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HEPATOBILIARY-PANCREAS

Peritoneal and pleural fluids may appear hyperintense on hepatobiliary phase using hepatobiliary MR contrast agents

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Abstract

Aim To describe the effect of hepatobiliary-specific MR imaging contrast agent (HBCA) administration on the signal intensity of peritoneal and pleural fluid effusions on T1-weighted MR images.

Materials and methods From October 2015 to May 2016 139 patients (mean 60±10 years old, 69 % males) with peritoneal or pleural effusions without biliary leakage who underwent HBCA-MRI (Gd-BOPTA or Gd-EOB-DTPA) at 1.5T and 3T were included from two centres. The fluid signal intensity was classified as hypo/iso/hyperintense before/after HBCA administration. The relative signal enhancement (RE) was calculated.

Results On hepatobiliary phase (HBP), peritoneal fluids appeared hyper/isointense in 88–100 % and pleural effusions in 100 % of the patients following Gd-BOPTA administration. All fluids remained hypointense following Gd-EOB-DTPA. The signal intensity of fluids increased with both HBCA but RE was significantly higher following Gd-BOPTA (p=0.002 to <0.001). RE was correlated with HBP acquisition time-point (r=0.42, p<0.001 and r=0.50, p=0.033 for peritoneal and pleural fluids).

Conclusion The signal intensity of pleural and peritoneal fluids progressively increases following HBCA administration in the absence of biliary leakage. Due to its later hepatobiliary phase, this is more pronounced after Gd-BOPTA injection, leading to fluid hyperintensity that is not observed after Gd-EOB-DTPA injection.

Key Points

- *Fluids appear hyper/isointense on HBP in most patients after Gd-BOPTA injection.*
- *Fluids remain hypointense on HBP after Gd-EOB-DTPA injection.*
- *RE of fluids increases with time after liver-specific Gd injection.*
- *RE of fluids is higher in patients with chronic liver disease.*

Keywords Liver · Contrast media · Bile ducts · Ascites · Pleural effusion

Abbreviations

CT	Computed tomography
HBCA	Hepatobiliary contrast agent
HBP	Hepatobiliary phase
HU	Hounsfield unit
MRI	Magnetic resonance images

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Introduction

Hepatobiliary contrast agents (HBCAs) are gadolinium chelates that are taken up by functional hepatocytes. Internalization is mediated by organic anionic transporting polypeptides (OATPs) expressed on the sinusoidal membrane of these hepatocytes [1]. Currently, there are two commercially available HBCAs: gadobenate dimeglumine or Gd-BOPTA (Multihance, Bracco Imaging, Milan, Italy) and gadoxetate disodium also known as gadoxetic acid or Gd-EOB-DTPA (Primovist / Eovist, Bayer, Leverkusen, Germany). Around 50 % of the injected dose of the latter is rapidly transported

through the hepatocytes and excreted into the bile, allowing an HBP image 20–120 min after injection. With gadobenate dimeglumine it is only 5% and the HBP is obtained 40 min–2 h after injection. HBCAs have been shown to be useful for the detection and characterization of focal liver lesions in three main clinical situations: small nodules on cirrhotic livers, pre-operative staging of liver metastases and the characterization of benign hepatocellular lesions discovered incidentally in patients without chronic liver disease [2–4].

After intracellular uptake HBCA are excreted into the biliary canals through multidrug resistance-associated proteins (MRPs). Thus, bile ducts appear hyperintense on T1-weighted HBP images [5], resulting in a positive cholangiography, while perihepatic fluids, when present, remain hypointense on T1-weighted images even during the HBP [6–8]. Several studies have reported that these HBCAs could be useful to detect biliary leakage or to assess bile duct injury on MR imaging by showing the increased signal intensity of perihepatic or peritoneal fluid during bile extravasation. This has mainly been reported with Gd-EOB DTPA [6, 7], while studies evaluating Gd-BOPTA are rare [8].

Several studies have reported an increased attenuation of peritoneal fluid during the delayed phase (defined as >10 Hounsfield units (HU)) of contrast-enhanced CT [9–14]. This enhancement pattern seems to be more frequent in patients with renal impairment or those with peritoneal carcinomatosis [9–14].

Since hepatobiliary MR contrast agents diffuse into the extravascular space, one could expect them to accumulate to a certain extent in peritoneal or pleural fluids. Yet, to our knowledge, clinical consequences of this, and especially possible enhancement of pleural and peritoneal fluids has never been described following their administration. Because we observed certain cases of fluid hyperintensity without bile leakage, we decided to perform this study.

Thus, the aim of this study was to assess the signal intensity of peritoneal and pleural fluid effusions following HBCA administration in T1-weighted images in a consecutive series of patients.

Material and methods

Patient population

This retrospective study was approved by the local **r**eview board and informed consent was waived. Between October 2015 and May 2016, 500 patients who underwent gadobenate dimeglumine (Gd-BOPTA)-enhanced or gadoxetic acid (Gd-EOB-DTPA)-enhanced MR imaging of the liver including HBP images were extracted from the databases of two imaging departments (250 patients from each centre). Inclusion criteria were the presence of any amount of fluid effusion in the pleural and/or peritoneal cavities, whatever the cause. Patients who did not receive an extracellular contrast agent, and those who underwent hepatobiliary MR contrast agent administration with no HBP images were excluded. Patients with biliary leakage, injury or biloma were excluded by screening their full medical chart.

