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CONTRAST MEDIA

Analysis of Lipiodol uptake in angiography and computed tomography for the diagnosis of malignant versus benign hepatocellular nodules in cirrhotic liver

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Abstract

Objectives To evaluate the diagnostic value of Lipiodol distribution in angiography and CT to differentiate between hepatocellular carcinoma (HCC) and benign nodules of LI-RADS 3 and 4 lesions observed in MRI of liver cirrhosis.

Methods This retrospective study included all patients with liver cirrhosis who had diagnosis of LI-RADS 3 or 4 lesions by MRI who underwent a Lipiodol-based angiography and post-interventional unenhanced CT- and liver biopsy. Two independent radiologists evaluated appearance, contrast enhancement, Lipiodol uptake in angiography, and morphological parameters (size, form, and density) of the lesions in unenhanced post-angiography CT. α-Fetoprotein (AFP) levels and pre-existing liver conditions were additionally taken into consideration. Differences between HCC lesions and benign nodules were analyzed. Sensitivity and specificity were calculated. $P < 0.05$ was considered as statistically significant.

Results Of 60 patients (men, $n = 42$ [70.0%]; women, 18 [30.0%]; mean age, 61 ± 9.1 years) 36 (60.0%) had HCC and 24 (40.0%) benign nodules. Clear visibility in angiography (sensitivity [se], 100%; specificity [sp], 87.5%) with homogeneous or lacunar Lipiodol enhancement (se, 86.1%; sp, 100%) in consecutive CT can be diagnosed as HCC lesions in cirrhotic liver. Lesion form ($p < 0.001$), round or oval, and intense contrast ($p < 0.001$) are minor features which can facilitate the findings. Furthermore, patients with HCC showed a larger lesion size in CT ($p = 0.026$).

Conclusion Clearly detectable lesions in Lipiodol-based angiography and a homogeneous or lacunar enhancement in post-angiographic non-contrast CT allow for differentiation of intrahepatic lesions classified as LI-RADS 3 or 4 into benign vs. malign liver lesions with high sensitivity and specificity in patients with liver cirrhosis. Definite diagnosis may not require an additional biopsy.

Key Points

- *Combination of clear visibility in Lipiodol-based angiography and homogeneous or lacunar enhancement in following native CT scan is HCC-defining.*
- *In lesions classified with MRI as LI-RADS 3 or 4, evaluation based on Lipiodol angiography and following plain CT performed is highly sensitive and specific for the differentiation between HCC and benign nodules in a cirrhotic liver.*
- *The results lead to an alternative pathway in the diagnosis of HCC in cirrhotic liver without the need of an additional liver biopsy.*

Keywords Ethiodized oil · Carcinoma, hepatocellular · Angiography · Tomography, X-ray computed · Liver cirrhosis

Abbreviations

ADC	Apparent diffusion coefficient
AFP	α-FetoProtein
BCLC	Barcelona Clinic Liver Cancer
CT	Computed tomography
cTACE	Conventional transarterial chemoembolization
HCC	Hepatocellular carcinoma
IRV	Inter-reader variability
LI-RADS	Liver Imaging Reporting and Data System

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MRI Magnetic resonance imaging
TAE Transarterial embolization

Introduction

Characterization of small unclear hepatic lesions defined by the Liver Imaging Reporting and Data System (LI-RADS) as stadium 3 or 4 into hepatocellular carcinoma (HCC) or benign nodules based on magnetic resonance imaging (MRI) and computed tomography (CT) remains challenging. Some HCCs are difficult to differentiate in a cirrhotic liver as they often do not show typical imaging criteria [1]. Benign regenerative nodules are commonly seen in the cirrhotic liver with similar morphological appearance as HCC lesions in contrast-enhanced MRI and CT as HCC lesions. Unambiguous diagnosis is a decisive factor for improved patient outcome [2]. Therefore, percutaneous biopsy of the suspected lesions is necessary to confirm the diagnosis. This intervention has various complications including bleeding or tumor seeding along the needle track [3].

Several imaging criteria have been validated to safely diagnose HCC only based on typical morphological findings such as contrast enhancement in the arterial phase followed by washout in the portal venous phase [4]. These criteria are highly specific even for small lesions [5]. However, not all questionable lesions show clear results and findings remain inconclusive. This leads to prolonged time to diagnosis which can be critical in patients with an advanced stage of disease and severely reduced hepatic conditions [6].

While the use of Lipiodol as tumor-seeking drug carrier and a micro-embolic agent in cTACE is widely established, Lipiodol may also allow pre-therapeutic tumor diagnosis [7]. To our knowledge, there is no study which analyzed imaging patterns of Lipiodol uptake in Lipiodol-based angiography and CT which may have the potential to increase sensitivity and specificity for the detection and definite diagnosis of HCC.

Lipiodol shows a distinctive, long-lasting uptake in various liver lesions [7]. It is commonly applied to visualize and localize hepatic tumors, to both vectorize and deliver chemotherapeutic drugs and to transiently embolize tumor-feeding arterioportal vessels in transarterial embolization (TAE) and conventional transarterial chemoembolization (cTACE).

The purpose of this study was to evaluate the role of Lipiodol in differentiating unclear hepatic lesions into HCC and benign regenerative nodules detected by MRI and classified as LI-RADS 3 and 4 in patients with cirrhotic liver disease.

Material and methods

This retrospective, single-center study was approved by the local institutional review board (IRB) with a waiver for written consent.

