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Highlights

- Hepatitis B virus infection is the main cause of liver cancer in Sub-Saharan Africa
- Little is known about the incidence among individuals on antiretroviral therapy
- This is among the first initiatives for liver cancer screening in the region
- 2% of HIV/hepatitis B Virus-coinfected adults had significant liver lesions
- A quarter had findings suggestive of schistosomiasis-induced liver damage

Screening for Hepatocellular Carcinoma among adults with HIV/Hepatitis B coinfection in Zambia: A Pilot Study

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Abstract

Background & Aims: Chronic hepatitis B virus (HBV) infection is the main cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa (SSA). In an established cohort of HIV/HBV-coinfected individuals on antiretroviral therapy (ART), we piloted an HCC screening initiative at two outpatient clinics in Lusaka, Zambia.

Methods: We performed abdominal ultrasound (AUS) and transient elastography in all patients.

Results: Among 279 HIV/HBV-coinfected patients, 165 (59.1%) were men, median age was 34 years (interquartile range 28-39) and median CD4 count 246 cells/µl (112-355). While 102 (36.6%) individuals had elevated transaminases, 114 (40.9%) had HBV levels >2000 IU/mL and 59 (24.6%) significant fibrosis. On AUS, 75 (26.9%) participants had hepatomegaly and 69 (24.7%) peri-portal fibrosis. Five patients had a liver lesion >1cm, an indication for confirmatory imaging.

Conclusions: In one of the first HCC screening initiatives in SSA, 2% of HIV/HBV-coinfected adults had significant liver lesions, and a quarter had findings suggestive of schistosomiasis-induced liver damage.

Keywords:

Hepatocellular carcinoma, sub-Saharan Africa, Screening, Hepatitis B Virus, HIV

Introduction

Chronic hepatitis B Virus (HBV) infection is the single most important cause of end-stage liver disease and hepatocellular carcinoma (HCC) worldwide (Akinyemiju et al., 2017). Its burden is particularly high in sub-Saharan Africa (SSA), where approximately 10% of the general population has chronic HBV infection (Schweitzer et al., 2015, Yang et al., 2017). Several additional factors, such as the environmental exposure to aflatoxin B1, HIV co-infection and unhealthy alcohol use, are frequent and might exacerbate the risk of HCC in HBV-infected individuals in the region (Kew, 2003, Nikolopoulos et al., 2009, Nouaman et al., 2018). According to the World Health Organization (WHO), the elimination of HBV as a public health problem by 2030 requires a 65% reduction in hepatitis-related mortality, which is mainly driven by HCC (WHO, 2017). However, due to the lack of diagnostic capacity and incomplete cancer registries, epidemiological data on the incidence of HCC from SSA are scarce.

The early diagnosis of HCC is key to reduce HBV-related mortality and can be achieved with the implementation of screening programs using 6-monthly abdominal ultrasound (AUS) measurements. If hepatic lesions are detected during AUS, further diagnostic procedures, including 4-phase computer tomography (CT), or repeat AUS, are needed to confirm the diagnosis, depending on the size of the lesions (European Association for the Study of the Liver, 2018). Although the presence of liver cirrhosis is the most important risk factor for developing HCC among people with chronic HBV, age, ethnicity and the presence of additional risk factors play a role. Current international guidelines recommend HCC screening for all HBV-infected patients of African origin after the age of 20 years, independent of the presence of cirrhosis (European Association for the Study of the Liver, 2018). Importantly, data on HCC incidence and risk factors among HIV/HBV-coinfected

individuals on tenofovir-containing antiretroviral therapy (ART) are very limited: in a large study from Europe, age at initiation of tenofovir was the most important predictor of this outcome besides cirrhosis (Wandeler et al., 2019). However, given the low number of patients of African origin included in the study, it remains unclear if the same risk factors should guide clinical decision on eligibility for HCC screening in African HIV clinics.

In light of the many structural challenges affecting health care systems in SSA, the collection of primary HCC incidence data is key to inform risk stratification and eligibility for HCC screening. Within a long-term prospective cohort of HIV/HBV-infected individuals at two primary care clinics in urban Zambia, we established an ultrasound-based pilot HCC screening program. Here, we present the results of the first ultrasound measurement from all patients included in the screening program and describe the main characteristics of individuals with at least one significant liver nodule.