HBCAs were used according to recent guidelines [15]. Figure 1 presents the flow chart of the study population. Overall, the study population included 139 patients, mean age 60±10 years old.

Magnetic resonance imaging

MR imaging was performed with a 3.0 T MRI scanner (Achieva; Philips Healthcare, Best, The Netherlands) using a phased-array surface coil in centre 1, and 1.5T (Avanto; Siemens, Erlangen, Germany) and 3T MR scanners (Discovery MR750, GE HealthCare, Milwaukee, WI, USA) in centre 2. MR scanners were equipped

with high performance gradients and 8-channel phased array coils. Patients fasted for 4–6 h.

Both protocols included a T2-weighted single-shot sequence, a T2-weighted fast spin-echo sequence with spectral fat saturation, and a transverse breath-hold 3D T1-weighted fat-suppressed spoiled gradient-recalled echo sequence before and after dynamic injection of contrast medium. A total of 0.05 mmol/kg of body weight (0.1 ml/kg) of Gd-BOPTA or 0.025 mmol/kg of body weight (0.1 ml/kg) of Gd-EOB-DTPA followed by a 20-ml (centre 1) or 15-ml (centre 2) saline solution flush were administered at 2 and 1 ml/s with a power injector. Triple arterial, portal venous and equilibrium phase sequences were obtained by bolus trigger (centre 1) or beginning 18–20 s after contrast administration (centre 2), then 60–70 s and 180–200 s after intravenous contrast administration, respectively, in both centres. The HBP images were acquired at 20 min (Gd-EOB-DTPA) or between 1 h 30 min and 2 h (Gd-BOPTA) after injection. A free-breathing fat-suppressed single-shot echoplanar diffusion-weighted (DW) MR sequence was obtained before contrast injection with *b* values of 0, 150 and 600 s/mm^2. Cardiac gating was not used.

Image analysis

MR images were retrospectively reviewed by consensus by two abdominal radiologists (MC resident, and MR senior consultant with 10 years of experience in the field of liver MR imaging) on a dedicated workstation (Carestream Health, Rochester, NY, USA). Readers were blinded to the clinicobiological data of patients and indications for MR imaging examinations.

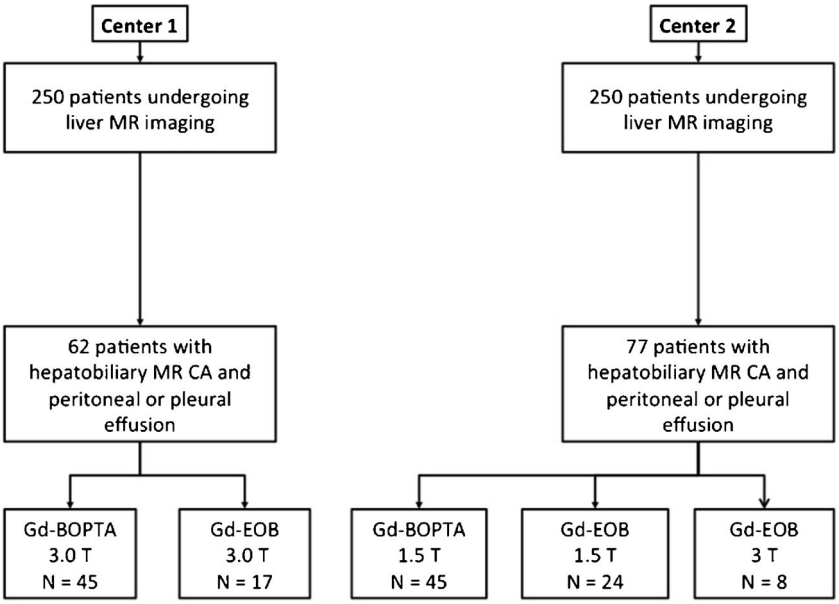

Fig. 1 Flow chart of the study population

Qualitative image analysis

Readers were asked to note the following items for qualitative image analysis: (1) location of the peritoneal fluid (perihepatic, perisplenic, right and left gutter, diffuse); (2) amount of fluid when present (mild-moderate or abundant), (3) signal intensity of fluid effusions on pre- and enhanced T1-weighted MR images following contrast administration on arterial and portal venous phase images, at 3 min and HBP images compared to muscle signal (defined as hypo-, iso- or hyperintense). Muscle was considered for comparison (as opposed to either the liver or fluid on precontrast images) because it does not uptake hepatobiliary MR contrast agent, so it is expected to appear hypointense on both precontrast and HBP images.

Quantitative image analysis

Readers were asked to place three ellipsoid regions of interest (ROIs) at different levels of fluid effusion on pre- and contrast-enhanced T1-weighted MR images on arterial and portal venous phase images, at 3 min, and HBP images. The exact position of the ROIs was ensured by copy pasting from one sequence to the next. ROIs were drawn to exclude the surrounding organ parenchyma and the standard deviation for each ROI was recorded. The mean signal intensity (SI) was calculated for each phase as the average of the three ROI values. The relative fluid enhancement (RE), was calculated by the following formula:

$$RE = |(SI_{post} - SI_{pre})| / (SI_{pre})$$

with SI_{pre} and SI_{post} corresponding to the average signal intensity of the fluid before and after contrast medium administration during the different phases.