Indication for Lipiodol-based angiography followed by CT-guided liver biopsy was set by the local multidisciplinary tumor board in patients prior to the treatment based on suspicious or unclear liver lesions in contrast-enhanced MRI, which were classified as LI-RADS 3 or 4. We retrospectively evaluated the CT scans, Lipiodol angiography records, and MR images using RIS (radiological information system) and PACS (picture archiving and communication system) software.

All patients participating in this study underwent a Lipiodol-based angiography which was followed by percutaneous CT-guided liver biopsy. This is according to our local standard procedure for unclear hepatic lesions. In patients with unclear findings, lesions are marked using Lipiodol to achieve optimal results in the CT-guided biopsy with a low occurrence of false-negative results or complications.

We excluded all patients whose biopsies showed a histopathologic entity other than HCC or benign regenerative nodules. Additionally, patients without a contrast-enhanced MRI prior to the angiography were excluded.

Lipiodol-based angiography

All interventions were performed by the same interventional radiologist with more than 25 years of experience. The angiographic approach was through the femoral artery in all cases. After introduction of the catheter (Boston Scientific), the abdominal and liver vessels were displayed using contrast medium iomeprol (Imeron®, Bracco). Subsequently, an overview angiography was made, followed by selective catheterization of the superior mesenteric artery and celiac trunk including an indirect portography to demonstrate vascular anatomy and ensure patency of the portal vein ruling out a portal vein thrombosis. Proceeding through the celiac trunk and common hepatic artery, a superselective catheterization of the segmental and subsegmental hepatic branches was performed using a microcatheter (Progreat®, Terumo) for the approach and desire placement. Subsequently, Lipiodol (Lipiodol Ultra-Fluid®) as both tumor visualizer and transient embolic agent was administered. All patients were transferred to our ward for 24-h surveillance.

CT-guided liver biopsy

Following the angiography, a percutaneous CT-guided puncture of the Lipiodol-marked lesion was performed within 2 to 24 h after angiography. Experienced radiologists decided the lesion to be punctured, taking into consideration the previous

Table 1 MR imaging protocol. Overview of the standardized MRI protocol parameters used on our 1.5-T MRI-scanner (Magnetom Aera; Magnetom Avanto-fit; Siemens). Dynamic sequences were acquired in transversal orientation. For the dynamic sequences, bolus tracking was used. Delay times are auto-adjusted considering the bolus track and breathing frequency

No	Sequence
1	T2w HASTE coronary/transversal
2	DWI (b50, b400, b800)
3	ADC-map (b50, b400, b800)
4	T1w VIBE pre-contrast transversal
5	T1w VIBE arterial phase transversal (delay 15 s)
6	T1w VIBE venous phase transversal (delay 45 s)
7	T1w VIBE (isotropic) venous phase coronary/transversal
8	T1w VIBE (isotropic) delayed phase transversal (delay 110 s)

contrast-enhanced MRI and lesion categorization as well as practical aspects of percutaneous puncturing and lesion size. CT-guided puncture of the lesion was performed according to our local standard. Prior to the biopsy, a plain CT scan of the upper abdomen was performed to plan the intervention. After completing the intervention, the biopsy probes were processed and histologically evaluated by our local Institute for Pathology. If no complications occurred, the patients were transferred to our ward for another 24-h surveillance.

MR imaging

All patients underwent a contrast-enhanced MRI performed ahead of the angiography.

MRI scans were produced using a 1.5-T MRI scanner (Magnetom Aera; Magnetom Avanto-fit; Siemens Healthineers). As contrast agent, gadoteric acid (Dotarem®, Guerbet), gadobutrol (Gadovist®, Bayer), or gadoxetic acid (Primovist®, Bayer) was administered. The scan protocol is given in detail in Table 1.

Image evaluation

The evaluation of the lesions in angiography and CT was blindly performed by two senior radiologists independently, each with more than 5 years of experience in diagnostic and interventional radiology, on a dedicated reading workstation. Cases were presented randomized to the readers to prevent bias. In cases of opposed results, a third blinded senior radiologist evaluated the images for decision.