Methods

Study population

Beginning in 2013, we enrolled consecutive adults (18+ years) with HIV/HBV-coinfection into a prospective cohort study at two public sector outpatient primary care clinics in Lusaka, Zambia (Vinikoor et al., 2017). All participants were HBsAg-positive (Alere Determine, Waltham, MA) and initiated tenofovir disoproxil fumarate (TDF)-containing ART, as per standard of care in Zambia. Starting in January 2015, we invited all participants to join our pilot HCC screening program. The University of Zambia (Lusaka) and the University of Alabama at Birmingham ethics committees approved the protocol and all patients signed an informed consent to participate in the study.

Study procedures

Detailed information on demographic and clinical characteristics, as well as laboratory measurements were collected prior to ART initiation and at 3 to 6-monthly intervals thereafter, using standardized data collection forms. The following laboratory tests were performed at least yearly: full blood count, alanine aminotransferase (ALT; normal <19U/L for women and <30 for men), creatinine, CD4+ cell count and hepatitis B e-antigen (HBeAg). HBV viral load (VL) was measured yearly using the COBAS AmpliPrep/ COBAS Taqman platform (version 2.0 Roche Molecular Systems, Pleasanton, CA). We screened for the presence of anti-HCV antibodies using a rapid test (OraQuick, OraSure Technologies, Bethlehem, PA) (Wandeler et al., 2016). Alpha-Fetoprotein (AFP) was measured in all participants with available stored serum samples at time of first AUS. The AUDIT-C questions were used to assess alcohol consumption levels, and unhealthy alcohol use was defined as an AUDIT-C score > 3 for women and > 4 for men. Liver stiffness was measured annually using transient elastography (TE, Fibroscan 402, Echosens, Paris, France) and results were categorized according to the Metavir liver fibrosis stage: F0-F1 if LSM <7.1kPa, F2-3 if 7.1-11kPa, F4 if >11.0kPa, as established previously (WorldHealthOrganization, 2015). An examination was deemed successful if at least 10 valid liver stiffness measurements (LSM) were obtained and it was considered very reliable if the interquartile range divided by median (IQR/M) was <0.1, reliable if IQR/M was 0.1–0.3, and poorly reliable if IQR/M was >0.3 (Boursier et al., 2013).

HCC surveillance protocol

In line with international recommendations, in January 2015, we asked participants to join our pilot HCC screening program und started to perform abdominal ultrasound imaging in all HIV/HBV-coinfected individuals (European Association for the Study of the Liver, 2018). As ultrasound imaging at cohort clinics was inconsistent, we transported patients to the

University Teaching Hospital (UTH), Lusaka's main referral hospital, located ~8 km away. Ultrasound examinations were performed in the early afternoon, prior to lunch, by one of three experienced radiographers at the Department of Radiology. The following characteristics were described using a standardized case-report form: liver mid-axillary diameter; portal vein diameter; presence of splenomegaly, ascites, intra-abdominal lymphadenopathy, and peri-portal fibrosis. Liver cirrhosis was diagnosed in the presence of at least one of the following: surface nodularity, overall coarse and heterogeneous echotexture, atrophy or segmental hypertrophy. Liver steatosis was diagnosed in the presence of increased echogenicity in comparison to the right kidney parenchyma and beam attenuation. Liver lesions were described in numbers, quality (hypo-, hyper-, or of mixed echogenicity), location, and the largest lesion was measured (in cm). When a liver nodule >1 cm was documented on AUS, a 4-phase CT scan was performed at UTH. The LI-RADS system was used to standardize the interpretation and reporting for diagnostic imaging (LI-RADS®, Version 2017).

