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FULL PAPER

Diagnostic value of Gd-EOB-DTPA-enhanced MR cholangiography in non-invasive detection of postoperative bile leakage

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Objective: To assess the diagnostic value of dynamic T₁ weighted (T1w) gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA)-enhanced MR cholangiography (MRC) for the detection of active bile leaks.

Methods: A total of 28 patients with suspected biliary leakage who underwent routine T₂ weighted (T2w) MRC and T1w Gd-EOB-DTPA-enhanced MRC at our institution from February 2013 to June 2016 were included in this study. The image sets were retrospectively analyzed in consensus by three radiologists. T1w Gd-EOB-DTPA-enhanced MRC findings were correlated with clinical data, follow-up examinations and findings of invasive/surgical procedures. Patients with positive bile leak findings in Gd-EOB-DTPA-enhanced MRC were divided into hepatobiliary phase (HBP) (20–30 min) and delayed phase (DP) (60–390 min) group according to elapsed time between Gd-EOB-DTPA injection and initial bile leak findings in MRC images. These groups were compared in terms of laboratory test results (total bilirubin, liver

enzymes) and the presence of bile duct dilatation in T2w MRC images.

Results: In each patient, visualization of bile ducts was sufficient in the HBP. The accuracy, sensitivity and specificity of dynamic Gd-EOB-DTPA-enhanced T1w MRC in the detection of biliary leaks were 92.9%, 90.5% and 100%, respectively ($p < 0.001$). 19 of 28 patients had bile leak findings in T1w Gd-EOB-DTPA-enhanced MRC [HBP group: $N = 7$ (36.8%), DP group: $N = 12$ (63.2%)]. There was no statistically significant difference in terms of laboratory test results and the presence of bile duct dilatation between HBP and DP group ($p > 0.05$). Three patients, each of them in DP group, showed normal laboratory test results and bile duct diameters.

Conclusion: Dynamic T1w Gd-EOB-DTPA-enhanced MRC is a useful non-invasive diagnostic tool to detect bile leak.

Advances in knowledge: Prolonged DP imaging may be required for bile leak detection even if visualization of biliary tree is sufficient in HBP and liver function tests, total bilirubin levels and bile duct diameters are normal.

INTRODUCTION

Bile leaks may be of both iatrogenic and traumatic origin. Iatrogenic injuries often result from cholecystectomy or hepatic surgery. The most commonly observed causative surgical procedures are open or laparoscopic cholecystectomy, hepatic transplantation, hepatic resection and liver biopsy.^{1–4} It is well known that, particularly owing to peritonitis, bile leak raises morbidity and mortality.⁵ Therefore, a prompt diagnostic and therapeutic approach is recommended in those patients. Diagnosis may be delayed because of the non-specific clinical findings. Ultrasound, CT and T₂ weighted (T2w) MR cholangiography (MRC) are diagnostic tools which may raise suspicion of biliary leakage. They are useful in detecting and localizing fluid collections and thus can lead to further investigation to ascertain the underlying cause and its adequate treatment.

However, they are insufficient to demonstrate potential communication between the biliary system and the fluid collection and generally provide non-specific findings.

To confirm that a detected fluid collection is of biliary origin, invasive methods such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous trans-hepatic cholangiography (PTC), T-tube cholangiogram, intraoperative cholangiogram or imaging-guided percutaneous drainage can be performed and may also admit a treatment of the leak.^{6,7}

However, owing to their invasive character, they carry a certain amount of risk for complications. In some patients with suspicion of bile leakage, there is eventually no need for interventional treatment. Thus, non-invasive

evaluation techniques may be preferred in first line depending on the clinical status of the patient. Non-invasive methods which can demonstrate an active leak from the biliary system are hepatobiliary scintigraphy and T_1 weighted (T1w) contrast-enhanced MRC. Hepatobiliary scintigraphy is a nuclear imaging method which shows the course of biliary excretion and a potential actual leakage. Its limitation is a poor spatial resolution, which impedes the detection of the leakage site. However, MRC with the use of hepatocyte-specific contrast agents is a recently emerged non-invasive diagnostic technique, which is an appropriate way to detect an active bile leakage, the underlying bile duct injury and anatomy.^{8,9} In addition, it facilitates the detection and characterization of liver lesions by acquisition of dynamic contrast images, which is also a major advantage in comparison with invasive techniques such as ERCP or PTC.^{10,11} Hepatocyte-specific contrast agents include mangafodipir trisodium (Teslascan™; GE Healthcare, Oslo, Norway), gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA) (Primovist™; Bayer-Schering Pharma, Berlin, Germany) and gadobenate dimeglumine (Gd-BOPTA) (MultiHance®; Bracco Imaging, Milan, Italy). Several studies assessed the benefit of these agents in terms of evaluation of the biliary system and approved them as valuable to detect iatrogenic or traumatic biliary leakage, to present cystobiliary communication in hydatid cysts, to differentiate biliary from extra-biliary lesions and to diagnose acute cholecystitis and biliary obstruction.^{12–25}