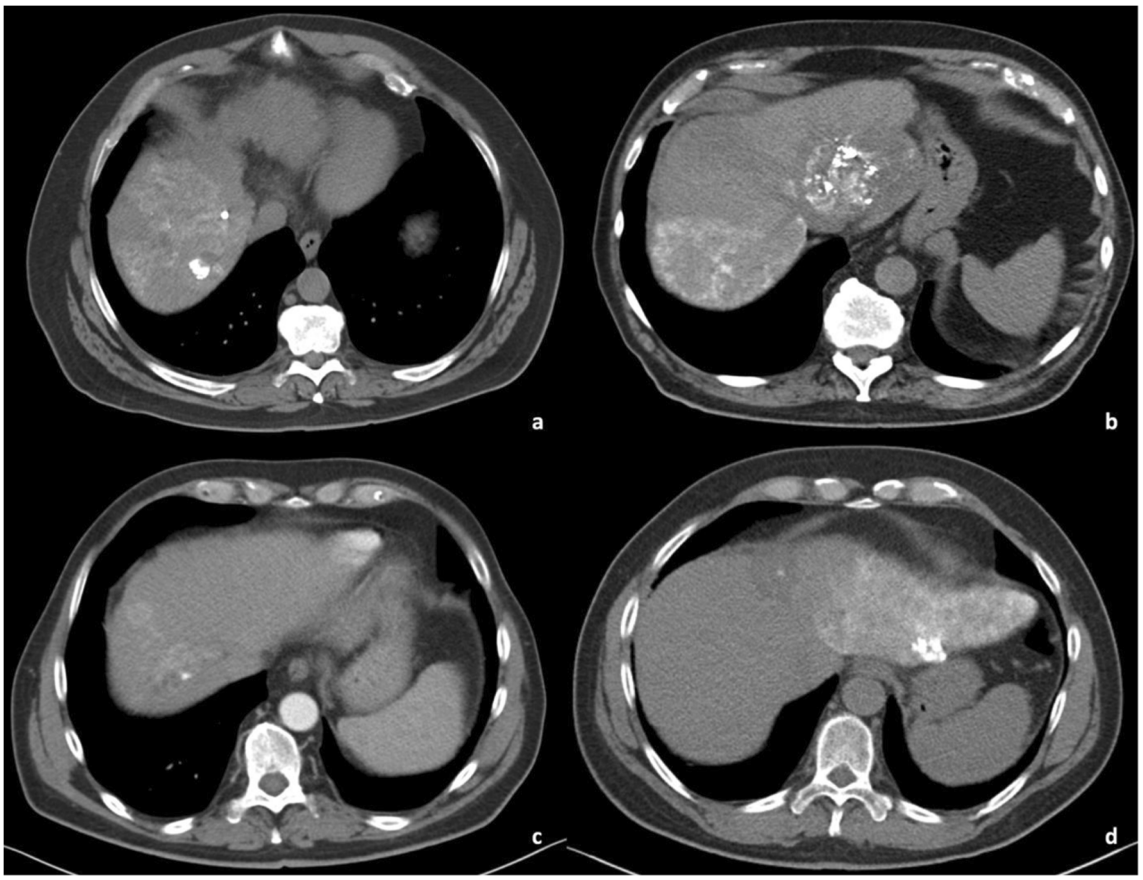

Fig. 1 Sample images for visual analysis of the Lipiodol enhancement in CT with homogenous (**a**) and lacunar (**b**) enhancement compared with an inhomogeneous (**c**) enhancement. Further samples for a weak (**c**) and strong (**d**) contrast in CT after the angiography

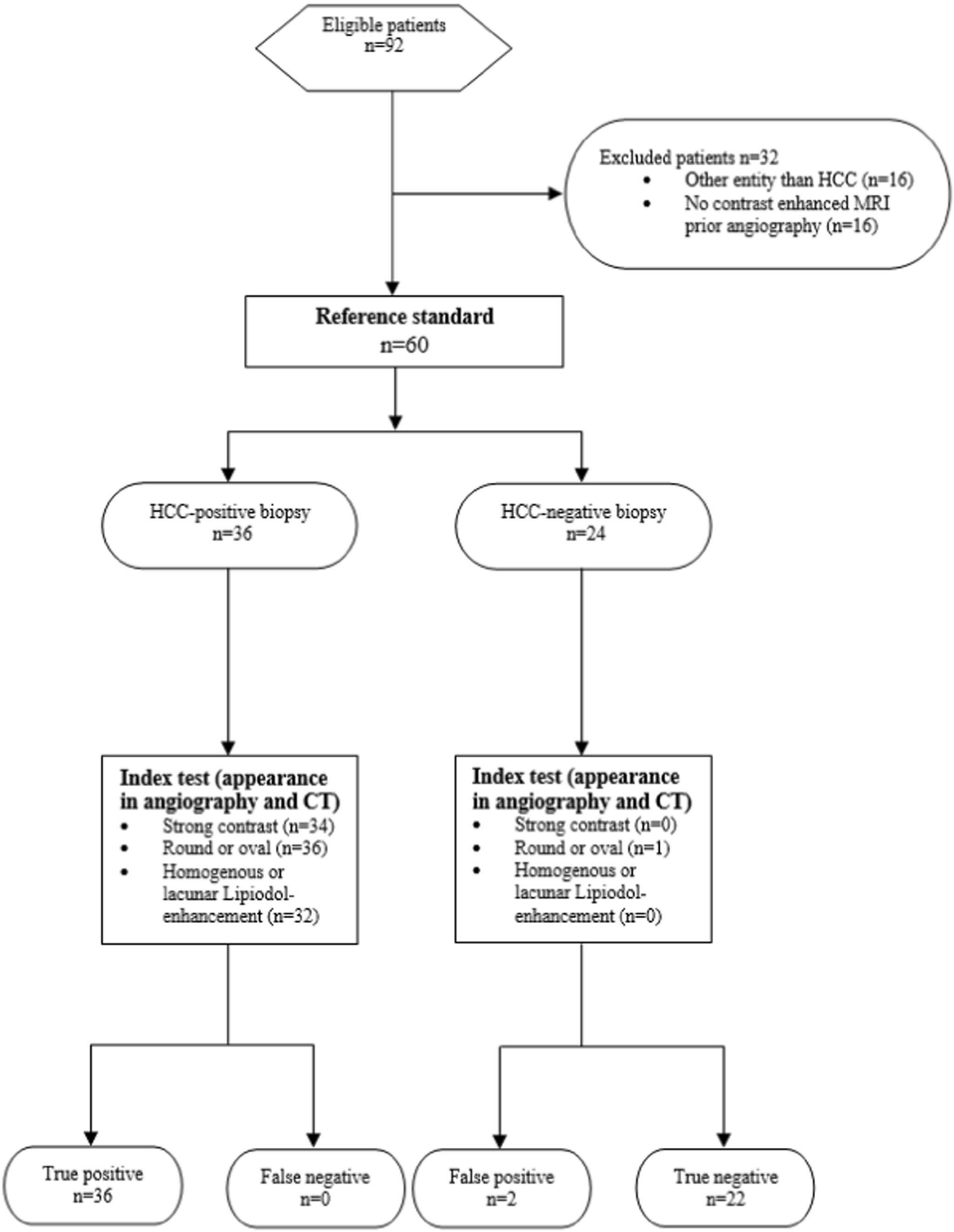

Fig. 2 Standards for Reporting of Diagnostic Accuracy (STARD) flowchart overview of patient inclusion and exclusion. HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; CT, computed tomography