Statistical analysis

Results are presented as means (standard deviation) or medians (ranges) for quantitative data, and as the number of cases (percentage of cases) for categorical variables. Comparison between subgroup features was performed with analysis of variance (ANOVA) and Student's t-test, the Mann-Whitney U test and the Kruskal-Walis test for continuous variables according to distribution. Qualitative data were compared with the Chi^2 or Fisher's exact tests when necessary. Tests were always two sided, and $p<0.05$ was considered to be significant. All analyses were performed using the Statistical Package for the Social Sciences software (version 20.0, IBM SPSS Inc., Armonk, NY, USA).

Results

Patient population

Patient characteristics are described in Table 1. The Gd-BOPTA 1.5T and 3T groups included 45 patients each, while the Gd-EOB-DTPA 1.5T and 3T groups included 24 and 25 patients, respectively. Most patients had peritoneal effusions (96–100 %) with pleural effusions in 11–21 % of patients. Peritoneal effusions were usually located in the perihepatic (44–72 %) and perisplenic spaces (46–73 %). The volumes of peritoneal and pleural effusions were more frequently mild (63–100 %). The four groups were comparable with regard to gender, mean age and laboratory test values except for the total bilirubin serum level and spleen size.

Table 1 Patient characteristics

	Gd-BOPTA		*p*-value Gd-BOPTA	Gd-EOB		*p*-value Gd-EOB	Global *p*
	1.5T	3.0T		1.5T	3.0T		
N patients	45	45		24	25		
M (%)	31 (69)	26 (58)	0.380	20 (83)	19 (76)	0.725	0.137
Mean age ± SD years	57±8	61±12	0.532	59±10	63±3	0.882	0.097
Indication for MR imaging							
Chronic liver disease	40 (89)	27 (60)		17 (71)	21 (84)		
Cancer staging	2 (4)	12 (27)	**0.005**	6 (25)	1 (4)	**0.039**	**0.015**
Other	3 (7)	6 (13)		1 (4)	5 (20)		
Laboratory tests (mean ± SD)							
INR	1.4±0.3	1.3±0.5	0.987	1.5±0.2	1.3±0.2	0.887	0.506
Creatinine umol/L	79±23	77±24	0.789	84±50	85±23	0.873	0.711
Total Bilirubin mmol/L	36±20	15±7	**0.040**	25±16	18±15	0.062	**0.031**
MELD*	14±3	11±5	0.214	14±4	12±4	0.956	0.127
Peritoneal effusion	44 (98)	43 (96)	1.000	23 (96)	25 (100)	0.489	0.718
Pleural effusion	8 (18)	5 (11)	0.550	5 (21)	0 (-)	**0.023**	0.350
Mean spleen size ± SD mm	154±36	123±24	**<0.001**	144±43	134±31	0.897	**<0.001**
HBP acquisition time-point (mean ± SD) minutes	100±21	125±18	**<0.001**	18±5	20±2	1.000	**<0.001**

Bold entries correspond to statistically significant results

*Only for patients with chronic liver disease

HBP hepatobiliary phase, *MELD* Model for End-Stage Liver Disease

Values are expresses as mean and standard deviation, or numbers with percentages in parentheses

Global *p*-value refers to the comparison of the four categories (i.e. Gd-BOTA 1.5T and 3.0T, and Gd-EOB-DTPA at 1.5T and 3.0T) all together

Qualitative image analysis

The details of qualitative image analysis are summarized in Table 2.

Fluid signal intensity

Peritoneal and pleural effusions were hypointense on pre-contrast images in most patients (138/139); peritoneal fluid was isointense in one patient in the Gd-BOPTA 3T group. All fluid effusions remained hypointense for up to 3 min (i.e. arterial phase, portal phase and 3-min phase).

In the 1.5T group, the peritoneal fluid was hyper- or isointense following Gd-BOPTA administration in 88 % of cases (Fig. 2) and pleural effusions were hyper- or isointense in 100 % of cases on the HBP images. In the Gd-BOPTA 3T group, the peritoneal fluid was hyper- or isointense during the HBP in 100 % of patients, and pleural effusions were hyperintense in all patients on HBP images.

Peritoneal fluid was hypointense in five patients in the Gd-BOPTA group. These five patients had cirrhosis and severe portal hypertension with voluminous ascites.

The signal intensity was significantly higher on HBP when compared to precontrast images for both peritoneal and pleural effusions and both field strengths in all cases ($p<0.001$).

The peritoneal fluid remained hypointense following Gd-EOB-DTPA administration in all patients (Fig. 3). The pleural fluid was hyperintense in two patients: a patient with cirrhosis and a mild pleural effusion and a patient with a gastric neuroendocrine tumour with a moderate pleural effusion. Both of these patients also had voluminous peritoneal fluid.

Factors associated with fluid hyperintensity on hepatobiliary phase images

A comparison of patients with and without hyperintense fluid on HBP images (i.e. hypo- and iso-intensity) are provided in Table 3.