However, most of the studies used mangafodipir trisodium, a hepatocyte-specific agent which has been removed from the market both in the USA and Europe in 2003 and 2012, respectively.^{12–19}

Only a limited number of studies exist which use Gd-EOB-DTPA (gadoteric acid disodium) and Gd-BOPTA (gadobenetic acid) as contrast agents in combination with MRC.^{20–25} Gd-EOB-DTPA and Gd-BOPTA are paramagnetic contrast agents which are both extracellular and hepatocyte-specific agents. Initially, they are distributed extracellularly in the body. Subsequently, approximately 50% of the injected dose of Gd-EOB-DTPA and 3–5% of Gd-BOPTA are taken up by the hepatocyte *via* an organic anion transport system and are excreted into the biliary system. They shorten the longitudinal relaxation time (T_1) of the bile and thereby admit a morphologic and functional assessment of the biliary tree.^{20,21} Thus, in case of bile leakage, enhanced bile which escaped out of the ductal system is seen as hyperintense collection on T1w images. Owing to its higher biliary excretion rate, Gd-EOB-DTPA provides adequate biliary imaging within a shorter period than Gd-BOPTA. Whereas intense enhancement of the biliary tree occurs as soon as 10 min after i.v. application of Gd-EOB-DTPA, there is a 60-min delay with Gd-BOPTA, which can be a practical reason in favour of using Gd-EOB-DTPA for functional assessment of biliary system. It has been reported that a 20-min delay after Gd-EOB-DTPA injection is sufficient for evaluation of the biliary tree in patients with normal liver function.²⁶ In patients with a dilated biliary system or impaired liver function, a 60–180-min delay was observed.²²

The purpose of this study was to assess the value of Gd-EOB-DTPA-enhanced MRC using additional delayed phase (DP) images for the diagnosis of active bile leaks.

METHODS AND MATERIALS

Ethical considerations

This retrospective observational study was approved by our institutional ethics committee, and informed consent was obtained from all patients.

Study group

From February 2013 to June 2016, 35 patients with high clinical suspicion of active biliary leakage underwent MRI at our institution. Out of these individuals, the patients in whom hepatobiliary contrast agents have been used were identified by radiology reports found in our institution (radiology information system/picture archiving and communication system) (Centricity 5.0 RIS-i, Barrington, IL 60010 USA, GE Healthcare). Institutional medical records of these patients were screened to obtain information about prior surgeries and to find clinical data, laboratory test (liver enzymes, total bilirubin) and interventional procedure results to correlate the MRC findings.

2 of 35 patients were excluded from this retrospective study owing to the fact that MRI was performed with a hepatobiliary agent other than Gd-EOB-DTPA. Two patients were excluded owing to low image quality caused by artefacts. Three patients were excluded because enough clinical information could not be obtained. In addition, two of these three patients showed no biliary excretion until 120–150 min without further DP images owing to their poor clinical condition. Both patients had elevated bilirubin and/or liver enzyme levels. One was diagnosed with transplanted liver failure and one had a complete biliary obstruction with dilated bile ducts caused by pancreatic cancer. Thus, a total of 28 patients with suspected biliary leakage who underwent routine T2w MRC and T1w Gd-EOB-DTPA-enhanced MRC were included in this study.

