Balkan Med J 2016;33: 275-82

The Impact of Gd-Eob-Dtpa-Enhanced MR Cholangiography in Biliary Diseases: Comparison with T2-Weighted MR Cholangiopancreatography

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Background: Contrast enhanced magnetic resonance cholangiography is a novel technique and promising method in demonstrating biliary tree anatomy and evaluating biliary disorders. However, to date, there are a limited number of studies that have focused on the impact of this technique.
Aims: We aimed to evaluate the additional role of contrast enhanced MR cholangiography (MRC) and compare contrast enhanced MRC with T2-weighted (w) magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of biliary disorders.
Study Design: Diagnostic accuracy study.
Methods: The T2w-MRCP and contrast enhanced MRC sequences of 31 patients whose gold standard test results were available were scored visually for the existence of pathological findings with regard to any of the biliary diseases. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) was used as the contrast agent. The correlation values were determined according to the statistical analysis made from those scores and the sensitivity, specificity and accuracy values of each sequence were detected as well.
Results: We detected that the correlation values with gold standard methods of contrast enhanced MRC sequences were significantly higher than the ones of T2w-MRCP sequences. The correlation ratios of T2w-MRCP sequences were between 26 and 34%, while those for contrast enhanced MRC sequences were between 81 and 83% for the first reader and the correlation ratios of T2w-MRCP sequences were between 10 and 61%, whereas those of contrast enhanced MRC were between 79 and 81% for the second reader The mean sensitivity, specificity and accuracy values of T2w-MRCP sequences were 14.3-42.5%, 85-89.2% and 59.3-72.5%, respectively, while the mean sensitivity, specificity and accuracy values of contrast enhanced MRC sequences were 100%, 86.7% and 93.2-93.3%, respectively.
Conclusion: We suggest that obtaining of contrast enhanced MRC sequences in addition to the T2w-MRCP can be useful in the diagnosis of many diseases in relation with biliary tree.
Keywords: Cholangiopancreatography, contrast enhanced MRC, gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, magnetic resonance

Although ultrasonography (US) and computed tomography (CT) are fast and practical, they are often insufficient in the diagnosis of many biliary disorders. The interventional techniques including percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) are known as gold standard methods in the diagnosis of biliary diseases and can be used for treatment as well. Nevertheless these techniques are invasive, operator-dependent and also they include various complications.

In many cases, T2-weighted (w) magnetic resonance cholangiopancreatography (MRCP) could provide an accurate diagnosis without the need for invasive diagnostic procedures. It does not involve any radiation risk, does not include any complications and does not require anesthesia. It can also be used

This study was presented as an electronic poster at the European Congress of Radiology, 6-10 March 2014, Vienna, Austria.

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Received: 14 November 2014 Accepted: 3 June 2015 • DOI: 10.5152/balkanmedj.2016.140872

Available at www.balkanmedicaljournal.org

Cite this article as:
Özmen E, Algın O, Evrimler Ş, Arslan H. The impact of Gd-Eob-Dtpa-enhanced MR cholangiography in biliary diseases: comparison with t2-weighted MR cholangiopancreatography. Balkan Med J 2016;33:275-82

in episodes of pancreatitis or cholangitis, and presents images on different planes as well. Although T2w-MRCP could be an answer for many indications related to biliary diseases, there are some special circumstances that require contrast enhanced MRC, including the detection of biliary leakage and functional evaluation of the biliary system (1-4).

To the best of our knowledge, there are only limited published reports that have focused on the impact of contrast enhanced MRC in the evaluation of biliary diseases and variations (5-9). Those studies were achieved mostly with Gd-BOPTA (Gadobenate dimeglumine, Multihance®; Bracco, Princeton, NJ) and Mn-DPDP (Mangafodipir trisodium, Teslascan®; Nycomed Amersham, Princeton, NJ). Gd-EOB-DTPA (gadoxetic acid, Eovist® or Primovist®; Bayer Healthcare, Wayne, NJ), which was placed on the market in recent years, could provide optimal biliary system visualization with fewer doses than Gd-BOPTA (10). Also, it could supply earlier imaging for biliary tract than Gd-BOPTA (11). In this study, we used Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) as a contrast agent and aimed to compare contrast enhanced MRC with T2w-MRCP, and to detect the correlations of both of these techniques with gold standard tests.