On univariate analysis, patients with hyperintense peritoneal fluid on HBP images were more frequently female (39 % vs. 24 %, $p=0.037$), with significantly smaller fluid volumes ($p=0.011$). There was a significant association between the type of contrast agent (all patients with hyperintense peritoneal fluid had received Gd-BOPTA injection, $p<0.001$). There was also a significant association between HBP acquisition time-point (mean 116±24 min in patients with hyperintense peritoneal fluid vs. mean 43±39 min in others, $p<0.001$). The type of contrast agent was the only feature associated with fluid hyperintensity on multivariate analysis ($p<0.001$).

Table 2 Qualitative imaging analysis

	Gd-BOPTA						Gd-EOB				*p*-values		
	A Peritoneal	B	*p*-value	C Pleural	D	*p*-value	E Peritoneal	F	*p*-value	G Pleural	*A vs. E*	C vs. G	B vs. F
	1.5T	3.0T		1.5T	3.0T		1.5T	3.0T		1.5T			
N	44	43		8	5		23	25		5			
Location													
Perihepatic	30 (68)	19 (44)					16 (70)	18 (72)					
Perisplenic	32 (73)	32 (73)					16 (70)	14 (56)					
Right gutter	6 (14)	1 (2)	0.090				5 (22)	2 (8)	0.308		0.560		0.063
Left gutter	4 (9)	0 (-)					0 (-)	0 (-)					
Diffuse	7 (16)	9 (-)					5 (22)	1 (4)					
Quantity													
Mild	28 (64)	34 (79)	0.155	5 (63)	4 (80)	1.000	14 (61)	22 (88)	0.050	0 (-)	1.000	0.222	0.137
Abundant	16 (36)	9 (21)		3 (37)	1 (20)		9 (39)	3 (12)		5 (100)			
Signal intensity													
Hypointensity	44 (100)	42 (98)		8 (100)	5 (100)		23 (100)	25 (100)		5 (100)			
Isointensity	0 (-)	1 (2)	0.494	0 (-)	0 (-)	1.000	0 (-)	0 (-)	1.000	0 (-)	1.000	1.000	1.000
Hyperintensity	0 (-)	0		0 (-)	0 (-)		0 (-)	0 (-)		0 (-)			
3-min phase													
Hypointensity	44 (100)	43 (100)		8 (100)	5 (100)		23 (100)	25 (100)		5 (100)			
Isointensity	0 (-)	0 (-)	1.000	0 (-)	0 (-)	1.000	0 (-)	0 (-)	1.000	0 (-)	1.000	1.000	1.000
Hyperintensity	0 (-)	0 (-)		0 (-)	0 (-)		0 (-)	0 (-)		0 (-)			
HBP													
Hypointensity	5 (12)	0 (-)		0 (-)	0 (-)		23 (100)	25 (100)		3 (60)			
Isointensity	8 (18)	5 (12)	0.060	2 (25)	0 (-)	0.487	0 (-)	0 (-)	1.000	0 (-)	**<0.001**	0.036	**<0.001**
Hyperintensity	31 (70)	38 (88)		6 (75)	5 (100)		0 (-)	0 (-)		2 (40)			
p-values													
Pre- vs. 3 min	1.000	1.000		1.000	1.000		1.000	1.000		1.000			
Pre-contrast vs. HBP	**<0.001**	**<0.001**		**<0.001**	**<0.001**		1.000	1.000		0.222			
3 min vs. HBP	**<0.001**	**<0.001**		**<0.001**	**<0.001**		1.000	1.000		0.222			