MR cholangiography protocol

MRI was performed by using a 1.5-T system (Optima 450w; GE Healthcare, Milwaukee, WI) in 13 patients, a 3.0-T system (MAGNETOM® Verio; Siemens, Erlangen, Germany) in 9 patients and a 1.0-T system (Signa™; GE Healthcare, Milwaukee, WI) in 6 patients with standard body or Torso coils. The sequences for the three MRI units consisted of standard MRC (heavily T2w Single-shot Fast Spin Echo (SSPE)/Half-Fourier Acquisition Single-shot Turbo Spin Echo (HASTE) images), respiratory-triggered axial T2w (FSE)/TSE images (additional fat-suppressed T2w Turbo spin echo (TSE) images in 3.0-T system) and dynamic contrast-enhanced T1w fat-suppressed three-dimensional (3D) gradient-echo sequence. Initially, T2w MRC images with respiratory-triggered 3D heavy T2w data were obtained to evaluate the existence of biliary duct dilatation or obstruction. Subsequently, i.v. administration of 0.1–0.2 mmol kg⁻¹ dose of gadoteric acid disodium (Gd-EOB-DTPA) (Primovist) using an automatic injector was performed. The injection rate was 2–3 ml s⁻¹. Dynamic images including pre-contrast, arterial, portal venous and equilibrium phase were acquired in the axial plane, followed by a 20–30-min hepatobiliary phase (HBP) image

acquired in axial and coronal planes by using VIBE (3.0 T), liver acquisition with volume acceleration-flex (1.5 T) and fast acquisition with multiphase elliptical fast gradient echo (1.0 T) sequences. Pulse sequence parameters at three different scanners used for contrast-enhanced dynamic imaging in this study are listed in detail in Table 1.

If the biliary tree was not visualized in HBP images, additional 120–150-min delayed Gd-EOB-DTPA enhanced images were acquired with the same pulse sequence, and the examination was ended if there was still no obvious enhancement of bile ducts. If biliary excretion of contrast medium was present and no biliary leak was detected in HBP images but elevated bilirubin or liver enzyme levels or very high clinical suspicion of bile leak exist, further images were acquired with additional 60–90-min delay. If bile leak was obvious, the examination was terminated. However, if bile leak was not evident, then further delayed (120–150 min, 210–240 min, 360–420 min, 18 h, 20 h and 24 h) images were obtained until bile leak was detected. In cases where liver enzyme and total bilirubin levels were normal and clinical suspicion was not high, the examination could be ended after HBP imaging or be prolonged up to 24 h depending on the radiologist choice.

MR images retrieved from a picture archiving and communication system (Centricity, v. 5.0 RIS-i) were retrospectively analyzed in consensus by an abdominal radiologist with a special focus on abdominal radiology for 28 years and two radiology specialists with 5 and 15 years' experience in general radiology including abdominal radiology. Only dynamic contrast-enhanced T1w fat-suppressed 3D gradient echo sequence images which were obtained multiphasically have been used to detect bile leakage. The following parameters were evaluated in the patients: (1) the presence of bile leak, (2) possible origin of

leakage in liver-transplanted group and (3) time interval between injection of Gd-EOB-DTPA and appearance of enhancing bile leakage.

Images were evaluated separately in a retrospective fashion and reviewed by consensus so that systematic assessment of the findings which might have not been detailed in each original report can be made. During the evaluation, the observers were blinded to clinical outcome of the patients. In none of the cases, consensus reading regarding the presence of bile leakage was different from the initial report.

Statistics

The statistical analysis was performed using SPSS® (Statistical Package For Social Sciences for Windows v. 11.5; IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). We used the Fisher's exact test to analyze the presence or absence of bile leak with the use of Gd-EOB-DTPA-enhanced MRC. A *p*-value of <0.05 was considered significant.

RESULTS

The study population consisted of 17 males and 11 females (age range, 27–77 years; mean age $\pm$ standard deviation, 52.50 years $\pm$ 15.25). The time interval between the surgeries and MRI examinations ranged between 2 days and 3 years (median, 23.5 days). The following surgical/interventional procedures were performed prior to MRC: metastatectomy (*n* = 2, 7.1%), partial hepatectomy for haemangioma (*n* = 1; 3.6%) and for cholangiocellular carcinoma (*n* = 2; 7.1%), cholecystectomy (*n* = 10; 35.7%), cystectomy (hydatid cyst) (*n* = 3; 10.7%), orthotopic liver transplantation (*n* = 7; 25%), nephrectomy for renal cell carcinoma (*n* = 1; 3.6%) and liver donation (*n* = 2; 7.1%).