Table 2 Patient characteristics

Characteristic	No. of patients / (%)
Age (years) median [range]	61 [27–81]
Sex	
Male	42 (70.0%)
Female	18 (30.0%)
Etiology	
HCV	22 (36.7%)
HBV	7 (11.7%)
HCV + HBV	1 (1.7%)
NASH	10 (16.7%)
Alcohol abuse	8 (13.3%)
Hemochromatosis	2 (3.4%)
Primary sclerosing cholangitis	2 (3.4%)
AFP (ng/ml)	
< 10	27 (45.0%)
10–400	27 (45.0%)
> 400	6 (10.0%)
Mean	469.6
Intrahepatic lesions	
1 lesion	14 (23.3%)
2 lesions	12 (20.0%)
3 or more lesions	34 (56.7%)
Tumor location (MRI)	
Right lobe	39 (65%)
Left lobe	19 (31.7%)
Both lobes	2 (3.3%)

HCV, hepatitis C virus; *HBV*, hepatitis B virus; *NASH*, non-alcoholic steatohepatitis; *AFP*, α-fetoprotein

For evaluation of the angiography, imaging series prior and after Lipiodol administration were presented. The readers were asked to analyze the vascularization (hypervascularized/visible vs. non-hypervascularized/non-visible).

CT evaluation was performed using the plain CT scan dataset of the upper abdomen used as biopsy planning scan. Lesions were categorized regarding the form, round and oval versus diffused and derounded. Lipiodol enhancement was categorized using three different enhancement patterns: inhomogeneous, lacunar defined as a lesion with partial homogeneous parts, and homogenous. Lacunar and homogeneous enhancements were considered as HCC-specific. Contrast level was analyzed by two categories: weak and strong compared to the surrounding liver tissue.

Categories were defined prior reading using example images and visual impressions (Fig. 1). The examples were presented to the readers for training before they started analyzing the studied population. Reader training was performed twofolded; after presenting imaging examples, readers had to rate sample patients for training and achieving optimal comparability. Inter-reader variability (IRV) was calculated using Cohen's kappa.

Statistical evaluation

For statistical analysis, SPSS V23.0 (IBM) was used. Continuous and categorical variables were compared using the Wilcoxon-Whitney-Mann test, exact Fischer's test, and chi-square test, and a concluding logistical regression was performed. Correlation was calculated using the Spearman rho. Sensitivity and specificity of the imaging parameters in angiography and CT were calculated based on positive and negative predictive values and the resulting true-positive rate and true-negative rate. P values < 0.05 were considered as statistically significant. IRV was categorized according to Landis and Koch from poor to almost perfect agreement [8].

Results

Patient characteristics

From March 2016 to February 2017, 92 consecutive eligible patients were screened. Thirty-two patients were excluded not fulfilling the inclusion criteria. In total, 60

Table 3 Sensitivity and specificity of the observed parameters for HCC in Lipiodol-based angiography—visibility and hypervascularization

	Lipiodol-based angiography		
	HCC-positive (visible/hypervascularized)	HCC-negative (non-visible)	Sensitivity/specificity
HCC-positive (histological)	36	0	100.0%
HCC-negative (histological)	3	21	87.5%
PPV	92.3%	–	–
NPV	–	100.0%	–

PPV, positive predictive values; *NPV*, negative predictive value; *HCC*, hepatocellular carcinoma

Table 4 SPSS analysis of patient data and morphological imaging parameters. *Comparison between HCC-group and regenerative nodule-group

	Total, *n* (%)	HCC, *n* (%)	Regenerative nodule, *n* (%)	*p* value*
No. of patients	60 (100%)	36 (56.7%)	24 (43.3%)	
Mean (± SD) AFP level (ng/ml) (SD)	469.6 (± 2260.1)	732.2 (± 2851.0)	108.5 (± 494.9)	< 0.001
Visibility in angiography				0.139
Visible (hypervascular)	39 (65.0%)	24 (70.6%)	15 (57.7%)	
Not visible (not hypervascular)	21 (35.0%)	10 (29.4%)	11 (42.3%)	
CT				
Lipiodol enhancement				< 0.001
Homogenous/lacunar	34 (56.7%)	34 (94.4%)	0	
Inhomogeneous	26 (43.4%)	2 (5.6%)	24 (100%)	
Contrast				< 0.001
Strong	34 (56.7%)	34 (94.4%)	0	
Weak	26 (43.4%)	2 (5.6%)	24 (100%)	
Form				< 0.001
Round/oval	36 (60.0%)	35 (97.2%)	1 (4.2%)	
Tapered/punctual	24 (40.0%)	1 (2.8%)	23 (95.8%)	
Mean lesion size (cm)	2.5	2.7	2.2	0.026
MRI				
Contrast enhancement				0.983
Positive	52 (86.7%)	33 (91.7%)	19 (79.2%)	
Negative	8 (13.3%)	3 (8.3%)	5 (29.8%)	
Form				< 0.001
Round/oval	40 (85.0%)	35 (97.2%)	5 (20.8%)	
Tapered/punctual	20 (15.0%)	1 (2.8%)	19 (79.2%)	
Mean ADC value (mm^2/s)	1110.7	1139.6	1070.5	0.155
Mean lesion size (cm)	2.5	2.9	2.0	0.006