MATERIALS AND METHODS

Study group

Ethics committee approval was obtained for this prospective study. T2w-MRCP and contrast enhanced MRC examinations were applied to 54 patients between the ages of 24 and 89, with the mean age of 55.3, who were referred to the radiology department of our hospital over a period of 8 months with the prediagnosis of biliary disease. The study protocol was explained in detail to all of the patients participating in the study and informed consent was obtained from all patients. Gd-EOB-DTPA (0.05 mL/kg; *Gadoxetic acid,* Primovist®, Bayer-Schering, Germany) was used as a contrast agent for contrast enhanced MRC. Twenty three of the 54 patients, whose ERCP, PTC or surgical and pathologic results could not be obtained, were excluded from the study. Thus, the remaining 31 patients were included in the study. Twenty of the 31 patients were men and 11 of them were women. Unconscious and non-cooperative patients, pregnant women, those with an allergy history, claustrophobic patients, those with implanted devices incompatible with MR such as pacemakers and those with impaired liver or kidney function were not included in the study.

MRI protocol

All of the MR images were obtained with a 1.5 Tesla MR Unit (*Achieva; Philips Healthcare, Best, Holland*), by using a phased-array body coil. All images were obtained by using the parallel imaging [sensitivity encoding (SENSE)] technique. All of the patients were asked to fast for at least 5-6 hours before the examination in order to prevent gallbladder contraction. T2w-MRCP and contrast enhanced MRC examinations were performed in supine position.

TABLE 1. MR imaging protocol of the study

Imaging Parameters	T2w-BTFE	T2w-TSE	T2w-SPAIR	3D-heavily T2w	CE-T1w
TR (ms)	3.6	950	728	1204	3.1
TE (ms)	1.78	80	80	650	1.46
Flip Angle	90	90	90	90	10
FOV	330x330	330x330	330x330	256x205	330x330
Matrix	252x242	280x275	280x275	260x260	200x180
Slice thickness (mm)	6	6	6	0.8	2.5
Time (sec)	17	30	30	327	16
Acquisition plane	Coronal	Axial	Axial	Coronal	Axial-coronal

FOV: field of view; BTFE: balanced turbo field echo; TSE: turbo spin echo; SPAIR: spectral adiabatic inversion recovery; CE: contrast enhanced; TR: time of repetition; TE: time of echo

Acquisition protocol of MRC examinations are summarized in Table 1. The acquisition of three-dimensional (3D) heavily T2w data was performed using respiratory triggering. Maximum intensity projection (MIP) images of 3D contrast enhanced T1w sequences and heavily T2w sequences were created with the non-commercial software that presents on MR devices following the acquisition of source images.

Contrast enhanced MRC images were obtained on arterial, venous and equilibrium phases after the intravenous administration of Gd-EOB-DTPA with the same parameters**.** The total MR examination time was about 25 minutes per patient. Although it depends on the prediagnoses of the patients, post-contrast T1w images at the 20th min (earlier phase) and 60th min (later phase) were obtained again. In patients with a suspicion of gallbladder disease, post-contrast T1w images were also obtained at 120th min in order to enable filling of the gallbladder with contrast agent. Those additional sequences which were obtained for late-phase contrast enhanced MRC images took approximately 5 minutes.

Image analysis

After MRC examinations, the images of all patients were loaded in the picture archiving and communications system (PACS). The demographic data and protocol numbers of all patients were recorded to the "MS excel, v. 2010" datasheet by the study coordinator who had 8 years of experience on MRC. The patients were randomized and collected in a table

and given to the two observers who had experiences of 5 and 3 years respectively on MRC. These observers evaluated all of the MRC images independently and were unaware of the clinic, laboratory and surgery findings. In addition, the observers reevaluated the same images at least 3 weeks after the first evaluation for intraobserver reliability analysis.

T2w-MRCP images including T2w-balanced turbo field echo (T2W-BTFE), T2w-turbo spin echo (T2W-TSE), T2w-spectral adiabatic inversion recovery (T2W-SPAIR), 3D heavily T2w sources and heavily T2w-MIP sequences and contrast enhanced MRC images including post-contrast T1w sequences in axial-coronal planes and post-contrast T1w MIP images were scored visually as follows in terms of the existence of biliary diseases; Score 0: No pathologic finding suggestive of biliary disease, Score 1: Some suspicious findings in favor of the investigated biliary disease, but these findings are insufficient for the diagnosis, Score 2: Adequate findings in favor of suspected biliary disease for the diagnosis.

