follow-up schedules after treatment of primary tumors to detect early liver metastasis have been proposed. These include the regular control of liver enzymes, routine chest X-rays and ultrasound investigation of the liver and several newly developed tumor markers [1, 2]. Recent reports have shown that these follow-up methods have high specificity but not high sensitivity for the early detection of metastasis from choroidal cancer [1, 3]. To increase diagnostic accuracy, the routine use of PET-CT as screening method for initial staging has been proposed [4]. However, follow-up protocols after tumor treatment have to take into account the balance between the need for accurate diagnostic procedures, the burden for the patient including radiation exposure during imaging procedures and cost-effectiveness of screening methods. Future follow-up schedules will likely be based on both imaging techniques and biohumoral markers.

Contrast-enhanced ultrasound (CEUS) is being increasingly employed in the clinic, typical patterns of vascular uptake and washout of contrast medium providing a clear advantage over conventional US in determining malignancy of lesions in the liver [5–7]. Up to date, no report has been published on the use of CEUS for the early detection of liver lesions from metastatic melanoma. We present the case of a 36-year-old patient who presented to our institution with a large metastatic lesion from a choroidal cancer in absence of symptoms and of liver enzymes elevation. Here, we describe CEUS features of liver metastasis and the correlation with other modern imaging methods, and propose the use of CEUS as standard investigation method for the follow-up of patients affected by choroidal cancer.

## Case Presentation

A 36-year-old patient presented to his general practitioner for a liver ultrasound investigation as routine follow-up procedure after treatment of a choroidal melanoma in 1996. This investigation showed an approximately 5 cm large lesion in liver segment VIII. The patient was thus admitted to our department for further investigation. The primary tumor had been treated by repeated ruthenium applications in 1996 and 2002. A laser treatment was also performed in 1997. Since the first diagnosis, the patient underwent, at 6 months intervals, regular ultrasound investigations of the liver and liver enzyme controls. Previous controls had failed to show any signs of liver metastasis. At the time of presentation at our institution, the patient did not report any relevant subjective complaints. Physical examination yielded no pathological findings. Biochemical parameters, including liver function tests, liver enzymes as well as several tumor markers (AFP, CEA, CA19–9, chromogranin A), were within normal range. A conventional US investigation, CEUS, a CT and a MRI were performed after the admission.

### *Conventional and CEUS*

Ultrasound examination was performed using a high-end sonographic scanner, (Acuson™ Sequoia 512; Siemens). The patient underwent a B-mode ultrasonographic and a color Doppler examination

using a 4-MHz multifrequency convex transducer (fig. 1). The contrast examination was performed with low-mechanical index (low-MI imaging, mean MI = 0.15), to avoid destruction of microbubbles. The contrast-enhanced examination was performed with low-mechanical index (low-MI imaging, mean MI = 0.15), to avoid destruction of microbubbles in real-time tissue harmonic imaging (Cadence™ contrast pulse sequencing imaging on the ACUSON™ Sequoia 512 ultrasound system). A bolus injection of 2.0 ml of a second-generation blood pool contrast agent (SonoVue®; Bracco, Milan, Italy), consisting of stabilized microbubbles of sulfur hexafluoride, was administered into an antecubital vein through an 18-gauge needle and was followed by a flush of a 10-ml saline solution. The entire liver was scanned for 5 min in accordance with the maximum circulation time of the contrast agent (fig. 2). The examination was digitally stored on magnetic-optical discs.

### MRI

Standard MRI examination was performed on a 32-channel 1.5 T MR system (Magnetom Avanto; Siemens Medical Solutions, Erlangen, Germany). The MRI examination included native and T<sub>1</sub>-, T<sub>2</sub>-weighted and 3D gradient echo sequences for early dynamic imaging as well as for imaging of the liver-specific phase. The slice thickness in these sequences was 3 mm in a single breath-hold examination that covers the entire liver. Gd-EOB-DTPA (Primovist; Bayer Schering Pharma, Berlin, Germany) was administered as a bolus at a dose of 0.025 mmol/kg body-weight via an antecubital i.v.-line (fig. 3).