Results

Patient Characteristics

Of 303 adults with HIV/HBV-coinfection enrolled in our cohort with a visit after January 2015, 279 (92.1%) had at least one AUS measurement. Median age of participants was 34 years (interquartile range [IQR] 28-39), and 40.9% were female. At initiation of ART, 118 (42.6%) participants reported unhealthy alcohol use, 53 (19%) were smokers, and 30 (10.8%) were overweight or obese (body mass index >25.5). The median CD4 count was 246 cells/µL (IQR 112-355) and 100 (37.3%) had a WHO clinical stage 3 or 4 at ART initiation. Of all individuals with available data at the time of ART initiation, 102 (55.7%) had elevated ALT

levels, 114 (59.7%) had HBV DNA levels >2,000 IU/ml, and 103 (38.0%) had a positive HBeAg test. Overall, 59 (24.6%) participants had a liver stiffness measurement compatible with significant fibrosis (Metavir ≥F2), of whom 16 (6.7%) had liver cirrhosis (Metavir F4). Of 147 patients with measured AFP levels, three had AFP levels way above 20ng/ml.

Liver ultrasound findings

At their first AUS, participants had been on tenofovir-containing ART for a median of 8 months (IQR 0-16). Efavirenz was the third agent for 97.1% of participants, whereas 2.9% were receiving a nevirapine-based ART regimen. In this cross-sectional analysis, 75 (26.9%) participants had hepatomegaly and 69 (24.7%) periportal fibrosis, whereas 6 individuals (2.2%) had signs of cirrhosis, and 4 (1.4%) had liver steatosis (Figure 1). Only one of 16 individuals with liver stiffness compatible with cirrhosis had signs of liver cirrhosis on ultrasound. Liver lesions ≥1 cm were documented in five (1.8%) patients, mostly appearing with hyperechoic pattern (Figure 2, Panel A). One patient had multiple lesions. All participants with liver lesions were male and aged <50 years, two were HBeAg-positive, four (80.0%) had elevated ALT levels and two had HBV DNA levels >2000 IU/ml at ART initiation. None of the five individuals with liver lesions showed an elevated AFP level at time of AUS. According to the updated EASL nomenclature, one individual would have been classified as HBeAg-positive chronic HBV infection (patient 1), three as HBeAg-negative chronic HBV infection (patients 2-4), and one as HBeAg-positive chronic hepatitis (patient 5). At the time of their first ultrasound measurement, all five patients had a HBV VL <100 IU/ml.

Two patients with focal lesions >1cm (patients 1 and 5, Figure 2A) were referred for further investigation by 4-phase CT scan. According to the LI-RADS categorization, lesions from both patients had a low probability of HCC on CT scan. Figure 2B shows radiological examinations

of patient 5, who had an HBeAg-positive chronic hepatitis B with a high viral load at baseline and liver cirrhosis. On ultrasound, a heterogeneous echotexture, surface nodularity of the liver and multiple focal hypo- and hyperechoic focal lesions were noted. On 4-phase CT scan, these lesions did not present any diagnostic HCC hallmarks, and were most likely hemangiomas. In two participants, there was a delay in recognizing the need for CT and on the next AUS liver lesions were no longer visible (patient 3) or had decreased in size (patient 4). Finally, one patient withdrew from the study for personal reasons before a CT could be performed (patient 2).

Discussion

Within a cohort of HIV/HBV-coinfected individuals in Zambia, we successfully engaged 279 in one of the first liver cancer screening initiatives for HBV-infected persons in SSA. At their first assessment, about 2% of our patients had a liver lesion that warranted further diagnostic testing with a 4-phase CT scan. Given the high proportion of participants with active hepatitis B, unhealthy alcohol use, and peri-portal fibrosis suggestive of schistosomiasis-induced liver damage, our findings highlight the need for the continued evaluation of HCC incidence in this population.

Our study demonstrated that imaging-based screening for HCC is feasible in resource-constrained settings, provided there is dedicated staff, skilled radiologists and access to adequate infrastructure. AUS were straightforward to perform at the referral center; however, having de-centralized and integrated access to AUS at front-line facilities would further increase feasibility. Although our study population consisted mainly of young HIV/HBV-coinfected individuals on tenofovir-containing ART, a significant proportion had relevant risk factors for the development of HCC: 7% had a liver stiffness measurement