In addition, consensus, which was scored by evaluating all sequences together, was included in statistical analyses. After the scoring procedure mentioned above, the two observers who made the scoring and the study coordinator performed an agreement meeting. In this meeting, MRC images, the findings of clinic-laboratory, gold standard methods (ERCP, PTC, and/or surgical & pathological results), and/or clinical follow up results of the all of the patients were evaluated together. The final diagnosis of the patients included in the study was also made together. All of the findings, especially the results of the gold standard methods, were considered together for the final diagnosis.

Statistical analysis

Statistical analyses were performed with the program of Statistica (version 8.0, Statsoft Inc; Tulsa, Oklahoma, USA). The sensitivity, specificity and accuracy values of the sequences were determined. In correlation analysis of the sequences, the correlation percents of sequences with the results of the gold standard tests were detected with Spearman Rank Order Correlations test. In this test, a p value below 0.05 was accepted as statistically significant. In addition, interobserver correlations and intraobserver reliabilities were calculated with Fleiss's kappa (κ) coefficient. Intra- and interobserver reliability ratios were expressed with the κ coefficient. The κ coefficient value is ordinarily between 0 and 1. "1" shows a complete agreement since "0" shows no agreement or agreement by chance (12). The κ value should be interpreted within the clinical framework. However, a κ value below 0.20 shows slight agreement, a κ value between 0.21-0.40 shows fair agreement, a κ value between 0.41 - 0.60 shows moderate agreement, a κ value between 0.61-0.80 shows substantial agreement and a κ value between 0.81-1.00 shows almost perfect agreement (13).

RESULTS

Findings of the gold standard methods

Fourteen of the 31 patients who were included in the study had no finding in favor of biliary disease on MRC images. For the remaining 17 patients, there was gallbladder perforation in 3, acute cholecystitis in 3, malign biliary obstruction in 3, choledochal cyst in 2, bilioenteric fistula in 1, biliary stricture due to surgery in 1, biliary system variation in 1, biliary leakage due to surgery in 1, choledocholithiasis in 1 and von Meyenburg disease in 1 patient. In 3 patients in whom malign biliary obstruction was detected, there was an ampullary tumor in 1, pancreas cancer in the head of the pancreas in 1 and Klatskin tumor in 1 patient**.** The patients with acute cholecystitis and gallbladder perforation were operated upon and their diagnoses were proven with histopathological examination results. The patients with bilioenteric fistula and choledocolithiasis were operated upon and the diagnoses were confirmed with operation results. The diagnoses of von Meyenburg disease and malign biliary obstructions were also confirmed with histopathological examination results after biopsy. PTC procedure was performed in 3 patients with malign biliary obstruction and ERCP procedure was applied in 3 patients who had stricture due to surgery, biliary system variation and biliary leakage, respectively. The interval between MRC examination and PTC or ERCP was less than or equal to 1 month.

In three patients with acute cholecystitis, we could not visualize the passage of contrast agent to the gallbladder in the 120^{th} min and the operation and pathology results of those patients were compatible with acute cholecystitis (Figure 1). US examinations only revealed supportive findings related to acute cholecystitis, including gallbladder wall thickening, biliary stone inside the lumen or in the neck of gallbladder and distension of the gallbladder.

Gallbladder perforation was detected on contrast enhanced MRC images in 3 of our patients and verification of the diagnosis was performed with operation and pathology results (Figure 2). In one of our patients who had a hydatic cyst surgery, a biliary leakage secondary to biliary injury was detected and the same finding was also seen on ERCP images (Figure 3). Heavily T2w-MIP image demonstrated abrupt termination of the common bile duct in the patient with choledocholithiasis. Neither heavily T2w-MIP image nor contrast enhanced MRC image could show the bile stone directly. However, contrast enhanced MRC could show the obstruction in contrast material passage through the distal part of the common bile duct (Figure 4).