### MS-CT

After local anesthesia with 10 ml of Scandicain 2%, the patient underwent liver biopsy by CT-guided fluoroscopy using a 16-gauge/10-cm biopsy needle, on a 128-detector MDCT (Somatom Definition AS; Siemens, Erlangen, Germany).

In comparison to standard US (fig. 1), CEUS imaging allowed to readily recognize the morphology and the malignant features of the metastatic lesions due to early contrast medium uptake (fig. 2a, b) and the rapid washout in the portal (fig. 2c) and late phases (fig. 2d). At CEUS, the lesion appeared hypoechoic versus the normal liver parenchyma. The resulting reverse image was comparable to that obtained by MRI performed with liver-specific contrast medium, where the morphology of the lesion was outlined by the lack of hepatocyte-specific contrast medium uptake (fig. 3).

A liver biopsy confirmed the suspected diagnosis of a liver metastasis from melanoma. The histological diagnosis was supported by typical morphological features as well as by positive staining for Melan A, HMB45 and S100 and by negative staining for KL1. Since the liver lesion was confined to the right liver lobe and did not show signs of portal vein invasion, the patient underwent right partial hepatectomy with curative intention. The procedure was performed successfully and the patient was discharged shortly thereafter.

### Discussion

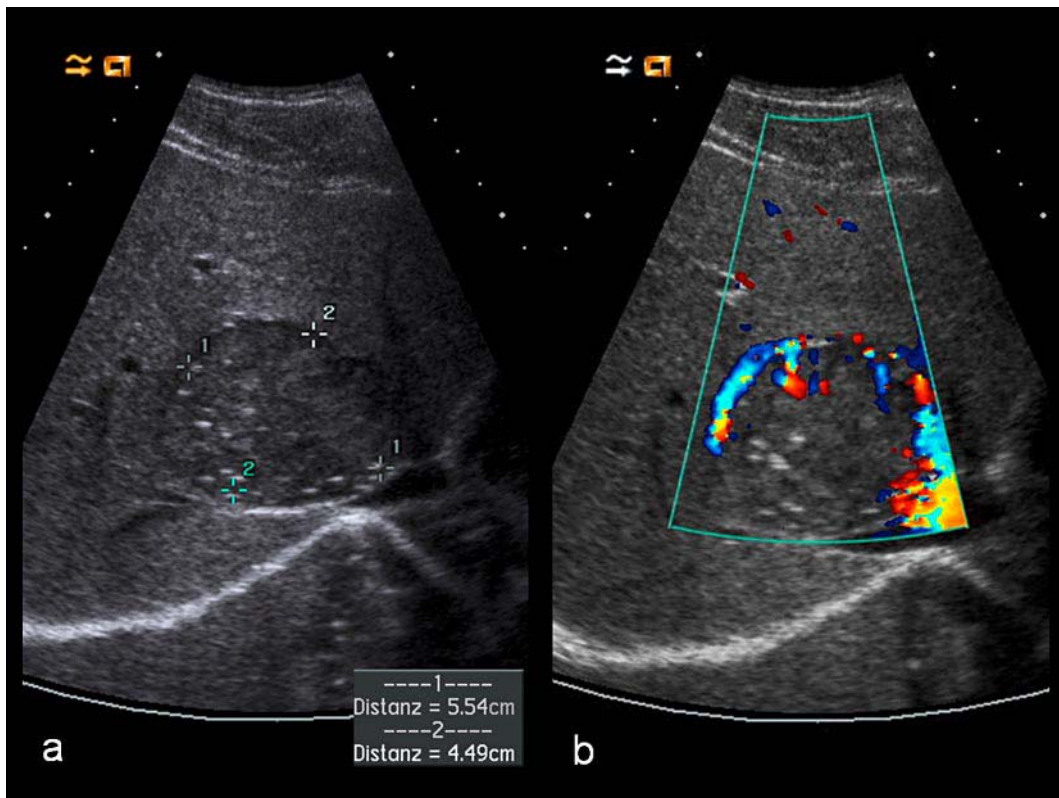
Upon diagnosis of choroidal melanoma, the detection of concomitant metastatic lesions or the early recognition of metastasis occurring after treatment of the primary tumor have major prognostic implications since in 80% of cases these lesions represent the only site of metastasis, and the median survival of patients not eligible for surgery is about 6 months [8]. Therefore, similarly to other malignancies preferentially causing metastasis in the liver, such as colon or breast cancer, early detection of liver lesions in the follow-up of choroidal cancer has important therapeutic and prognostic pitfalls [8].