patients, 18 females and 42 males, who completely met the inclusion criteria were included in the study and evaluated. Figure 2 provides a STARD flowchart of patient inclusion. Mean patient's age was 61 years (range, 27 to 81 years). Causes for liver cirrhosis were hepatitis C virus infection ($n = 22$, 36.7%), hepatitis B virus infection ($n = 7$, 11.7%), co-infection of hepatitis B and C ($n = 1$, 1.7%), alcohol abuse ($n = 8$, 13.3%), nonalcoholic steatohepatitis (NASH) ($n = 10$, 16.7%), hemochromatosis ($n = 2$, 3.4%), or primary sclerosing cholangitis ($n = 2$, 3.4%). In eight cases, the patients developed cirrhosis of unclear origin (Table 2).

Lipiodol angiography was performed in all patients ($n = 60$) without complication. No complications occurred related to the angiography. The mean volume of Lipiodol given during the angiography was 6.4-ml Lipiodol per

Table 5 Sensitivity and specificity of the observed parameters for HCC in computed tomography—Lipiodol enhancement in CT

	Lipiodol enhancement		
	HCC-positive (homogeneous/lacunar)	HCC-negative (diffused)	Sensitivity/specificity
HCC-positive (histological)	32	4	88.9%
HCC-negative (histological)	0	24	100.0%
PPV	100.0%	–	–
NPV	–	85.7%	–

PPV, positive predictive values; *NPV*, negative predictive value; *HCC*, hepatocellular carcinoma

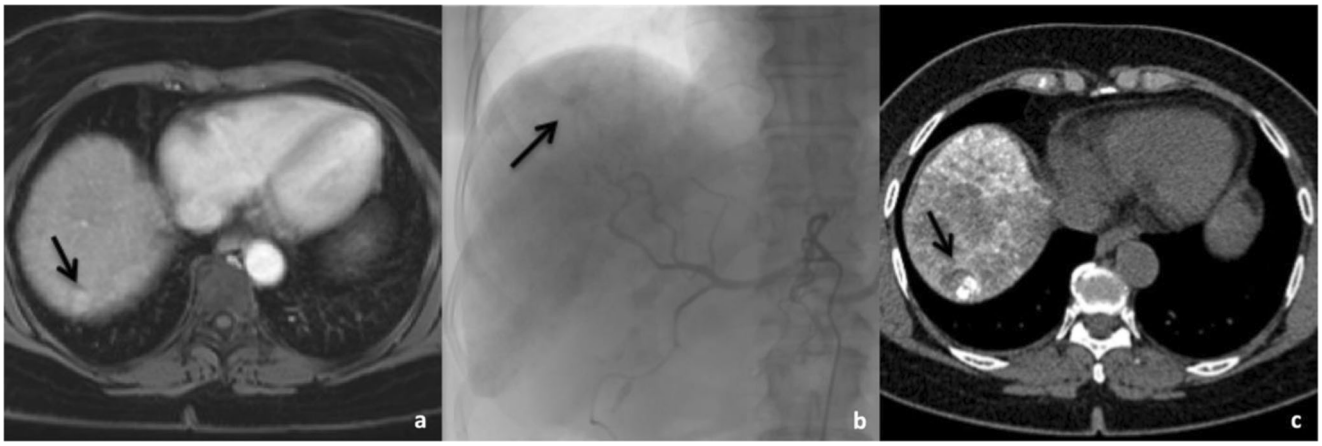

Fig. 3 A 61-year-old female patient with NASH cirrhosis in Child-Pugh A stage. The AFP level was 8.1 ng/ml at the initial determination. A suspicious liver lesion in segment VIII was found based on contrast-enhanced MRI 2 weeks before Lipiodol-based angiography. The lesion was measured a diameter of 1.9 cm and is located in segment VIII. **a** The lesion shows a positive enhancement in MRI without HCC typically washout (arrow). **b** Angiogram reveals the hypervascularized liver lesion (arrow). **c** CT scan after TAE during the CT-guided biopsy of the unclear liver lesion. An incomplete homogeneous/lacunar Lipiodol occupancy, a high contrast, and a strong enhancement could be seen, state lesion as HCC (HU 186) (arrow)

session, ranging from 2 ml for a super-selective to 15 ml in lobar application (95% confidence interval [CI], 5.6–7.2 ml).

After the hepatic lesion was marked with Lipiodol, CT-guided liver biopsy was successfully performed, hitting the target lesion in all 60 patients (100%). Thirty-six patients (60.0%) had histopathologically confirmed HCC while the remaining 24 patients (40.0%) showed benign regenerative nodules. The majority of the lesions was found in the right lobe ($n = 39$ patients; 65.0%). Nineteen patients (31.7%) had lesions in the left lobe and two patients (3.3%) had lesions infiltrating both lobes. A total of 14 patients (23.3%) presented only with one lesion, 12 patients (20%) with two lesions, and 34 patients (56.7%) with multiple lesions (Table 2).