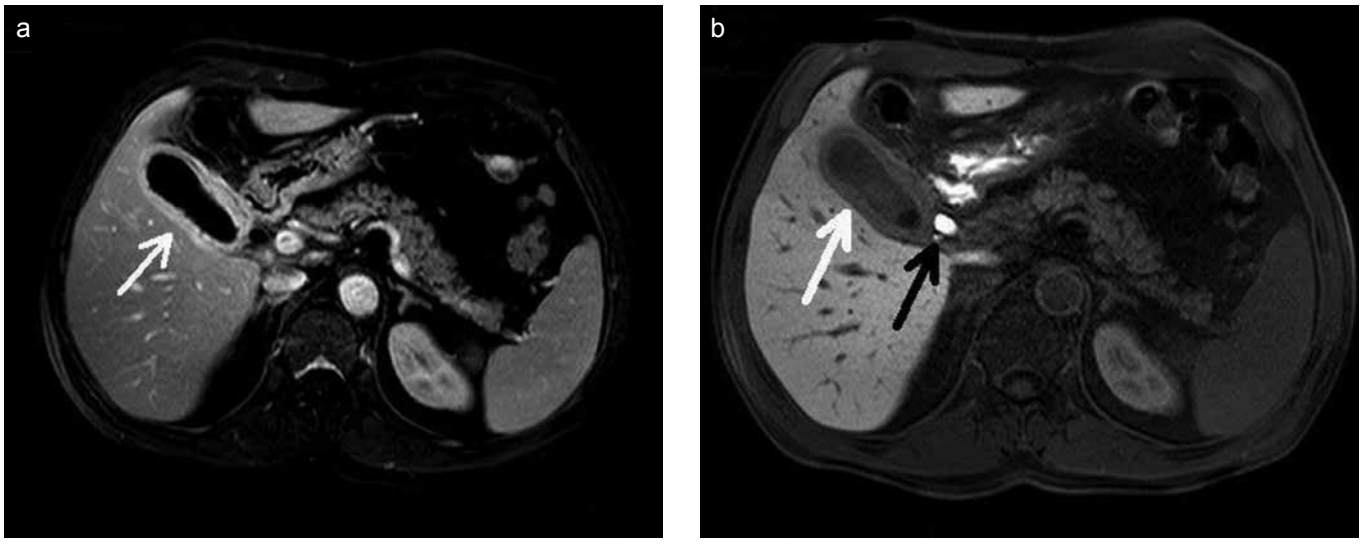

FIG. 1. a, b. A 58 year-old man with acute cholecystitis. Axial contrast enhanced T1w sequence which was obtained in the 4th min after contrast material injection depicts the avid enhancement of gallbladder wall (arrow) (a). Axial contrast enhanced T1w sequence which was obtained in the 120th min after contrast material injection demonstrates that the contrast material did not pass through the gallbladder lumen (white arrow), but the common bile duct was filled with contrast material (black arrow) (b).