Current protocols for the early detection of metastasis from choroidal melanoma are represented by regular control of liver enzymes and ultrasound investigation of the liver. Upon detection of liver enzyme abnormalities or pathological findings at US, CT or MRI scans are usually performed [9]. However, it has recently been shown that liver

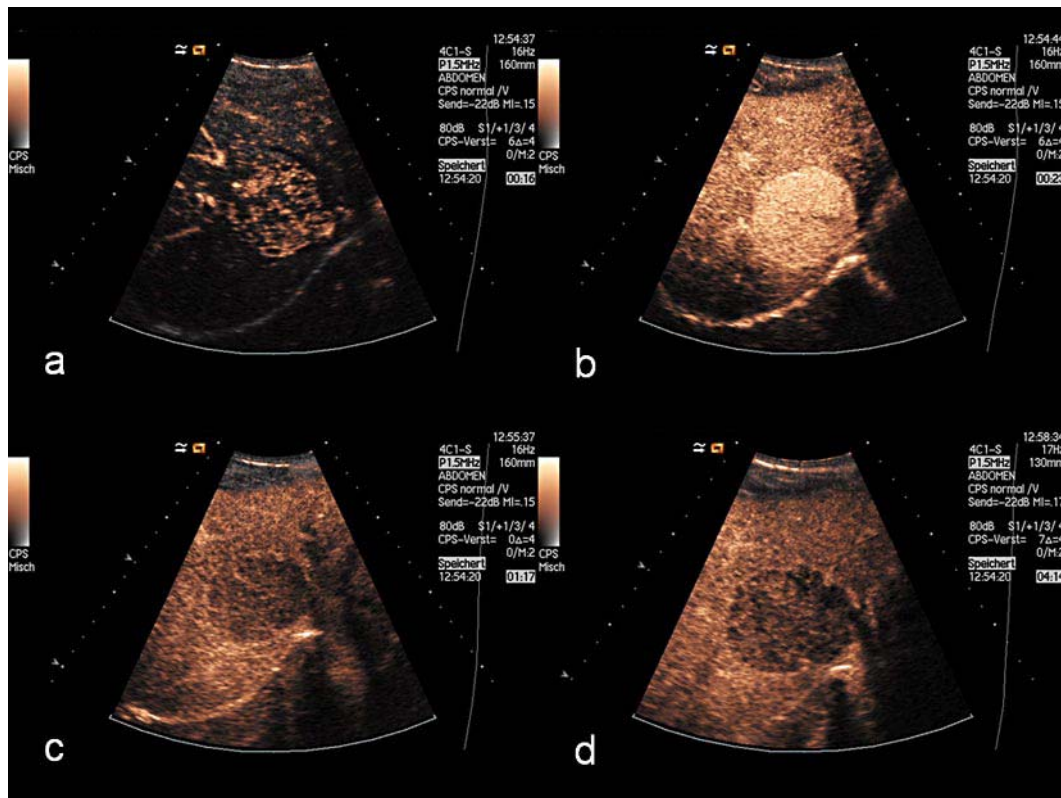
ultrasound as well as elevated liver enzymes are of limited sensibility for the early detection of liver metastasis [3, 9]. The limits of these standard follow-up methods and the need of prolonged follow-ups are exemplified by the present case where the patient presented with a large metastatic lesion which likely grew undetected over an extended period of time in the absence of biochemical abnormalities or subjective complaints many years after the treatment of the primary tumor. In order to increase diagnostic accuracy, alternative methods besides conventional US and liver enzymes have been proposed. Recently, for example, several biohumoral markers [2], or the utilization of PET-CT for the staging of choroidal melanoma [4] have been proposed and their combined use might allow for earlier diagnosis of liver metastasis. However, follow-up methods after the diagnosis of choroidal melanoma should not only be as accurate as possible, but should also be sustainable along a virtually life-long follow-up in terms of risks connected with radiation exposure, patient compliance, availability and cost-effectiveness.