The mean AFP level in the whole study cohort was 469.6 ng/ml, 732.2 ng/ml in the HCC group, and 108.5 ng/ml in the regenerative node group, respectively, with a statistically significant difference among AFP levels comparing both groups ($p < 0.001$).

Lesion and imaging evaluation

Two-folded training set evaluation revealed an almost perfect agreement between both readers with an IRV of $\kappa = 0.912$ ($p < 0.001$). The lesion evaluation by the two independent readers showed overall and for the individual parameters an almost perfect agreement with $\kappa = 0.910$ ($p < 0.001$) for all criteria, for lesion form $\kappa = 0.891$ ($p < 0.001$), Lipiodol enhancement $\kappa = 0.867$ ($p < 0.001$), contrast level $\kappa = 0.900$ ($p < 0.001$), and visibility in angiography $\kappa = 0.917$ ($p < 0.001$).

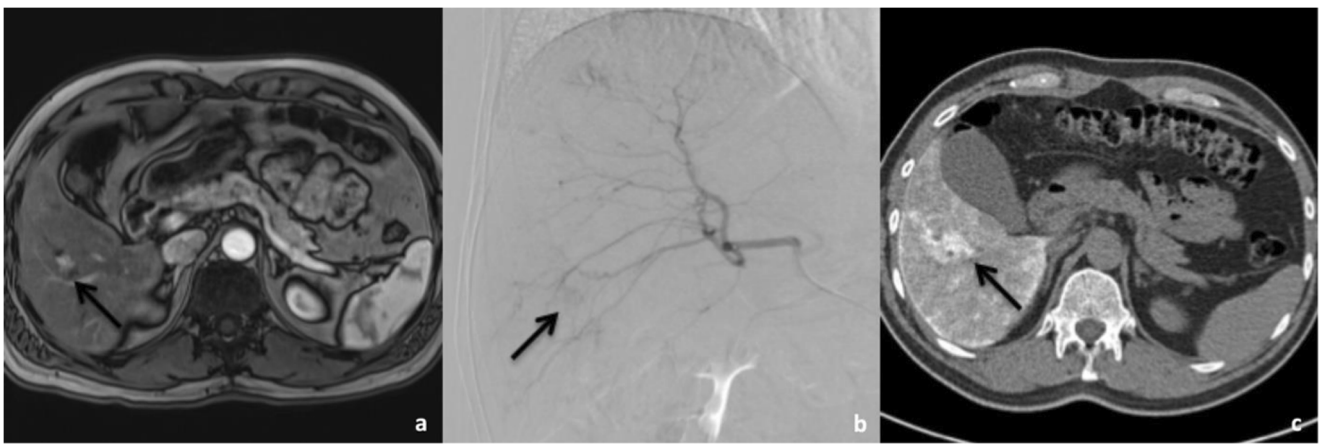

Fig. 4 A 48-year-old male patient with chronic HBV infection and regenerative nodule. Initial AFP level was 2 ng/ml. The nodule had a diameter of 1.2 cm and is located in segment VI. It shows a positive enhancement in MRI, 4 months prior angiography (**a**) and angiography (**b**). In the post-TAE-CT, the lesion appeared inhomogeneous with a weak contrast and reduced Lipiodol uptake (**c**)

Table 6 Sensitivity and specificity of the observed parameters for HCC in computed tomography—contrast in CT

	Contrast		
	HCC-positive (strong)	HCC-negative (weak)	Sensitivity/specificity
HCC-positive (histological)	34	2	94.4%
HCC-negative (histological)	0	24	100.0%
PPV	100.0%	–	–
NPV	–	92.3%	–

PPV, positive predictive values; *NPV*, negative predictive value; *HCC*, hepatocellular carcinoma

Magnetic resonance imaging

In the initially performed MRI, all investigated lesions showed a non-HCC-typical morphological appearance. Forty-one patients (68.3%) were classified as LI-RADS 3 and 19 (31.7%) as LI-RADS 4. LI-RADS 3 lesions presented a non-rim arterial phase hyperenhancement < 20 mm in 11 cases (26.8%) and an arterial phase hypo- or isoenhancement in 30 cases (73.2%), hereof 12 cases (40.0%) < 20 mm with a major feature (enhancing capsule or nonperipheral washout) and 18 patients (60.0%) > 20 mm with no additional major feature. Patients categorized as LI-RADS 4 showed in 10 cases (52.6%) a non-rim arterial phase hyperenhancement, seven (70.0%) < 20 mm with enhancing capsule, and three (30.0%) ≥ 20 mm with no major feature. Nine patients (47.4%) showed an arterial phase hypo- or isoenhancement with 5 cases (55.6%) < 20 mm plus two major features and 4 cases (44.4%) ≥ 20 mm with one major feature.

Angiography

Based on the Lipiodol angiography, 39 (65.0%) patients presented with hypervascularized and clear visible lesions. Twenty-one (35.0%) patients had lesions that did not appear during the treatment due to a small lesion size or a non-hypervascularized appearance. Positing clear visible lesions in angiography as HCC-suspect, sensitivity is calculated 100% with a specificity of 87.5% (area under the curve [AUC], 0.938; CI, 0.858–1.000; $p = 0.040$) (Table 3).

Computed tomography

Mean lesion size in CT was 2.5 cm, ranging from 0.7 to 6 cm. HCC lesions had a mean diameter of 2.7 cm, while regenerative nodules were measured with a mean size of 2.2 cm. Statistical analysis showed a significant difference between HCC and regenerative nodes regarding tumor size in CT ($p = 0.026$) (Table 4).