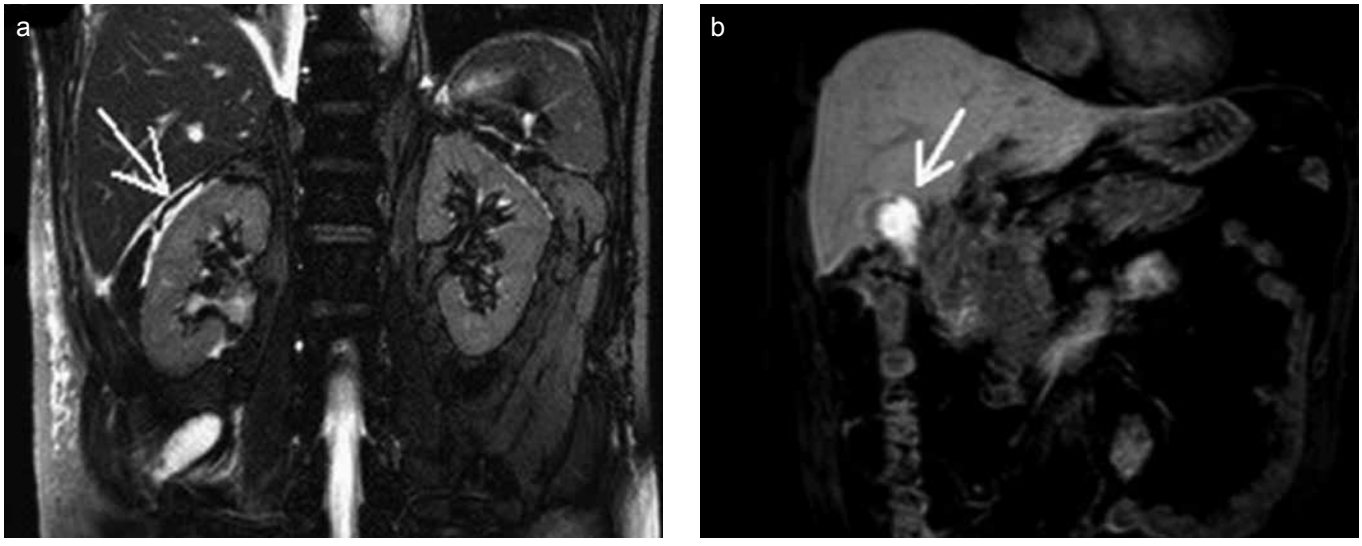

FIG. 2. a, b. A 64 year-old man with gallbladder perforation. T2w-BTFE sequence shows subhepatic fluid collection (arrow) (a). Coronal contrast enhanced T1w sequence which was obtained in the 120th min after contrast material injection shows the leakage of contrast material to the outside of the gallbladder (arrow) (b).

Sensitivity, specificity and accuracy values

The sensitivity values of T2w-MRCP sequences were between 14 and 25% for the first reader, while they were between 14 and 60% for the second. The sensitivity values of contrast enhanced MRC sequences were 100% for all. The specificity values of T2w-MRCP sequences were between 90 and 92% for the first reader and between 80 and 87% for the second reader. The specificity value of the contrast enhanced MRC sequence was 87% for both readers. The accuracy values of contrast enhanced MRC sequences were significantly higher than those of T2w-MRCP sequences ($p<0.05$) (Table 2).

Correlation analysis with gold standard tests

Contrast enhanced MRC sequences were significantly correlated with the gold standard test results for the first reader, while contrast enhanced MRC and 3D heavily T2w-source images were significantly correlated with the gold standard test results for the second reader ($p<0.05$). The other sequences were not correlated significantly with gold standard test re-

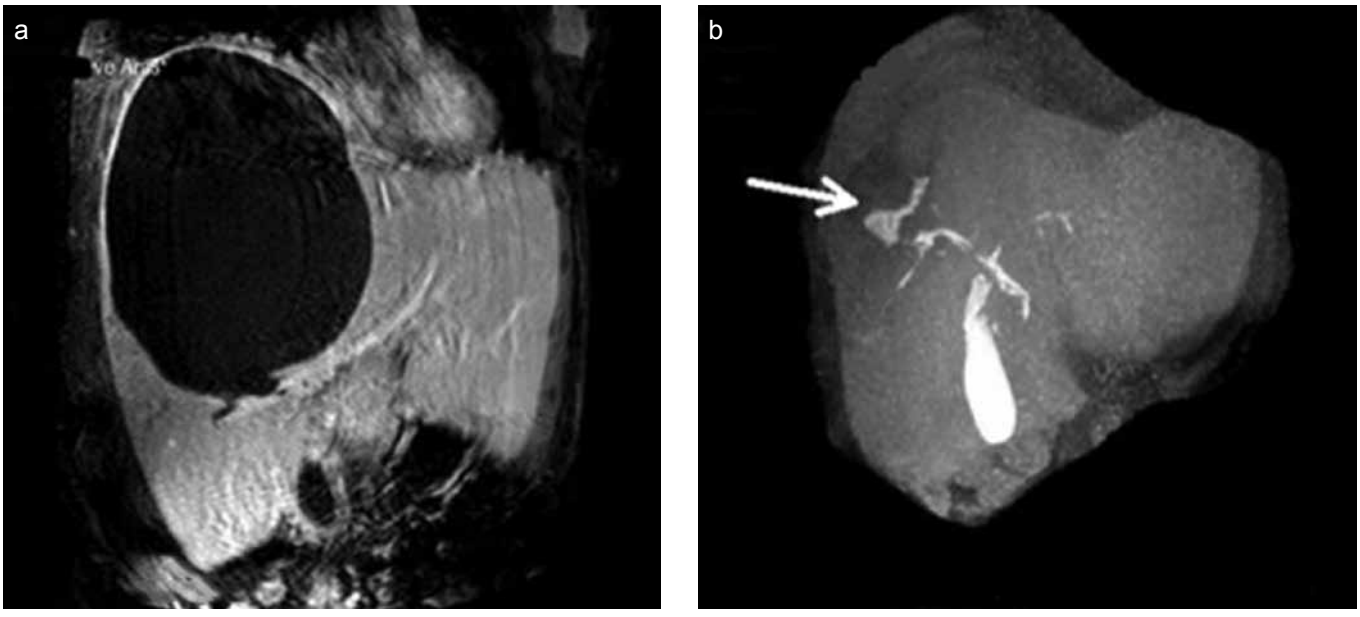

FIG. 3. a, b. Pre and post-operative MR images of a 39 year-old woman with biliary leakage after the hydatid cyst operation. Coronal contrast enhanced T1w image which was obtained before the surgery demonstrates a huge hydatid cyst at the right liver (a). Contrast enhanced T1w-MIP image confirms the leakage of contrast material outside of biliary system (arrow) (b).