Table 1. Imaging parameters used for dynamic contrast-enhanced T₁ weighted fat-suppressed three-dimensional gradient-echo sequence

Imager	3.0 T (Siemens)	5.5 T (GE)	1.0 T (GE)
Vendor-specific acronyms	VIBE	LAVA-flex ^a	FAME
Matrix size	320 × 260	320 × 224	256 × 256
Slice thickness (mm)	3.0	6.0	7.0
Slice spacing	20% (distance factor)	50% overlap	0.0
Repetition time (ms)	3.92	4.3	Minimum
Echo time (ms)	1.39	2.1	^b
Flip angle (°)	9	12	12
Reduction factor	2	2	–
Averages	1	1	1
FOV (mm)	380 × 308	360 × 288	480 (phase FOV: 0.55)
Bandwidth	400 Hz/Px	83.33 kHz	62.50 kHz
Acquisition time (min : s)	1 : 08	3 : 18	3 : 20

FAME, fast acquisition with multiphase elliptical fast gradient echo; FOV, field of view; LAVA, liver acquisition with volume acceleration; VIBE, volume interpolated breath-hold examination.

^aFlex is appended to LAVA sequence to indicate a faster 2-point Dixon method.

^bThis value is not seen on the system.

Table 2. Patients with confirmed bile leak—reference standard and corresponding MR cholangiography (MRC) findings

Patient No.	Age	Sex	Prior surgery	Time interval (from surgery to MRC) (days)	MRI field strength (T)	Performed delayed images (min)	Bile leak in MRC (yes/no)	Time point of detection (min)	Reference standard confirming bile leak
1	41	F	Metastectomy	7	1	20	Yes	20	Percutaneous drainage
2	54	F	Cholecystectomy	90	1	20, 60, 140, 250, 390	Yes	390	Percutaneous drainage
3	36	F	Cholecystectomy	13	1	20, 60	Yes	60	Percutaneous drainage
4	54	F	Metastectomy	32	1	20, 60, 120	Yes	120	Percutaneous drainage
5	28	M	Liver transplantation	8	1,5	20, 60, 120	Yes	120	T-tube Cholangiogram, Intraoperative Cholangiogram
6	61	M	Cholecystectomy	2	1,5	20, 60, 120	Yes	120	Percutaneous drainage
7	57	M	Partial hepatectomy	107	1,5	20, 60, 120	Yes	120	PTC
8	31	F	Liver transplantation	25	3	20	Yes	20	Percutaneous drainage
9	53	M	Cholecystectomy	5	1	20	Yes	20	ERCP
10	74	M	Partial hepatectomy	90	1,5	20, 60, 150	No	—	PTC, T-Tube cholangiogram
11	72	M	Partial hepatectomy	92	3	20	Yes	20	Percutaneous drainage
12	56	F	Cholecystectomy	11	1	20, 60, 120, 240	Yes	240	PTC
13	77	M	Cholecystectomy	3	3	20, 60	Yes	60	T-tube Cholangiogram
14	60	M	Cystectomy	54	1	20, 60	Yes	60	Percutaneous drainage
15	42	M	Liver donation	2	1	20, 90	Yes	90	Percutaneous drainage
16	55	M	Nephrectomy	120	3	20, 60, 120, 210	Yes	210	ERCP percutaneous drainage
17	32	F	Liver transplantation	22	3	20, 90, 150, 210, 360, 1200	No	—	PTC
18	54	M	Liver transplantation	14	3	20, 60	Yes	60	Intraoperative Cholangiogram
19	45	M	Liver transplantation	10	3	30	Yes	30	Percutaneous drainage
20	27	F	Cholecystectomy	8	1	20	Yes	20	PTC
21	51	M	Liver transplantation	52	1	20	Yes	20	Percutaneous drainage

ERCP, endoscopic retrograde cholangiopancreatography; F, female; M, male; PTC, percutaneous transhepatic cholangiography.

Patients with detected bile leak *via* interventional and/or surgical procedures are listed in detail in [Table 2](#).

Analysis of T1w Gd-EOB-DTPA-enhanced MRC images resulted in 19 true-positive, 7 true-negative and 2 false-negatives cases. No false-positive diagnosis was made. The accuracy, sensitivity and specificity of dynamic Gd-EOB-DTPA-enhanced T1w fat-suppressed 3D gradient-echo sequence in detection of biliary leaks were 92.9% [(19 + 7)/(19 + 0 + 2 + 7)], 90.5% [19/(19 + 2)] and 100% [7/(0 + 7)], respectively.