Bold entries correspond to statistically significant results

HBP hepatobiliary phase, *NC p*-value not calculated for lack of value

No patient had pleural effusion with Gd-EOB-DTPA at 3.0 T

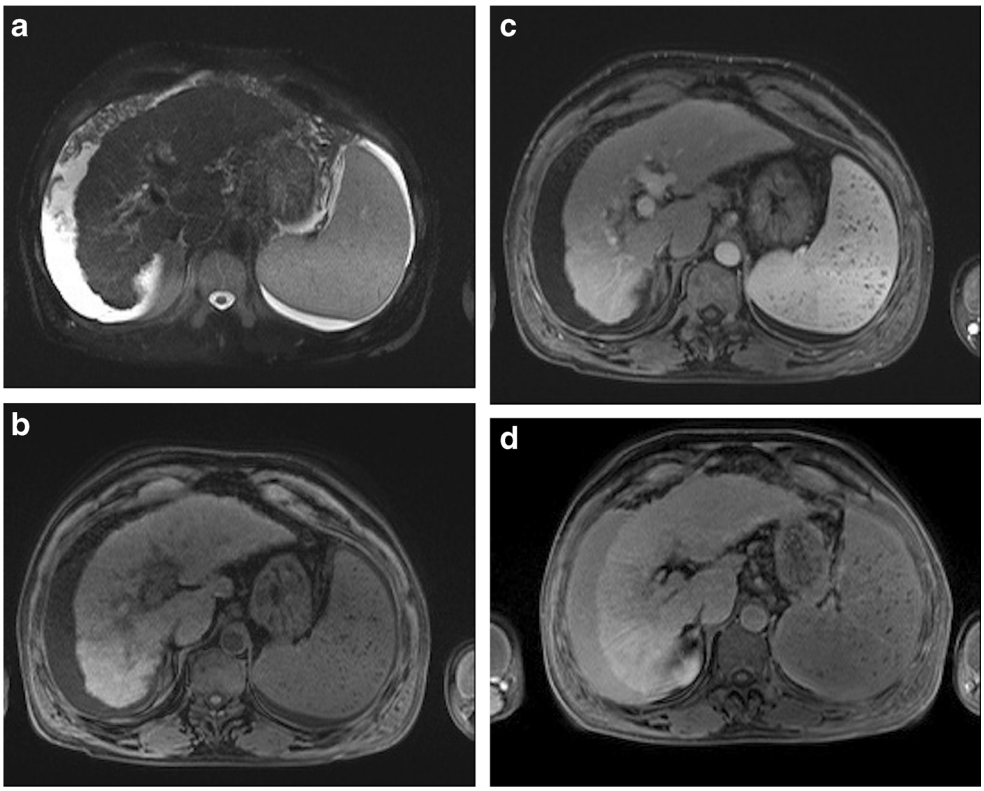

Fig. 2 MR imaging (1.5T) in a 55-year-old male with alcoholic-related cirrhosis. Peritoneal fluid (arrow) was depicted and showed signal hyperintensity on T2-weighted images (**a**), and hypointensity on pre-contrast T1-weighted fat saturated images (**b**). After Gd-BOPTA injection, peritoneal fluid signal remained hypointense on portal venous phase images (**c**), but appeared hyperintense on hepatobiliary phase images when compared to the muscle (**d**)

For pleural fluid, the acquisition time-point of HBP images was the only feature associated with fluid hyperintensity on univariate analysis (mean 102±39 min in patients with hyperintense fluid vs. mean 46±38 min in others, $p<0.001$).

Quantitative image analysis

Details of quantitative image analysis are provided in Table 4.

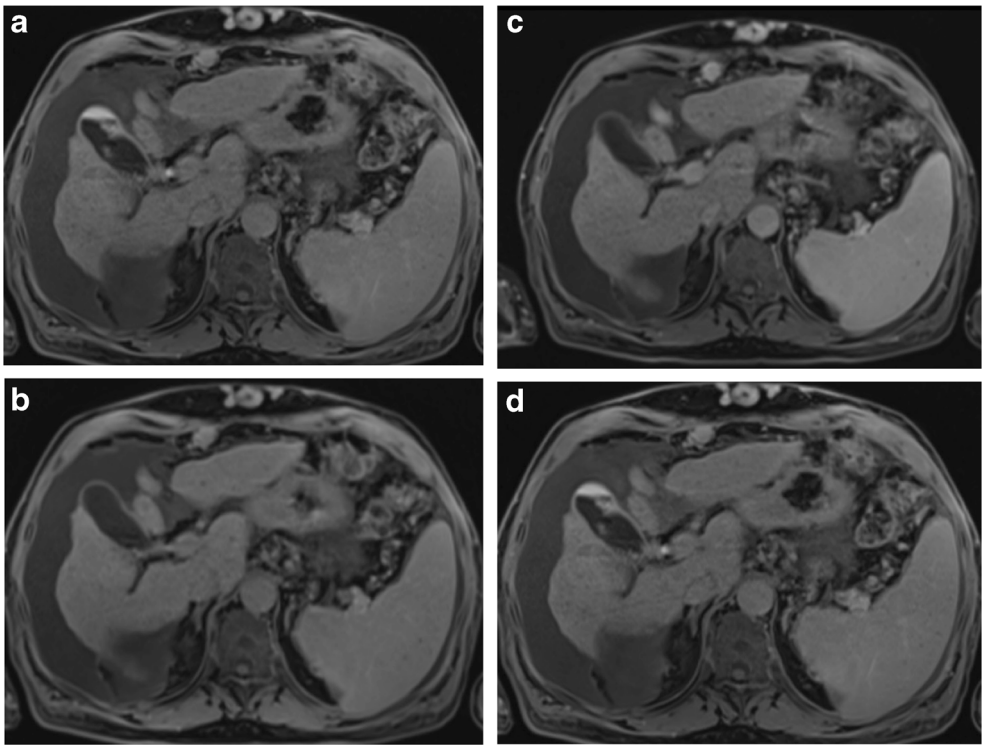

Fig. 3 MR imaging (1.5T) in a 65-year-old male with HBV-related cirrhosis. Peritoneal fluid (arrow) was depicted and showed signal hyperintensity on T2-weighted images (**a**), and hypointensity on pre-contrast T1-weighted fat saturated images (**b**). After Gd-EOB-DTPA injection, peritoneal fluid signal remained hypointense on portal venous phase images (**c**), and on hepatobiliary phase images when compared to muscles (**d**)