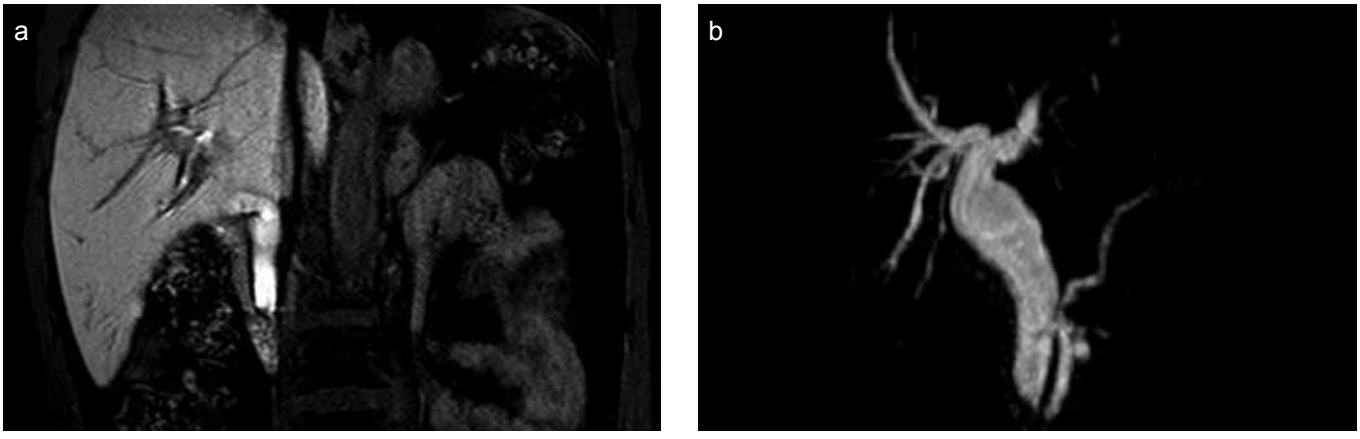

FIG. 4. a, b. Preoperative MR images of a 61 year-old woman with choledocholithiasis. Heavily T2w-MIP image demonstrates abrupt termination of the common bile duct in the patient with choledocholithiasis (a). Contrast enhanced MRC shows the obstruction in contrast material passage through the distal part of the common bile duct (b).

sults. The correlation ratio between the consensus and gold standard tests was the highest, with a ratio of 88% (Table 3).

Reliability analysis

In interobserver correlation analysis, there was almost perfect correlation between two observers for contrast enhanced MRC sequences (κ=0.94); for the interobserver correlation, κ values were between 0.56 and 0.89 for T2w-MRCP**.** The intraobserver correlation analysis indicated that κ values for intraobserver correlation were between 0.78 and 0.84 for contrast enhanced MRC sequences, while they were between 0.39 and 0.7 for T2w-MRCP sequences.

DISCUSSION

The current algorithm for investigating any biliary disorders is to perform US examination since it is easy, non-invasive and does not involve ionizing radiation. In cases where the findings are non-diagnostic, T2w-MRCP should be considered (14). T2w-MRCP highlights the biliary tree, especially with heavily T2w sequences. However, in some circumstances, T2w-MRCP might be insufficient, especially in the diagnosis of acute cholecystitis biliary leakage and gallbladder perforation (5,14,15). We suggest that contrast enhanced MRC sequences can increase the diagnostic performance of