In 19 (67.9%) of 28 patients with bile leak findings on Gd-EOB-DTPA-enhanced MRC images, diagnosis could be confirmed with at least 1 interventional and/or surgical procedure ([Figures 1–4](#)).

In each patient, visualization of bile ducts was sufficient in the HBP. MRC findings conforming to bile leak were observed at HBP images (20–30 min) in 7 (36.8%) out of 19 patients (HP group). The other 12 (63.2%) patients had bile leak findings in additional delayed images (DP group), not in HBP images. The latest phase in which bile leak was detected was in one case after a delay of 390 min. In 11 of 12 patients, images with initial leak findings were of 60–90-min ($n = 5$), 120–150-min ($n = 4$) and 210–240-min ($n = 2$) delay. The mean level of total bilirubin was elevated in both groups, being slightly higher in patients in whom bile leak findings were detected in DP images ($1.29 \pm 0.94 \text{ mg dl}^{-1}$) than in patients with positive bile leak findings observed in HBP ($1.18 \pm 0.28 \text{ mg dl}^{-1}$). However, this difference was statistically not significant ($p = 0.33$). No statistically significant difference between both groups was detected neither

concerning liver enzyme levels ($p = 0.650$) nor the presence of duct dilatation ($p = 1$) ([Table 3](#)). In three patients of the DP group, levels of total bilirubin and liver enzymes were normal and no bile duct dilatation was observed. Whereas in HBP group at least one of these parameters was abnormal.

In both approved false-negative cases (7%), HBP imaging revealed Gd-EOB-DTPA excretion into the bile ducts. One of them had a prior hepatectomy for cholangiocellular cancer and showed no bile leak in T1w MRC images until 150 min after Gd-EOB-DTPA application. However, PTC was performed thereafter and showed biliary leakage. This patient had normal bilirubin and liver enzyme levels but showed dilated bile ducts in MRC. The other patient, a receiver of orthotopic liver transplant, had no bile leak findings in MRC, even in 20-h delayed image. However, bile leak was proved *via* PTC and T-tube cholangiogram. This patient had very high levels of bilirubin and liver enzymes.

In true-negative cases ($n = 7$; 25%), in addition to clinical findings non-invasive radiological follow-up examinations ($n = 6$) and ERCP findings ($n = 1$) were consistent.

Based on MRC findings, of the five patients liver transplanted with a bile leak, the origin of the leakage was located at the duct-to-duct anastomosis site ($n = 3$) and the cut edge of the liver ($n = 2$). Bile leak was confirmed in all of them *via* interventional and/or surgical procedures. Concerning the leak site, MRC and interventional procedure findings were compliant in two of these five patients who had liver transplantation. In both of them, MRC and T-tube cholangiogram and/or intraoperative

Figure 1. A 55-year-old male patient with a history of nephrectomy due to renal cell carcinoma: fluid collection in hepatoduodenal ligament and pre-hepatic space (white asterisks) is barely identified in pre-contrast T₁ weighted (T1w) image (a). Fat-suppressed T₂ weighted image shows perihepatic fluid collections (black asterisks) (b). A 210-min delayed gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced T1w MR cholangiography image (c) confirms the bile content of this collection (black asterisks), which is originating from the common bile duct (arrow).

Figure 2. A 60-year-old male patient with a history of surgical removal of hydatid cyst located in liver segments 6 and 7: defective tissue (arrow) is seen in the location of the excised hydatid cyst in pre-contrast T_1 weighted (T_1w) image (a hyperintense signal in abdominal aorta is artificial) (a). Dynamic contrast-enhanced T_1w fat-suppressed three-dimensional gradient-echo sequence image shows no obvious enhancement in portal venous phase (b). Bile leak into this location (arrow) extending from the right posterior bile duct is observed in 60-min delayed gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced T_1w MR image (c). Corresponding heavy T_2 weighted MR cholangiography image (d).

cholangiogram revealed duct-to-duct anastomosis site as the leak source. However, in two patients in whom MRC displayed the cut edge of the liver as the leak source, confirmation of bile leak was made *via* percutaneous drainage and thus, correlation of leak site could not be made. In one of them, ERCP was performed and revealed no positive finding. The other patient underwent a T-tube cholangiogram which also was negative. In the remaining one patient with duct-to-duct anastomosis site as suspected leak source, a correlation of the source site could not be made owing to lack of information in medical records. Bile leak was confirmed *via* percutaneous drainage.