consistent with liver cirrhosis and 60% had a high HBV VL at the time of ART start. The prevalence of liver cirrhosis among people with HBV in our study is in line with the results of a recent meta-analysis, which showed similar estimates across SSA, and did not find evidence of a significant difference between HIV-infected and uninfected individuals (Surial et al., 2020). Interestingly, most individuals with liver stiffness compatible with cirrhosis did not have signs of liver cirrhosis on ultrasound. This finding could be explained by the higher sensitivity of elastography to diagnose cases of early, well-compensated cirrhosis, or by the impact of schistosomiasis in increasing liver stiffness (Hashim and Berzigotti, 2021). The prevalence of additional HCC risk factors was also high in this population: 43% of individuals reported unhealthy alcohol use and regular exposure to aflatoxin is widespread in the region. The need for HCC surveillance in non-cirrhotic patients treated with potent antiviral therapy is debated, as long-term suppression leads to the regression of liver fibrosis and cirrhosis and reduces the incidence of HCC (Marcellin et al., 2013, Wandeler et al., 2019). However, given the high burden of HCC risk factors in SSA, HCC surveillance recommendations will have to be informed by prospective HBV cohorts with long-term HCC surveillance, such as the one described here.

In our cross-sectional analysis, five (2%) HIV/HBV-coinfected individuals had an indication to undergo liver CT-scan because of a liver lesion >1cm on ultrasound. In two participants, this procedure was able to help exclude an HCC. One patient was lost to follow-up before a CT scan could be performed, and in the other two participants, a CT scan was not performed as the size of the lesions had reduced in subsequent AUS examinations. None of the participants showing liver lesions on AUS had elevated levels of AFP at time of AUS. In resource-limited settings, access to 4-phase CT scan to confirm or rule out HCC is limited due to the required infrastructure, including consistent power supply, supplies, specific contrast

and syringes, and the needed expertise in using and maintaining the device. Furthermore, the 4-phase protocol, which involves complex timing of contrast injection, is rarely done in SSA and hence additional training is needed. Finally, the interpretation of contrast enhancement during the different phases of the procedure and standardized reporting require an experienced radiologist familiar with these procedures. Given the many challenges associated with the implementation of 4-phase CT or MRI in low-income countries, the use of potential HCC biomarkers should be evaluated to strengthen risk stratification and diagnosis of HCC.

We found a high proportion of individuals with periportal fibrosis, a finding suggestive of schistosomiasis. The prevalence of schistosomiasis reaches 88% in endemic parts in Zambia, and related non-cirrhotic portal hypertension is a major cause of variceal bleeds in the region (Sinkala et al., 2020). Schistosomiasis may potentiate hepatic injury in the presence of HBV or hepatitis C virus (HCV) infections and experimental and clinical studies have suggested that schistosomiasis promotes the development of HCC (El-Tonsy et al., 2013). However, biomolecular mechanism explaining the link between S. mansoni infection and HCC are still unknown and it remains unclear whether schistosomiasis needs to be considered as an additional risk factor for the development of HCC. The systematic assessment of exposure to schistosomiasis should be included in studies assessing risk factors for HCC in endemic regions.

We provide data from one of the first HCC screening initiatives among HBV-infected individuals in SSA. The following aspects make this clinical research platform unique in the region: (i) Our patients had a comprehensive diagnostic work-up, including HBV virological analyses, alcohol assessment and transient elastography, before the initiation of HCC screening, (ii) we avoided selection bias by securing the participation of a large majority of

our patients with weekly transport to the radiology department, (iii) ultrasound examinations were conducted by one of three experienced radiologists who reported their results on a standardized form, (iv) we confirmed the diagnosis of HCC with a state-of-the-art 4-phase CT scan protocol, and **(**v) we peformed AFP measurements when stored sampes were available at same time of AUS. However, the cross-sectional nature of this analysis and the absence of cases of HCC in the first round of ultrasound assessments does not allow us to draw any conclusions on the burden of end-stage live-disease in this population. An inherent limitation of the use of abdominal ultrasound is its low sensitivity for small tumors, which might have led to the under-estimation of the proportion of patients with clinically relevant nodules. Furthermore, AFP measurements where only available in 53% of all patients. Finally, the characterization of risk factors for liver disease could have been improved by the systematic measurement of aflatoxin B1 and schistosomal infection.