Table 3 Factors associated with fluid signal intensity on HBP images

	Peritoneal				Pleural		
	Hyper	Hypo- Iso	Univariate *p*-value	Multivariate *p*-value	Hyper	Hypo Iso	Univariate *p*-value
No. of patients	69	68			13	5	
M (%)	42 (61)	52 (76)	**0.037**		10 (77)	3 (60)	0.433
Mean age ± SD years	60±10	60±10	0.999		60±10	55±11	0.443
Indication of MR imaging							
Chronic liver disease	47 (68)	57 (84)			8 (62)	2 (40)	
Cancer staging	13 (19)	7 (10)	0.096		4 (31)	3 (60)	0.477
Other	9 (13)	4 (6)			1 (8)	0 (-)	
Location							
Perihepatic	25 (36)	27 (40)					
Perisplenic	12 (17)	29 (42)					
Right gutter	63 (91)	58 (85)	0.070				
Left gutter	66 (96)	62 (91)					
Diffuse	62 (90)	51 75)					
Quantity							
Mild	55 (78)	43 (63)	**0.011**		9 (69)	3 (60)	0.561
Abundant	12 (22)	25 (37)			4 (31)	2 (40)	
MR field strength							
1.5T	31 (45)	36 (53)	0.222		8 (62	0 (-)	0.150
3.0 T	38 (55)	32 (47)			5 (38)	5 (100)	
Contrast agent							
Gd-BOPTA	69 (100)	20 (29)	**<0.001**	**<0.001**	11 (85)	2 (40)	0.099
Gd-EOB	0 (-)	48 (71)			2 (15)	3 (60)	
Lab test (mean±SD)							
INR	1.4±0.5	1.3±0.2	0.539		1.3±0.3	1.0±0.6	0.265
Creatinine umol/L	76±21	87±38	0.082		76±15	92±42	0.165
MELD*	12±4	13±4	0.323		15±2	15±11	0.963
Bilirubin mmol/L	22±15	27±12	0.336				
HBP acquisition time-point (mean ± SD)							
min	116±24	43±39	**<0.001**		102±39	46±38	**0.014**

Bold entries correspond to statistically significant results

HBP hepatobiliary phase

*Only for patients with chronic liver disease

Relative enhancement

The mean RE of peritoneal and pleural fluids for both field strengths and contrast agents increased from the arterial phase to the HBP (Fig. 4). RE was not significantly different for the arterial, portal venous or 3-min phases, while RE was significantly higher for the HBP than the arterial, portal venous and 3-min phases (*p*-values from 0.011 to <0.001), except for the 3-min and HBP in the 3T group with Gd-EOB-DTPA and for pleural fluid in the 1.5T group with Gd-EOB.

Additional HBP phase images were obtained in three patients in the Gd-EOB-DTPA 1.5T group at 35, 40 and 45 min because the biliary ducts were not visible at 20 min. RE of the peritoneal fluid ranged from 0.94 to 1.78 and was greater than at 20 min (no *p*-value provided due to the small sample size). These three patients had chronic liver disease, with impaired liver function

Overall, RE during the HBP was significantly greater in the Gd-BOPTA than in the Gd-EOB-DTPA groups (p=0.002 and <0.001). There was a significant correlation between HBP RE and the acquisition time-point of these images (r=0.42, p<0.001 and r=0.50, p=0.033 for peritoneal and pleural fluids, respectively).

The RE of peritoneal and pleural fluids following Gd-BOPTA was significantly higher in patients with chronic liver

Table 4 Quantitative imaging analysis

	Gd-BOPTA						Gd-EOB				*p*-values		
	A Peritoneal	B	*p*	C Pleural	D	p	E Peritoneal	F	*p*	G Pleural	*A vs. E*	C vs. G	B vs. F
N	1.5T 44	3.0T 43		1.5T 8	3.0T **5**		1.5T 23	3.0T 25		1.5T 5			
Relative enhancement													
Arterial phase	-0.03±0.18	-0.41±0.29	**<0.001**	0.00±0.30	-0.64±0.10	**<0.001**	0.04±0.24	-0.30±0.25	**<0.001**	-0.09±0.16	1.000	**0.005**	0.447
Portal phase	0.07±0.23	-0.23±0.42	**<0.001**	0.07±0.32	-0.52±0.09	**<0.001**	0.07±0.15	-0.20±0.19	**0.009**	-0.10±0.08	1.000	**0.027**	1.000
3-min phase	0.17±0.39	-0.07±0.53	**0.032**	0.31±0.36	-0.43±0.14	**0.007**	0.12±0.25	-0.06±0.20	0.646	0.26±0.44	1.000	**0.019**	1.000
HBP	2.56±2.39	1.45±1.13	**0.006**	1.42±0.76	0.84±0.65	0.392	0.43±0.38	0.04±0.41	1.000	0.32±0.27	**<0.001**	0.619	**0.002**
p-value*													
Arterial vs. portal	1.000	1.000		1.000	1.000		1.000	1.000		1.000			
Arterial vs.3 minutes	1.000	0.125		1.000	1.000		1.000	**0.013**		0.353			
Arterial vs. HBP	**<0.001**	**<0.001**		**<0.001**	**<0.001**		**<0.001**	**<0.001**		0.188			
Portal vs. 3 minutes	1.000	1.000		1.000	1.000		1.000	0.452		0.323			
Portal vs. HBP	**<0.001**	**<0.001**		**<0.001**	**<0.001**		**0.001**	**0.011**		0.171			
3 minutes vs. HBP	**<0.001**	**<0.001**		**0.001**	**<0.001**		**0.001**	0.976		1.000			

