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Gadoxetate-Enhanced Magnetic Resonance Cholangiography for Prognostic Purposes in Primary Sclerosing Cholangitis

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ABSTRACT

Aim: To assess the prognostic role of MRC in the follow-up of patients with primary sclerosing cholangitis (PSC). Methods: The study included 52 consecutive PSC patients who underwent MRC with Gd-EOB-DTPA at the baseline and at every 2-year follow-up. The prognostic value of the MRC was assessed using an adaptation of the original Amsterdam classification validated for endoscopic retrograde cholangiography. Images were scored from I to V, based on the severity of biliary strictures and dilations. Results: The mean follow-up was 122.3±8.7 months, and a total of 89 MRC was collected. Twenty-three patients (44.2%) had a final MRC score ≤III, while for 29 (55.8%) it was >III. Patients with MRC scores >III had significantly higher alkaline phosphatase levels, more severe liver stiffness, a higher rate of biliary complications in the baseline than patients with MRC scores ≤III. At 2-year follow-up, MRC scores >III correlated significantly with serum transaminases, GGT, and alkaline phosphatase levels. Multivariate analysis showed that the occurrence of biliary complications and the indication for a liver transplant were significantly associated with a final MRC score >III. Conclusions: MRC scores based on image features and contrast enhancement pattern after Gd-EOB-DTPA administration can provide prognostic information in PSC.

Keywords: Primary sclerosing cholangitis, magnetic resonance cholangiography, gadoxetate disodium, prognostic score, liver transplantation

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the intra- and extra-hepatic biliary tree that leads to the formation of multifocal bile duct strictures and ultimately to end-stage liver disease (1, 2).

PSC is considered a rare disease, with highly variable rates of occurrence: in North America and Europe, it has an incidence in the range of 0 to 1.3 cases per 100,000 population per year, with the highest rate in Norway (3), while the prevalence of PSC is around 0-16.2 per 100,000 population (4). PSC is more common in males, with a male-to-female ratio of 1.70 (5).

It can be diagnosed in children, adults, and the elderly, the mean age at diagnosis being around 40 years (5, 6).

The International PSC Study Group (IPSCSG) sponsored a multi-center and uniquely powered outcome study involving a cohort of more than 7,000 patients seen at 37 centers across 17 countries and spanning more than 30 years of clinical observation (7). This study recorded differences in the disease's presentation by geographical region, which involved its association with inflammatory bowel disease, the small duct variant, and the onset of malignant complications (7). In fact, PSC is the main risk factor for cholangiocarcinoma (CCA): PSC patients have a 400-fold higher risk than the general population and a 10-15% higher lifetime risk of developing CCA (8,9). About one in three CCAs is found in the first year after PSC has been diagnosed, while the remainder is identified with a frequency of about 1.5% per year (9). The diagnosis of CCA in PSC patients is often challenging and may be delayed because of the difficulty of distinguishing between benign dominant strictures and CCA, and because there are no standard screening programs in place or diagnostic algorithms available.

Establishing the prognosis for PSC patients and promptly diagnosing complications of the disease are among the main challenges of this disease. Invasive techniques have been employed in several studies, particularly ERCP. In a retrospective study on 129 patients with PSC who underwent ERCP to assess their biliary tree abnormalities, high-grade strictures and diffuse strictures on intrahepatic ducts were identified as indicators of a poor prognosis (10). A scoring system for biliary tree abnormalities in PSC was proposed by a Dutch group, based on the severity of biliary alterations and intra- and/or extra-hepatic biliary tree involvement evident on ERCP (11). This classification was further refined in an attempt to correlate bile duct modifications with the natural history of the disease (12). When a prognostic model based on this modified Amsterdam classification applied to ERCP was developed, it demonstrated a correlation with transplant-free survival (13), and this model was also validated in a Norwegian cohort of PSC patients (14).