In summary, during the initial phases of an HCC surveillance initiative in urban Zambia, we found a high prevalence of liver cirrhosis and periportal fibrosis among adults with HIV/HBV coinfection and 2% had liver lesions warranting CT scan. We were able to include the majority of patients in our cohorts into the HCC screening program, owing to the high dedication of our study staff and the collaboration with a highly motivated tertiary care radiology department. Considering the logistical and financial challenges to be addressed, for such a program to be sustainable, inclusion of participants based on optimized risk stratification and simplification of diagnostic tools will be key. Therefore, the assessment of the diagnostic accuracy of AFP and new promising biomarker panels in larger prospective cohorts in the region is crucial. As HCC events are expected to occur frequently in young people with non-cirrhotic HBV infection in SSA, it will be crucial to assess HCC incidence and

identify related risk factors in prospective studies with systematic surveillance programs, as in our Zambian cohort.

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Authors' contribution

CR, MV and GW designed the study. CR and GW wrote the first draft of the manuscript. CR, HC, GM, BC and VS collected data. CBM supported study implementation. All authors contributed to interpretation of data, critically reviewed the manuscript and agreed on its final version.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical Approval

The University of Zambia (Lusaka) and the University of Alabama at Birmingham ethics committees approved the protocol and all patients signed an informed consent to participate in the study.

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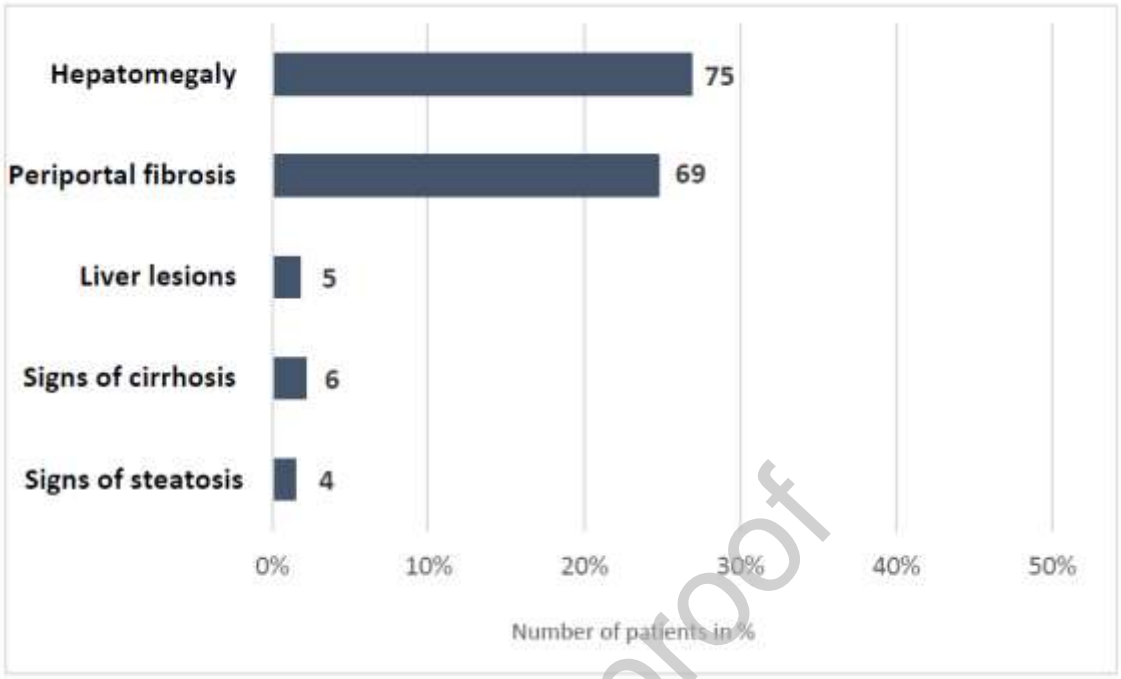
Figure 1. Main findings at first ultrasound screening (n= 279)



Hepatomegaly was defined as liver diameter >15cm; patterns of periportal fibrosis was registered and graded according to the Niamey classification [15]; signs of cirrhosis were defined as any of the following: surface nodularity, overall coarse and heterogeneous echotexture, atrophy or segmental hypertrophy; steatosis were defined by increased liver echogenicity compared to right kidney parenchyma and beam attenuation.