Bold entries correspond to statistically significant results

HBP hepatobiliary phase

**p*-values corresponding to post hoc test of the matched ANOVA comparing the different phases

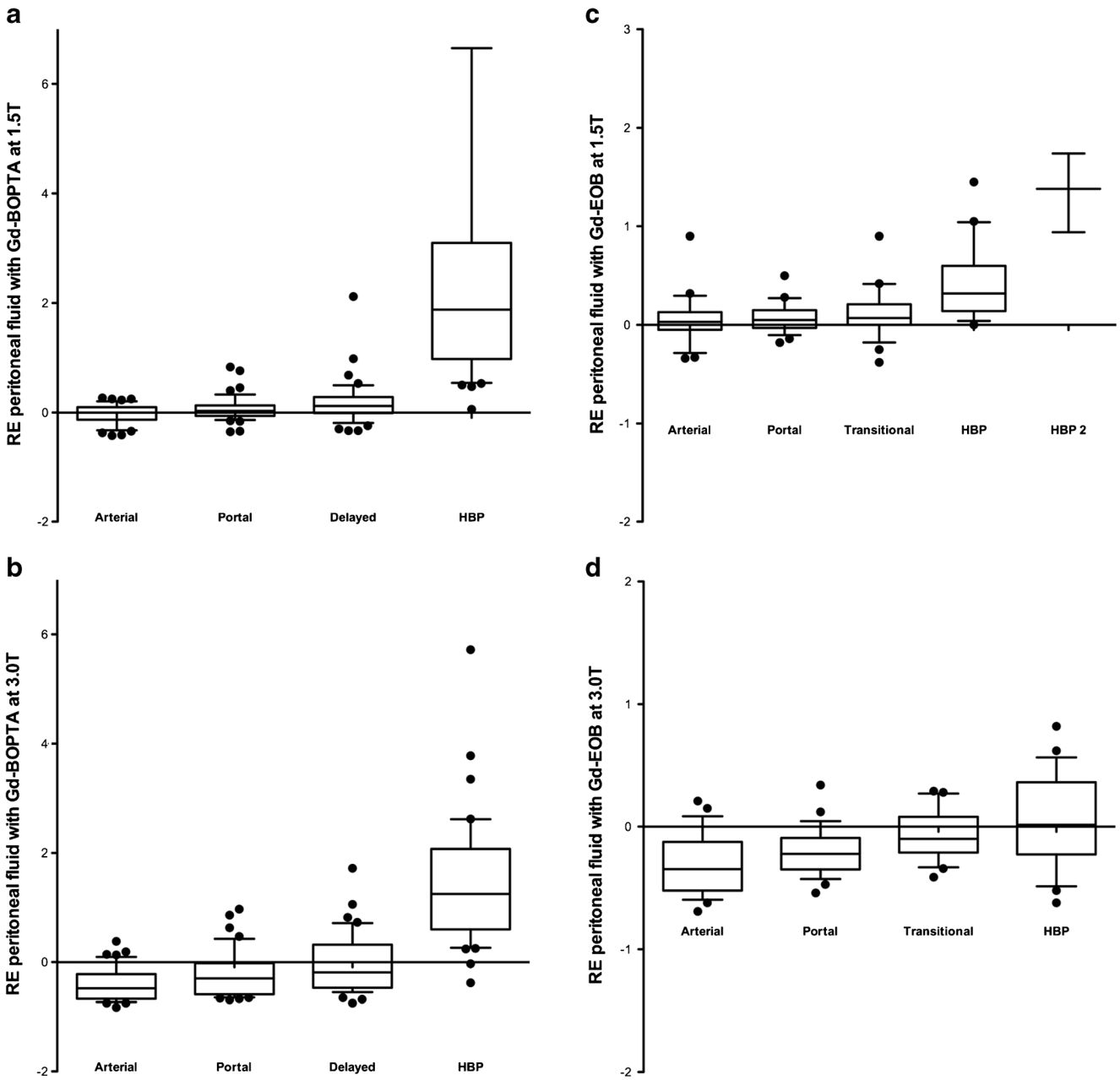

Fig. 4 Relative enhancement (RE) of peritoneal fluids after injection of Gd-BOPTA (**a, b**), and Gd-EOB-DTPA (**c, d**), at 1.5T (**a, c**), and 3T (**b, d**). Signal intensity progressively increased over time from pre-contrast to hepatobiliary phase images for both contrast agents, but it was significantly more marked after Gd-BOPTA injection

disease than in the others (p=0.009). No significant difference was found in the RE of peritoneal and pleural fluids following Gd-EOB-DTPA administration depending on the patient population (Table 5).

Table 5 Comparison of RE and SNR on the HBP images according to the indication of the MR examination

HBP	Chronic liver disease	Gd-BOPTA				Gd-EOB		
		Cancer staging	Other	p global	Chronic liver disease	Cancer staging	Other	*p*-value
Relative enhancement	2.4±2.1	0.9±0.6	0.9±0.4	0.009	0.2±0.4	0.5±0.4	0.2±0.4	0.350

RE relative enhancement, *HBP* hepatobiliary phase

Discussion

The present study showed that the signal intensity of pleural and peritoneal fluids on T1-weighted GE sequences increased progressively over time following HBCA administration, in the absence of any biliary or vascular leakage. The percentage of increase was dependent upon the type of contrast agent, and was significantly higher with Gd-BOPTA. Thus, pleural and peritoneal fluids were hyperintense on HBP images in most patients who received Gd-BOPTA, and remained hypointense in patients following Gd-EOB-DTPA administration. These results were independent of the MR field strength (i.e. 1.5T or 3T).