ERCP has recently been replaced with magnetic resonance cholangiography (MRC) for the diagnosis of PSC for its non-invasiveness, sensitivity, specificity, and repeatability (15). One study that applied a model for scoring PSC-related alterations on MRC has been published so far (16), in which radiological parameters were used to build a progression risk score from a total of 289 three-dimensional MRC images obtained with and without gadolinium from 64 patients, but no correlation with clinical outcomes was considered. MRC with gadolinium was also used in the follow-up of a Norwegian cohort of patients with inflammatory bowel disease to establish the prevalence of PSC, which proved to be 8.1% (17).

Gadodexate disodium (Gd-EOB-DTPA, Primovist®) is a liver-specific contrast agent that has a hepatic uptake and a 50% biliary excretion under normal conditions (18). The hepatic uptake of Gd-EOB-DTPA enables the acquisition of T1-weighted MRC images and an analysis of the timing and characteristics of biliary excretion as indicators of parenchymal function (19). In assessing PSC patients, Gd-EOB-DTPA has been found complementary to T2-weighted MRC for the study of the liver and biliary tree, providing additional diagnostic and functional information (20). Nilsson et al recently used MRC with Gd-EOB-DTPA to quantify total and segmental liver function in 12 patients with PSC (21). Furthermore, a study addressing the assessment of liver function in patients with PSC using a variable flip-angle-based fast 3D T1 mapping sequence has been recently proposed (22). The aims of the present study were, therefore: 1) to define a score for abnormalities in the biliary tree and liver parenchyma; and 2) to test this composite score for prognostic purposes in patients with PSC.

MATERIAL AND METHODS

This study included 52 consecutive PSC patients seen at our outpatient clinic (Department of Surgery, Oncology, and Gastroenterology, Gastroenterology Unit, University of Padova) between 2004 and 2016, who had at least a 1-year follow-up. PSC was diagnosed in the presence of elevated serum markers of cholestasis (alkaline phosphatase [AP] and γ-glutamyl-transferase [γGT]), and characteristic bile duct changes with multifocal strictures and segmental dilations on MRC or ERCP, once secondary causes of sclerosing cholangitis had been excluded.

From 2004 onwards, PSC patients were prospectively registered and routinely followed up with a clinical examination and biochemical tests every 4-6 months. The mean follow-up was 122.3±8.7 months. The biochemical parameters measured were: AST, ALT, γGT, AP, bilirubin, albumin, red and white cell counts, prothrombin time, CA 19-9. Levels of AST, ALT, GT and AP have expressed as the number of times the upper limit of normal (xULN), to balance biochemical tests with different cutoffs adopted at outside laboratories.

The Mayo risk score was calculated at the time of PSC being diagnosed and when MRC was performed. Liver ultrasound was performed every 6 months. Data on any onset of bacterial cholangitis, pancreatitis, gallbladder and/or common bile duct stones, hepatobiliary malignancies (including CCA, hepatocellular carcinoma [HCC] and gallbladder cancer), portal hypertension, liver transplantation [LT] or enrolment on the waiting list for LT were recorded during the follow-up. ERCP with brushing ± stent placement was performed in the event of dominant strictures apparent on MRC, with or without cholangitis, or if CCA was suspected on clinical grounds. Liver stiffness, measured at different times during the follow-up using transient elastography (TE), was available and recorded in 36 patients.

All patients were screened for IBD (unless it had been identified prior to the diagnosis of PSC) with colonoscopy and multiple biopsies, and ulcerative colitis (UC) or Crohn's disease (CD) were diagnosed as explained elsewhere (23). MRI images were obtained with a 1.5 Tesla system (Avanto, Siemens Medical System, Erlangen, Germany, maximum gradient strength up to 45 mT/m; rise time 0,2 msec; slew rate up to 200 mT/m/msec). In patients who had fasted for at least 6 hours beforehand, pineapple juice was administered per os as a negative contrast a few minutes before image acquisition to reduce artifacts due to gastrointestinal content. MR cholangiograms were obtained using a 32-channel body phased-array receiver coil. Dominant strictures were defined as stenosis of the common duct <1.5 mm in diameter, or <1.0 mm of a hepatic duct (within 2 cm of the bifurcation) (24).