TABLE 2. Sensitivity, specificity, and accuracy values of the sequences

	Sensitivity (%)			Specificity (%)			Accuracy (%)		
Sequences	1st Observer	2nd Observer	Mean	1st Observer	2nd Observer	Mean	1st Observer	2nd Observer	Mean
T2w-BTFE	16.7	16.7	16.7	90	80	85	62.5	56.2	59.3
T2w-TSE	20	16.7	18.3	90	80	85	66.7	56.2	61.4
T2w-SPAIR	20	14.3	17.1	90	80	85	66.7	52.9	59.8
3D-heavily-T2w-sources	25	60	42.5	91.7	86.7	89.2	65	80	72.5
Heavily T2w-MIP	14.3	14.3	14.3	90.9	85.7	88.3	61.1	61.9	61.5
Axial-CE-T1w	100	100	100	86.7	86.7	86.7	93.3	93.1	93.2
Coronal-CE-T1w	100	100	100	86.7	86.7	86.7	93.3	93.3	93.3
CE-T1w-MIP	100	100	100	86.7	86.7	86.7	93.3	93.1	93.2
Consensus	100	100	100	86.7	86.7	86.7	93.5	93.5	93.5

BTFE: balanced turbo field echo; TSE: turbo spin echo; SPAIR: spectral adiabatic inversion recovery; MIP: maximum intensity projection; 3D: three dimensional; CE: contrast enhanced

TABLE 3. The correlations between the sequences and gold standard methods

Sequences*	Correlation Percent*	
	1st Observer (%)*	2nd Observer (%)*
T2w-BTFE*	26	15
T2w-TSE*	32	15
T2w-SPAIR*	32	10
3D heavily T2w-sources*	34	61*
Heavily T2w-MIP*	26	35
Axial CE-T1w*	81*	79*
Coronal CE-T1w*	83*	81*
CE-T1w-MIP*	81*	79*
Consensus*	88*	88*

*: statistically significant ($p<0.05$); BTFE: balanced turbo field echo, TSE: turbo spin echo; SPAIR: spectral adiabatic inversion recovery; MIP: maximum intensity projection; 3D: three dimensional; CE: contrast enhanced

T2w-MRCP. In our study, the sensitivity and accuracy values of contrast enhanced MRC sequences were higher than those of T2w-MRCP. In addition, contrast enhanced MRC findings correlated better with gold standard test results than T2w-MRCP findings. To date, there have only been a limited number of published reports that have focused on the impact of contrast enhanced MRC (5-9,15,16). Among those studies, Krishnan et al. (5) reported that the sensitivity of detection of cystic duct patency for contrast enhanced MRC was 76% and Salvolini et al. (16) indicated that T2w-MRCP could determine 64% while contrast enhanced MRC could detect 100% of the patients with biliary complications after surgery (5,15). Kantarcı et al. (14) also suggested that contrast enhanced MRC in addition to T2w-MRCP increases the accuracy in detecting bile leaks.

Currently, there are two contrast agents which can be used to perform contrast enhanced MRC: Gd-EOB-DTPA and Gd-BOPTA. Gd-EOB-DTPA, which has been used in recent years, can diffuse in the extracellular space quickly and is taken up by hepatocytes, similar to Gd-BOPTA. However, the biliary extraction ratio of Gd-EOB-DTPA is about 50% and significantly higher than Gd-BOPTA (6). This allows a functional evaluation of the biliary system within 20 minutes after administration of the contrast agent in the patients with normal liver function (5,17-19). In recent years, Dahlström et al. (20) compared Gd-BOPTA and Gd-EOB-DTPA enhanced MRC images in terms of biliary tract enhancement in 10 healthy volunteers. In that study, it was emphasized that biliary tract enhancement started earlier and lasted longer with Gd-EOB-DTPA (20). The recommended dose of Gd-EOB-DTPA is 0.025 mmol/kg and is also ¼ of Gd-BOPTA (10).

In our study, the patients were recommended to fast for about 4-6 hours prior to MRC procedure to enable filling of the gallbladder. As the passage of the contrast agent to the gallbladder could be difficult in postprandial period due to the increase of internal gallbladder pressure, this may reduce the success of contrast enhanced MRC imaging (5). Although some authors recommend the administration of anti-peristaltic drugs (e.g. glucagon), we did not need to use it since we achieved fast sequences and peristaltic artifacts were minimal (21).

Our second important finding was that the correlation values with gold standard tests of contrast enhanced MRC sequences were significantly higher than T2w-MRCP sequences when we consider all of the biliary disorders. Consensus results, which were obtained by evaluating all of the sequences together, showed the highest correlation values with gold standard tests. This indicated that the sequences were complementary to each other and should be evaluated as a whole. Besides, inter and

intraobserver agreement values of the contrast enhanced MRC sequences were higher than those of T2w-MRCP. These results also showed us that contrast enhanced MRC can provide more reliable results than T2w-MRCP images.