DISCUSSION

Bile leak, most often seen after laparoscopic cholecystectomy, is associated with an increased morbidity and mortality and therefore has to be diagnosed and treated promptly. T_2w MRC is a helpful technique for diagnosing many biliary disorders, but it is insufficient for evaluating the biliary excretion. Hence, T_2w MRC is not an adequate technique concerning the detection of active biliary leakage.^{23,27–29} Although, T_1w Gd-EOB-DTPA-enhanced MRC is an imaging technique which admits functional assessment of the biliary system owing to the fact that Gd-EOB-DTPA, a hepatocyte-specific contrast agent, is excreted *via* the bile ducts.

Our results show that T_1w Gd-EOB-DTPA-enhanced MRC is a useful non-invasive diagnostic tool to detect bile leak, in particular if performed with prolonged DPs. Besides two false-negative cases, MRC findings were consistent with related clinical, interventional and/or surgical findings in each patient with observed

Gd-EOB-DTPA excretion into biliary system. Thus, our study results suggest high accuracy (92.9%) in bile leak detection by Gd-EOB-DTPA-enhanced MRC (100% specificity and 90.5% sensitivity).

Alegre Castellanos et al (2012)²⁵ also assessed the value of Gd-EOB-DTPA-enhanced MRC for detection of bile leaks in 23 patients and reported a diagnostic accuracy of 100% by HBP imaging 20 min after Gd-EOB-DTPA injection.

However, in our study, we detected bile leak in 12 out of 28 patients in additional DP images after HBP imaging. In 1 out of these 12 patients, bile leak was even not observed until 390 min after i.v. Gd-EOB-DTPA injection. Thus, we could emphasize the importance of prolonged DP images in case of bile leak suspicion.

Cieszanowski et al (2013)²² also evaluated the value of contrast-enhanced MRC with additional delayed images in detecting bile leak and noted the highest sensitivity rate when 20–25-min, 60–90-min and 150–180-min delayed images were combined. The latest DP images they acquired were 150–180 min after i.v. Gd-EOB-DTPA application, whereas we performed additional delayed images and observed 3 patients with bile leak not obvious until >210-min delay.

The need of additional DP images in some patients can be attributed to altered transport mechanisms in hepatocyte cell membrane. Recent studies have shown that, owing to impairment of hepatocyte function, cirrhosis, elevated serum alanine

Figure 3. 54-year-old male patient with history of orthotopic liver transplantation: fluid collection is seen in portal hilus (asterisk) in the fat-suppressed T_2 weighted TSE image (a). Collection cannot be perceived in pre-contrast T_1 weighted (T1w) image (b). A 60-min delayed gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced T1w MR cholangiography image demonstrates extravasation of contrast material from duct-to-duct anastomosis site into the portal hilus and lesser sac (asterisks) (c).

aminotransferase, alkaline phosphatase levels and owing to transport mechanism alterations, elevated bilirubin levels diminish the hepatocyte-uptake of Gd-EOB-DTPA leading to a delay of visualization of the biliary tree and thus to a delay of its extrabiliary detection in case of biliary leakage.^{30,31}

In addition, there can be an impairment of excretion. Gd-EOB-DTPA is transported from the cytosol to the bile duct *via* multidrug resistance protein 2, which is considered to be responsible for the excretion of several substances, including bilirubin. Consequently, elevated bilirubin excretion leads to a diminished excretion of Gd-EOB-DTPA. If bile duct obstruction occurs, another multidrug resistance protein, multidrug resistance protein 3, is upregulated and provides the back transport of bilirubin and other substances to the bloodstream.³² Thus, high levels of bilirubin and biliary obstruction presenting with bile duct dilatation may impair the excretion of Gd-EOB-DTPA. In such cases, both the visualization of bile ducts and bile leakage may be delayed or prevented.