The imaging protocol consisted of the following sequences:

- spoiled gradient-echo imaging steady-state precession (FLASH) used as a localizer (repetition time/echo time 7/2.66, flip angle 20 degrees, slice thickness/intersection gap, 8 mm/50%; signal average 2; matrix 154 x 256; scan time 0:14);
- Breath-hold multislice T2-weighted half-Fourier acquisition turbo spin echo (HASTE) in axial orientation (TR/TE 2000/85;

flip angle 150°; slice thickness/intersection gap 6 mm/30%; signal averages 1; matrix 194 x 320; iPAT 2; turbo factor 233; scan time 1:30);
- Multiple breath-hold coronal-oblique one thick slab T2-weighted (HASTE) sequences (TR/TE 4500/789; flip angle 180°; slice thickness/intersectional gap 60 mm/50%; signal averages 1; matrix 307 x 384; scan time 4:30) to identify the biliary tree orientation. Single-slice sections were used to choose the most appropriate plane for acquiring turbo spin-echo 3D breath-triggered sequences, and for dynamic study;
- breath-triggered 3D turbo spin-echo 3D MRC sequences with the parallel imaging technique (TR/TE 1600/622; flip angle 180°; section thickness/intersection gap 1.5 mm/50%; signal averages 1; matrix 380 x 384; iPAT 2; scan time 3:51). The same sequence was subsequently used on the axial plane;
- breath-hold 3D fat-suppressed spoiled gradient-echo (VIBE) (TR/TE 3.72/1.35; flip angle 10°; section thickness/intersection gap 160/20%; signal averages 1; matrix 230 x 256; scan time 0:18) acquired in the axial plane and in the coronal-oblique plane parallel to the common bile duct before and after iv. administration of Gd-EOB-DTPA (25 µmol/kg, Primovist, Bayer Schering Pharma), at 1-2 mL/s with a power injector, followed by a 20-mL saline flush. Hepatobiliary phase images were obtained 20 minutes after injecting the contrast; additional delayed MR images were obtained at 30 and 40/45 minutes (when contrast enhancement of the bile ducts is considered poor) until biliary tree filling was sufficient.

The prognostic value of the MRC was analyzed using an adaptation of the Amsterdam classification validated for ERCP (13, 14). Images were interpreted jointly by two experienced radiologists. The following were assessed: (1) visualization of all first, second, third, and fourth-order biliary branches based on a four-point scale; (2) presence of biliary strictures or dilations; (3) enhancement of the liver parenchyma.

The presence and degree of ductal stenosis and dilations were assessed on a 3-point scale. Intra-hepatic and extra-hepatic tracts were considered separately. Strictures were graded as: no strictures = 1; mild strictures (narrowing <75%) = 2; severe strictures (narrowing >75%, decreased arborization, severe pruning) = 3. Dilations were graded as: no dilations = 1; mild dilations (IHBD 4 mm; RHD and LHD 7-8 mm; CBD 11-14 mm) = 2; marked dilations (IHBD 5 mm; RHD and LHD 9 mm; CBD 15 mm; saccular dilatations) = 3. Enhancement of the liver parenchyma after Gd-EOB-DTPA administration was scored as homogenous or non-homogenous, depending on the contrast enhancement pattern.

A score was assigned to each sector, based on the presence and severity of strictures and dilations (Table 1). The resultant score can be read at the intersection of the extrahepatic row with the intrahepatic column in Table 2. An extra point was added to the overall score for non-homogeneous contrast enhancement patterns after Gd-EOB-DTPA administration, obtaining a final MRC score from I to VI. Patients were then divided into two groups by final MRC score ≤ III versus > III.

In a second step, the contrast enhancement pattern was scored as homogeneous = 0; non-homogeneous with less than 25% of the hepatic parenchyma functionally excluded = 1; non-homogeneous with 25-50% of the parenchyma excluded =2; non-homogeneous with more than 50% of the parenchyma excluded = 3. Patients were divided into two groups by contrast enhancement pattern scoring 0-1 versus 2-3.