The technical parameters of MRC are also very important and can affect the success of the radiologic examination. There were different results in some published reports that focused on choledocholithiasis in the literature. Kats et al. (22) determined the sensitivity of T2w-MRCP as 100% in choledocholithiasis, whereas Angulo et al. (23) found it to be 50%. We thought that these differences in the literature are related to the technical disparity in those studies and with the variety of biliary diseases in the study groups.

3D heavily T2w-source and post-contrast T1w acquisitions with small and cubic voxels can be reconstructed to high-resolution multiplanar reformatted and MIP images (23). Non-isotropic acquisition with a larger voxel size has some limitations in the detection of intraductal abnormalities, because small structures that make signal-voids, such as small stones, could be obscured due to the partial volume effect of the intraductal liquid signal intensity. Thus, thin slices should be evaluated carefully in some conditions including the existence of small stones or subtle mural irregularity (23). In our study, the sensitivity, specificity and accuracy values of 3D heavily T2w-source images were higher than those of heavily T2w-MIP images. The mean sensitivity, specificity and accuracy values of 3D heavily T2w-source images were 42.5%, 89.2% and 72.5%, respectively, while the sensitivity, specificity and accuracy values of heavily T2w-MIP images were 14.3%, 88.3% and 61.5%, respectively. In addition, the sensitivity and specificity values of 3D heavily T2w-source images were the highest among those of all T2w-MRCP sequences.

We think that contrast enhanced MRC sequences could also be helpful in the determination of any possible connection between the liver and peribiliary cysts and bile ducts. MR cholangiography can detect hydatid cysts and demonstrate post-interventional complications including biliary leakage or fistulization, especially on delayed-phase images (24). We did not see any connection between the liver cysts and bile ducts in any of our 5 patients. There were hydatid cysts in 3 of them. However, we also know that we may not visualize the passage of contrast agent to the hydatid cysts, since the internal pressure of hydatid cysts is high, even if those are connected with the bile ducts. Thus, it would not be proper to say that there is no connection with the biliary system for hydatid cysts when we could not see the passage of contrast agent into these cysts on contrast enhanced MRC images. However, Kantarci et al. (25) reported that contrast enhanced MRC is superior in the detection of communication hydatid cyst with biliary system with a sensitivity of 87.4% and accuracy of 90.5%.

The major drawback of our study is the limited number of patients for each group of biliary diseases. Thus, we could not assess the sensitivity, specificity, and accuracy values separately for each subgroup. More extensive and comprehensive studies are needed for each biliary disease mentioned above. Our second limitation was the need for additional sequences to obtain delayed contrast enhanced MRC sequences. However, we achieved 3 additional sequences in the patients with acute cholecystitis and 2 additional sequences for the remaining patients. Those sequences took about 5 min. In addition, although we detected sensitivity, specificity and accuracy values of each T2w-MRCP sequence separately, we did not evaluate and score all of the T2w-MRCP sequences together. Thus, the last limitation of our study was that we could not exhibit data regarding the sensitivity, specificity and accuracy values of the T2w-MRCP technique. However, we exhibited the sensitivity, specificity and accuracy values of consensus which was obtained by evaluating all of the T2w-MRCP and contrast enhanced MRC sequences together.

In conclusion, the sensitivity, specificity, and accuracy values of Gd-EOB-DTPA enhanced MRC were significantly higher than those of the T2w-MRCP in the diagnosis of biliary diseases. Also, the ratios of correlation with gold standard methods of the contrast enhanced MRC images were significantly higher than the T2w-MRCP images. It would be useful to obtain contrast enhanced MRC sequences in addition to the T2w-MRCP sequences for the diagnosis of biliary diseases.

Ethics Committee Approval: Ethics committee approval was obtained for this prospective study from Yıldırım Beyazıt University School of Medicine (B.30.2.YBÜ.006.06.01/5).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.O., O.A.; Design - E.O., O.A.; Supervision - H.A.; Resource - O.A.; Materials - E.O., Ş.E.; Data Collection and/or Processing - E.O., Ş.E.; Analysis and/or Interpretation - E.O., Ş.E.; Literature Search - E.O.; Writing - E.O.; Critical Reviews - O.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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