Regarding the Lipiodol enhancement on CT, 28 patients (46.7%) had lesions with inhomogeneous enhancement, 22 (36.7%) had lacunar enhancement, and 10 patients (16.7%) presented with a homogenous Lipiodol enhancement. Homogeneous and lacunar homogeneous enhancements were significantly more frequent in the HCC group compared with inhomogeneous enhancement ($p < 0.001$). No benign nodule showed homogenous or lacunar enhancement. A homogenous or lacunar Lipiodol enhancement of the lesions in CT was calculated with a sensitivity of 88.9% and a specificity of 100% for prediction of HCC (AUC, 0.896; CI, 0.813–0.978; $p = 0.042$) (Table 5).

Almost all HCC lesion (34 of 36, 94.4%) had a strong contrast between the lesion and the perilesional tissue in the unenhanced, while all benign nodules (24 of 24, 100.0%) showed only weak contrast (Figs. 3 and 4). Therefore, a strong lesion contrast in unenhanced CT is an excellent marker for

Table 7 Sensitivity and specificity of the observed parameters for HCC in computed tomography—form in CT

	Form		
	HCC-positive (round/oval)	HCC-negative (diffused/derounded)	Sensitivity/specificity
HCC-positive (histological)	35	1	97.2%
HCC-negative (histological)	1	23	95.8%
PPV	97.2%	–	–
NPV	–	95.8%	–

PPV, positive predictive values; *NPV*, negative predictive value; *HCC*, hepatocellular carcinoma

Table 8 Sensitivity and specificity of the Lipiodol enhancement pattern in following CT for patients with clear visible and hypervascularized lesions in previous angiography. Homogeneous or lacunar enhancement is HCC-defining

	Lipiodol enhancement in CT for patients with clear visible lesions in angiography		
	HCC-positive (homogeneous/lacunar)	HCC-negative (diffused)	Sensitivity/specificity
HCC-positive (histological)	31	5	86.1%
HCC-negative (histological)	0	3	100.0%
PPV	100.0%	–	–
NPV	–	37.5%	–

PPV, positive predictive values; *NPV*, negative predictive value; *HCC*, hepatocellular carcinoma

HCC with a high sensitivity of 94.4% and a perfect specificity of 100% (AUC, 0.910; CI, 0.828–0.992; $p = 0.042$) (Table 6).

Lesion shape after angiography revealed a tapered or punctual impression in 24 patients (40.0%) and round/oval in 36 cases (60.0%). Thirty-five of 36 patients (97.2%) with round or oval lesions had HCC. Only one HCC patient (2.8%) showed a tapered/punctual impression. Compared with the appearance of benign nodules, the results are highly statistically significant ($p < 0.001$), yielding a sensitivity of 97.2% and a specificity of 95.8% for defining HCC lesions, respectively (AUC, 0.874; CI, 0.801–0.969; $p = 0.037$) (Table 7).

The combination of the verified criteria also reveals quite similar results. Combining two independent HCC-suspicious criteria revealed an overall sensitivity of 97.2% and a specificity of 95.8% (AUC, 0.965; CI, 0.909–1.000). Combination of homogeneous/lacunar Lipiodol enhancement in CT with hypervascularization in angiography revealed a high specificity (specificity, 100%; sensitivity, 86.1%; AUC, 0.931; CI, 0.861–1.000). The addition of a third or fourth criteria showed no additional benefit, neither for sensitivity nor for specificity.

With a look on a diagnostic pathway, lesion analysis in Lipiodol angiography showed the highest sensitivity with 100% (specificity 87.5%) for detecting HCC-positive lesions. These lesions appeared clearly visible with a hypervascularization. Analyzing this suspected lesion in the flowing native CT scan only by the Lipiodol enhancement pattern, a specificity of 100% is reached with a positive predictive value of 100% and a sensitivity of 86.1% (AUC, 0.931; CI, 0.845–1.000) for lesions with homogeneous/lacunar enhancement pattern (Tables 3 and 8).

These results may lead to new diagnostic pathway with a high sensitivity and specificity without the need for an invasive biopsy (Fig. 5).

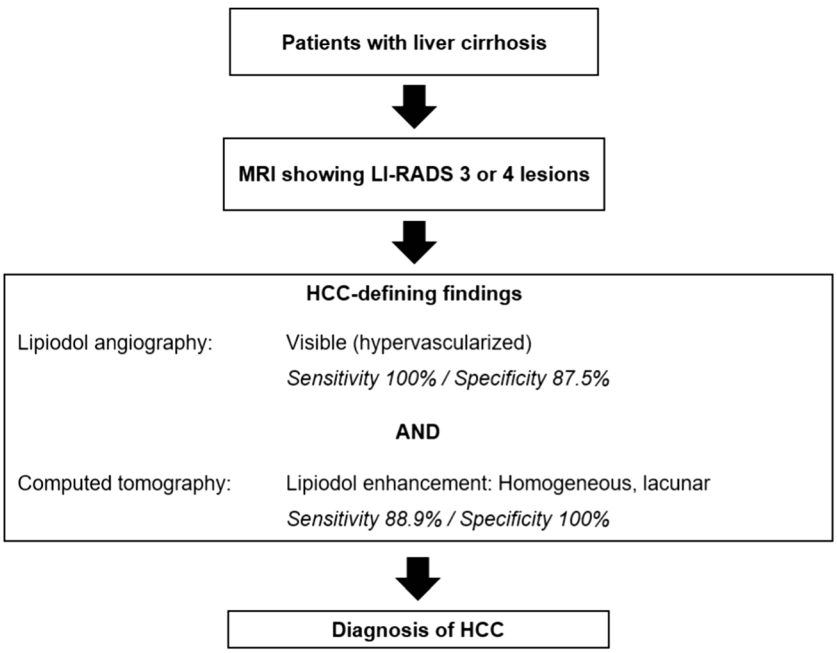

Fig. 5 Diagnostic flowchart and HCC-suspect findings in Lipiodol-based angiography and computed tomography for differentiating hepatocellular carcinoma and benign hepatic nodes