Progressive and delayed enhancement of peritoneal fluid has already been described in the literature following administration of iodinated contrast agents [9–14] in the absence of intra-abdominal vascular injuries or hemoperitoneum. In a recent study, Akari et al. showed that ascites attenuation increased on CT (>10 HU) in most patients (92 %) who underwent abdominal oncological endovascular interventions, in the absence of blood extravasation [14]. In another study, Benedetti et al. reported that 63 % of patients who underwent CT less than 1 day after receiving a contrast-enhanced CT scan showed delayed enhancement of ascites [12]. These observations suggest that some contrast medium diffuses into biological fluids. The present study shows that a similar phenomenon occurs with HBCA. It is interesting to note that this has never been reported with extracellular MR contrast agents.

Peritoneal and pleural membrane dynamics allow contrast agents to pass because most of them are composed of mid-sized molecules [15, 16]. Contrast agents pass into the peritoneal or pleural cavities and are reabsorbed via pores and lymphatics [18, 19] by a mechanism that is similar to peritoneal dialysis [20]. The degree of peritoneal or pleural permeability to contrast agents and thus the degree of fluid enhancement can be influenced by several factors including biokinetics, the delay after administration, the amount of fluid, the presence of abnormal conditions affecting the peritoneum or the pleura, and renal function [9–14].

In this study, the delay of the HBP was probably an important cause, as fluid enhancement was strongly dependent upon time after contrast medium injection. This is supported by the fact that the signal intensity of fluids was significantly increased in the small subgroup of patients who received Gd-EOB-DTPA and underwent more delayed HBP acquisition. A 20-min delay might not be enough to observe enhancement, which would have been observed if HBP images were obtained later. Indeed, HBP were acquired at the minimum and maximum recommended acquisition time-points after Gd-EOB-DTAP and Gd-BOPTA, respectively. As a consequence, the possible differences between contrast agents were maximized, and might be different in other centres. This is also supported by reports in contrast-enhanced CT [9–13], and suggests that the hepatospecificity of contrast agents does not play a role. Thus, it may also be observed with extracellular contrast agents.

Our results showed that fluid signal hyperintensity was inversely correlated to the amount of fluid, which has also been reported in CT [9, 12, 14]. This may be due to dilution, with lower concentrations of contrast medium in large amounts of fluids.

Certain authors have suggested that peritoneal malignancies could favour peritoneal fluid enhancement due to increased vascular permeability of neo-vessels in peritoneal metastases, or the production of tumour-factors [9, 13, 17, 18]. Although MR imaging was performed in some patients in this study for cancer staging, fluid enhancement also occurred in patients with no malignancies or chronic liver diseases, and enhancement was greater in the latter. This could be due to increased vascular dilatation from portal congestion in patients with portal hypertension.

The correlation between the delayed enhancement of effusions in serosal cavities and renal function is controversial. Benedetti et al. found that delayed enhancement increased for each mg/dl increase in serum creatinine level [12]. However, Akari et al. showed that neither the creatinine level nor the eGFR was correlated with increased CT attenuation of peritoneal fluid on multivariate analysis [14]. In our study, no patient had severe renal impairment and serum creatinine levels remained in the normal or close to normal range. Therefore, no conclusion can be drawn regarding the influence of renal elimination of contrast agents on fluid signal intensity on HBP images.

These findings may be of importance for clinical practice. The hyperintense signals of peritoneal (and to a lesser extent pleural) fluids on HBP T1-weighted MR images could be misinterpreted as biliary leakage, especially in patients with a recent history of surgery or interventional procedures. Indeed, authors have shown that HBCAs are most useful for the detection of bile leakage [8, 21, 22], because contrast agents taken up by hepatocytes are excreted into the biliary system. Thus, the site of bile leakage and extravasation of bile into the peritoneum can be identified by T1-weighted MR cholangiography [5–7, 15, 23–27]. The present results suggest that the risk of misinterpretation is probably higher with Gd-BOPTA because 79 % and 17 % of patients with no bile leakage had hyperintense or isointense peritoneal fluid during the HBP, respectively [8]. Yet, since we did not specifically study patients with bile leak, our results need further validation before recommending not to use Gd-BOPTA for the diagnosis of bile leakage on MR imaging.

Besides the retrospective design, this study has several limitations. First, several parameters, such as the acquisition time-point of the HBP (especially between the Gd-BOPTA 1.5T and 3T groups) and the volume of contrast varied in the two centres. Second, when performing a HBP after 120 min the patient needs repositioning. The distance to the coil and to the

transmitter/receiver settings is therefore changed. This may affect the obtained signal. Therefore, the relative signal enhancement of effusions compared to baseline can only be considered as an estimate. Third, serum albumin was not evaluated in all patients and was not included in the present analysis. Finally, objective measurement of pleural and peritoneal fluid signal intensity may be biased, especially in patients with small fluid volumes.

In conclusion, the signal intensity of pleural and peritoneal fluids progressively increased in all patients following HBCA administration independent from the MR field. However, variations in signal intensity were more marked with Gd-BOPTA and were higher in patients with chronic liver disease. The resulting hyperintense images of peritoneal fluid on T1-weighted MR images during the HBP following Gd-BOPTA should be interpreted with caution to prevent misdiagnoses in clinical practice.

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Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- multicentre study

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