CEUS is being increasingly employed in the clinic for several diagnostic purposes and has proven especially effective in discriminating malignant from nonmalignant lesions [10]. In particular, CEUS provides a significant advantage in the identification and in the definition of the malignant character of liver tumor lesions [6]. Recently, we could also show that CEUS is more accurate than multislice computed tomography in the prediction of malignancy and benignity of liver tumors [7] and evidence is accumulating on the fact that CEUS has a diagnostic reliability comparable to that of contrast-enhanced MRI with a liver-specific contrast agent, and an even higher diagnostic certainty of >90% compared with contrast-enhanced multidetector spiral CT [11, 12]. The employment of CEUS in the follow-up of cancer patients offers an alternative strategy for frequent and repeated investigations; due to the increasing evidence on its diagnostic accuracy, reproducibility and availability as diagnostic tool, its cost-effectiveness and the lack of radiation burden, CEUS appears as a promising candidate for the follow-up of choroidal melanomas after treatment.

In summary, the case of a young patient presenting with a large metastatic lesion, occurring 13 years after the diagnosis of choroidal melanoma, and no signs of liver enzyme elevation exemplifies the need for novel alternative diagnostic methods. By illustrating distinct CEUS features of a metastatic choroidal melanoma we propose the employment of this technique in the follow-up of these patients.

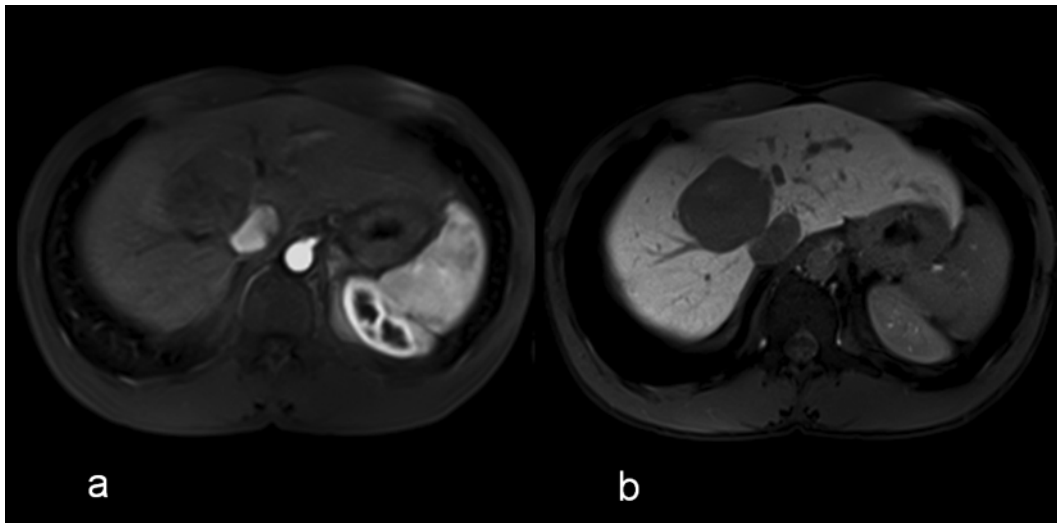


**Fig. 1.** Baseline scan (a) showing a single isoechoic metastasis with maximum diameter of  $5.5 \times 4.5$  cm in segment VIII. In color Doppler examination (b), the lesion shows some peripheral vascularity.



**Fig. 2.** In the early arterial phase (a), 16 s after SonoVue injection, the lesion displays a strong enhancement, most of the liver parenchyma being only partially filled with contrast medium. During the arterial phase (b), the lesion shows a strong, homogenous enhancement. In the portal venous phase (c), there is partial washout of contrast medium from the lesion, here appearing hypo-enhancing compared to the homogeneously enhancing normal liver. In the delayed phase (d), 4 min after injection of contrast medium, the lesion shows a hypoechoic, sharply circumscribed punched-out enhancement defect.





**Fig. 3.** Hypovascular liver metastasis in the arterial (**a**) and hepatocyte phase (**b**) with a T<sub>1</sub>-weighted 3D-gradient echo sequence after bolus injection of Gd-EOB-DTPA. In the hepatocyte phase (**b**), the margins of the lesions appear very clear and sharply delineated from increased contrast between the metastasis (no liver-specific uptake) and surrounding liver parenchyma (regular uptake).

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