Discussion

In this retrospective study, we could show that the assessment of the entity of unclear liver lesions (LI-RADS 3 or 4 classified by MRI) based on imaging criteria of Lipiodol-based angiography and post-interventional unenhanced CT of the liver has similar diagnostic value as the gold standard liver biopsy. Distinctive hypervascularized and clear visible appearance in angiography and a typical homogeneous or lacunar Lipiodol enhancement in consecutive unenhanced CT scan are HCC-defining. Round or oval form and strong contrast support the diagnosis. The isolated parameters show a high sensitivity and specificity in the diagnosis of HCC and can be used in clinical assessment of suspect and unclear intrahepatic lesions. An additional biopsy of these lesions may not be required anymore to secure the diagnosis.

Commonly, LI-RADS 3 or 4 lesion, especially in cirrhotic liver, indicates the need for a diagnostic confirmation, for example by an invasive biopsy. As the lesions are often not clearly visible in ultrasound or CT, a Lipiodol-based angiography with the aim to tag unclear liver lesions is commonly performed enabling a safe and reliable biopsy of even small lesions. Lipiodol is commonly applied in angiography to visualize and localize hepatic tumor lesions, to vectorize chemotherapeutic drugs, and transiently embolize tumor-feeding arteries during angiography. The embolizing property of Lipiodol when administered during TAE or cTACE is well investigated [9, 10]. Now, the use of Lipiodol-based angiography in tumor diagnostics is yet to be evaluated. In this study, we isolated several individual parameters which we suspected of allowing distinction between HCC lesion und benign intrahepatic nodes with a high diagnostic accuracy.

Retention of Lipiodol in liver lesions with altered cell structure, for example HCC, lasts for weeks and up to several months which can be used to identify this suspect lesions in angiography [6, 11]. The prolonged persistence of ethiodized oil in tumors is explained by tumor hypervascularization and increased angiogenesis, absence of reticulo-endothelial system and Kupffer cells phagocytizing the agent, all combined with the lack of lymphatic drainage [12]. Our results revealed that clear visible lesions in angiography have a 100% sensitivity for HCC and can be used as a first step in lesion differentiation. Previous studies already assessed the use of Lipiodol as contrast medium in the detection of HCC, but only for patients with secured HCC. Li et al and Zheng et al performed bland C-arm CT scans immediately after Lipiodol administration during TACE. Their results proved that unenhanced CT after Lipiodol angiography had a high diagnostic sensitivity even for small HCC lesions [2, 13]. Their results are in agreement with our results.

In post-angiography unenhanced CT, homogeneous or lacunar Lipiodol enhancement had a 100% specificity with 88.9% sensitivity for HCC. We believe that newly described imaging criteria in CT can be used to differentiate and specify lesions detected in the previous Lipiodol angiography. Based on the initial results of this study, we suggest that those patients do not require an invasive biopsy for lesion diagnosis.

In comparison, clear visible lesions in the angiography, showing an inhomogeneous Lipiodol enhancement pattern in CT, require further evaluation by biopsy to differentiate between HCC and benign nodes.

Following the results of our study, we classified strong Lipiodol contrast in CT and a round or oval form as HCC-suggestive but not HCC-defining as these criteria cannot securely differentiate between HCC and benign nodules.

The results of our study may suggest a new diagnostic pathway in differentiating unclear but suspect intrahepatic lesions. Patients with LI-RADS 3 or 4 lesions should receive a Lipiodol-based angiography followed by an unenhanced CT scan. Clear visible lesions in angiography with a homogeneous or lacunar Lipiodol enhancement pattern in CT can be diagnosed as HCC. This might eliminate an invasive biopsy in these patients. Patients with unclear and inconclusive findings still require an additional invasive biopsy of lesions. To our knowledge, our study represents the first attempt using Lipiodol enhancement to differentiate between HCC and benign nodules in cirrhotic liver.

The isolated diagnostic imaging parameters can be probably used for automated diagnostic algorithm differentiating unclear hepatic lesions. This approach is topic of actual research and still under investigation [14].

We acknowledge that this retrospective study had several limitations. The intention of this study was to test its feasibility. Therefore, the patient cohort was rather small and a study including a prospective design, multiple centers, and a larger cohort should follow. The imaging-based tumor evaluation does not provide tumor grading which is required in clinical trials to evaluate patterns of vascular invasion or asses the expression of keratin 19 [15–17]. In those cases, invasive biopsy is still necessary.

Clear visible lesions in Lipiodol-based angiography in combination with a homogeneous or lacunar enhancement in following native CT scan are imaging parameters which have high diagnostic value to differentiate HCC and benign lesions. For patients presenting LI-RADS 3 or 4 lesions in MRI along with liver cirrhosis, the results of our study may provide a path for imaging-based HCC evaluation based on new imaging criteria to overcome the necessity for invasive biopsy.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Marcel C. Langenbach.

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Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

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