However, in our study, mean total bilirubin levels were elevated both in HBP and DP group with a slightly higher mean level in DP group. Abnormal liver function tests and bile duct dilatation were also observed in both groups without any statistically significant difference. Furthermore, in each patient, visualization of bile ducts was possible in the HBP. In three patients in DP group, laboratory test results were even normal and bile duct dilatation was not present, whereas in each patient of the HBP group, at least one of these parameters was abnormal. We think that one possible cause of late extrabiliary visualization of Gd-EOB-DTPA might be the presence of small volume leaks.

Therefore, we suggest that additional DP images (>30 min) should be taken for each patient with a high clinical suspicion of bile leak even in cases where liver function test results and total bilirubin levels are normal, no bile duct dilatation is observed and biliary excretion is sufficient in HBP images. However, larger population studies are needed to confirm this finding and assess further contributive factors for late extrabiliary visualization of Gd-EOB-DTPA in bile leaks.

In our study, five of seven patients with orthotopic liver transplantation had a bile leak. Bile leaks may occur at the cut surface of partial liver grafts, at liver surface owing to injury during surgery, the cystic duct remnant, the T-tube exit site or at the surgical anastomosis site. Formerly, T-tube was known as the strongest risk factor for bile leak. However, nowadays, they are rarely employed duct-to-duct anastomosis, which is the preferred anastomosis technique and thus, bile leaks most frequently occur at cut sites, anastomosis site or cystic duct stump.^{33,34}

In our patients, the observed bile leak sources in Gd-EOB-DTPA-enhanced MRC were at the cut surface of the transplanted liver ($n = 2$) and at the duct-to-duct anastomosis site ($n = 3$). In both cases with bile leak source at the cut edge of the liver, T-tube cholangiogram and ERCP revealed no positive diagnosis. However, confirmation of bile leak existence could be made by percutaneous drainage of the collection. Thus, we can emphasize the role of MRC in detecting biliary leakage if interventional procedures fail to identify the leak.

Our study has several limitations. First, the sample size was relatively small. Second, because of the retrospective nature of

Figure 4. A 53-year-old male patient with history of cholecystectomy: pre-contrast T_1 weighted (T_1w) image (a) demonstrates a fluid collection in cholecystectomy site (arrow). Wall formation of this collection (big arrow) is depicted in T_2 weighted (T_2w) image (b). Cystic duct stump and adjacent common hepatic duct are also seen (small arrow). Peripheral enhancement of the fluid collection is seen in the equilibrium phase of dynamic contrast T_1w image (c). Hepatobiliary phase image of gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DTPA)-enhanced T_1w MR cholangiography (MRC) (d) presents enhancement of the fluid collection consistent with bile leak (big arrow). Gd-EOB-DTPA excretion into cystic duct stump and adjacent common hepatic duct is also seen (small arrow). Corresponding heavy T_2w MRC image (e).

this study, a certain degree of selection bias could not be avoided. Third, in six out of seven patients without bile leak findings on Gd-EOB-DTPA-enhanced images, verification of MRC

findings was not made with invasive/surgical procedures but with clinical follow-up and non-invasive radiological examinations. Fourth, as the MR images were reviewed by three

Table 3. Bile duct dilatation, liver function tests and total bilirubin levels in hepatobiliary phase (HBP) group vs delayed phase (DP) group

Groups with MRC findings confirming to bile leak	Bile duct dilatation		<i>p</i> -value	LE		<i>p</i> -value	Bilirubin levels (mg dl ⁻¹) ^a	<i>p</i> -value
	Yes	No		High	Normal			
HBP group (<i>n</i> = 7)	2 (28.6%)	5 (71.4%)	1	4 (57.2%)	3 (42.9%)	0.65	1.18 (±0.28)	0.33
DP group (<i>n</i> = 12)	3 (25%)	9 (75%)		5 (41.7%)	7 (58.3%)		1.29 (±0.94)	

LE, liver enzymes (Aspartate Aminotransferase, alanine aminotransferase).

^aData are mean ± standard deviation.

radiologists in consensus, we could not assess interobserver agreement or reproducibility between the radiologists.

In conclusion, dynamic Gd-EOB-DTPA-enhanced T1w fat-suppressed 3D gradient-echo sequence is a useful non-

invasive diagnostic tool for detecting bile leak. Bile leak may not be detected until prolonged DP images even if visualization of bile ducts was sufficient in HBP image and liver enzyme levels, total bilirubin levels and bile duct diameters are normal.

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