Figure 2. Summary of patients with liver lesions. Main characteristics of the five patients with liver lesions (Panel A) and radiological examinations (US and 4-phase CT) of patient 5 (Panel B)

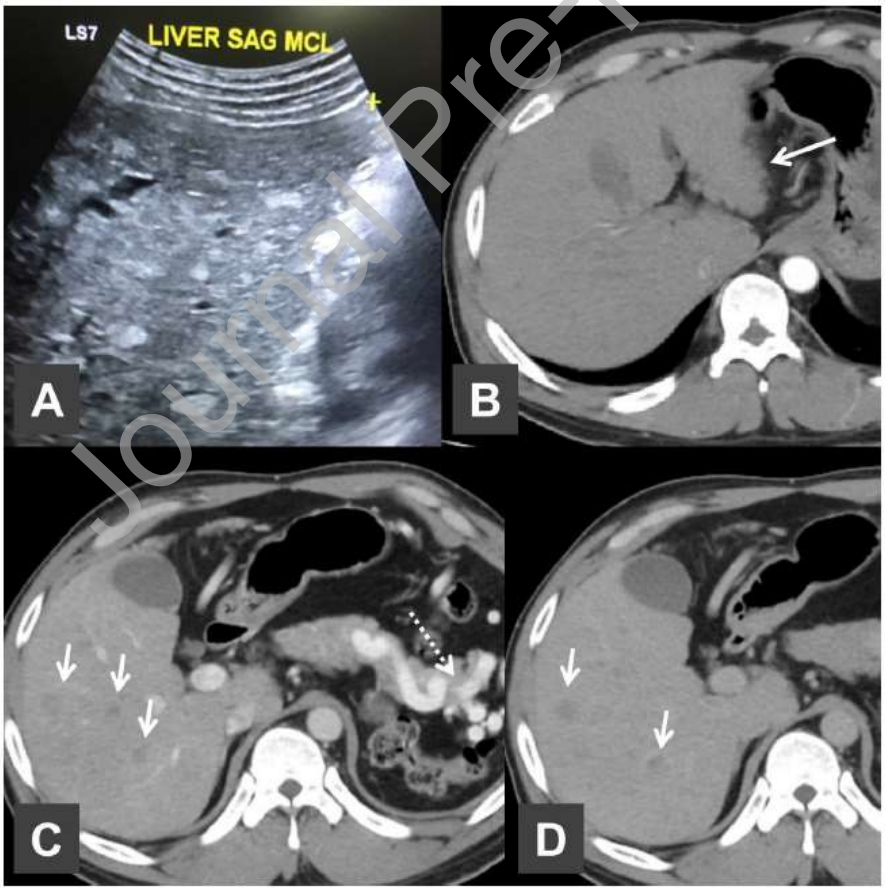
Panel A.

Patient	Characteristics at ART start							Ultrasound findings			
	Sex	Age	CD4+ Count (cells/ul)	HBe Ag	ALT, U/L (IQR)	HBV DNA (IU/mL)	TE	Cirrhosis	Type lesion	No. lesions	Largest lesion (cm)
1	M	35	135	pos	38	52	F0	no	Hyperechoic	Single	2.2
2	M	29	174	neg	27	missing	F0	no	Hyperechoic	Single	1.7
3	M	38	237	neg	52	16600	F0	no	Hyperechoic	Single	1.4
4	M	47	259	neg	30	171	F0	no	Hyperechoic	Single	1
5	M	34	171	pos	71	39356310	F4	yes	Hypo- and Hyperechoic	Multiple	2.1

Abbreviations: HBeAg, hepatitis B surface antigen; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; TE, transient elastography; M, male; pos, positive; neg, negative.

Fibrosis stage F0-F4 was graded according to the METAVIR scoring system.

Panel B.



Imaging findings in patient 5: The liver tissue is highly cirrhotic and shows an inhomogeneous hypo- and hyperechogenic structure in b-mode ultrasound (A). In the

multiphase CT scan (B-D), the arterial phase (B) reveals a cirrhotic nodular surface of the liver (arrow in B), however, there are no focal lesions with an arterial hyperperfusion. Comparable to the ultrasound examination, the liver tissue is highly inhomogeneous with multiple nodules also in the portal venous (small arrows in C) and the late contrast phase (small arrows in D). Due to an elevated portal venous pressure, large portocaval collaterals can be seen (dotted arrow in C).