Differences between the two groups divided by final MRC score were analyzed in terms of: liver function tests (LFTs) and Mayo risk score at the time of MRC, performed at the baseline and at a 2-year follow-up; Ca 19-9 levels; and clinical events (bacterial cholangitis, pancreatitis, gallbladder or common bile duct stones, dominant strictures requiring endoscopic/surgical treatment, hepatobiliary malignancies) occurring at least a year after performing MRC; LT or enrolment on waiting list for LT; association with IBD; and liver stiffness. Pancreatitis, gallbladder or common bile duct stones and dominant strictures were considered together as 'other biliary complications'. Differences between patients grouped by contrast enhancement pattern were also examined in terms of the same variables as above. An example of how images were assessed and MRC scores were constructed is shown in Fig. 1. The study protocol was reviewed and approved by the local ethical committee. The investigation was conducted in accordance with the principles of Good Clinical Practice, and the ethical standards established in the 1964 Helsinki Declaration and its subsequent amendments.

Liver stiffness measurement

Liver stiffness (LS) was measured by TE using a FibroScan® (EchoSens, Paris, France) as described in previous studies (25). A single dedicated operator obtained the measurements in the right lobe of the liver through the intercostal spaces at a median depth of 55 mm. Ten validated measurements were obtained for each patient and the minimum success rate (the ratio of successful to total acquisitions) was calculated to be 60%. The final LS result was the median of the ten valid measurements and was expressed in kiloPascal (kPa). The measurement procedure took less than 5 minutes per patient.

STATISTICAL ANALYSIS

For the statistical analysis, the Shapiro-Wilk test was used to study the normal distribution of the continuous variables. To compare differences in the distribution of frequencies of categorical variables between groups, the chi-square test, and Fisher's exact test were used where the expected frequencies were ≥5 and <5, respectively. To test the differences between two groups' continuous variables, Student's t-test, and the Mann-Whitney test were applied in the case of normally and not normally distributed variables, respectively. Logistic regression was performed for the multivariate analysis, adjusting for age at the time of MRC and sex. A value of $p<0.05$ was considered statistically significant. The statistical analyses were completed using Stata statistical software, version 11.2 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 89 MRC images was collected in 52 patients. MRC was conducted once in 27 patients (at the baseline for diagnostic purposes), twice in 15, three times in 8, and four times in 2 patients. Thirty patients (57.7%) had associated IBD: UC in 24; CD in 5; and indeterminate colitis in one. Two patients developed a hepatobiliary malignancy during the follow-up, one a gallbladder cancer, the other a hepatocellular carcinoma. Two patients underwent liver transplantation for liver failure, and two are currently on the waiting list for LT. At the baseline, 23 patients (44.2%) had MRC scores ≤III, and 29 (55.8%) >III; 39 patients (75%) had a contrast enhancement graded as 0-1 and 13 (25%) had grades 2-3. Patients with final MRC scores ≥III had significantly higher alkaline phosphatase levels, more severe liver stiffness, a higher rate of bacterial cholangitis, and more biliary complications at the baseline than patients with final MRC scores ≤III (Table 3). After adjusting for sex and age, multivariate analysis showed that both total biliary

complications (OR 7.61, 95% CI 1.45-40.03, p=0.017) and bacterial cholangitis (OR 12.19, 95% CI 1.38-107-91, p=0.025) were independently associated with a final MRC score >III. The contrast enhancement pattern after Gd-EOB-DTPA at the baseline was graded as 0-1 in 39 patients, and as 2-3 in 13 (Table 4). This latter group showed a significantly higher AST, ALT, and AP, but no significant differences in terms of clinical complications, hepatobiliary malignancies or indications for LT. At the 2-year follow-up, a score ≥III correlated significantly with serum transaminases, □GT, and alkaline phosphatase levels. Among the 25 patients who had at least two MRC, 7 had a worsening MRC score and a significant increase in Mayo risk score (0.49 ± 0.55 vs -019 ± 0.67, p=0.009) during the follow-up.

DISCUSSION

The results of our study confirm that our MRC score based on a PSC patient's cholangiographic features and contrast enhancement pattern with Gd-EOB-DTPA can provide prognostic information on the disease's severity. Our proposed composite score is based on the presence and severity of biliary tree strictures and dilations, and on the contrast enhancement pattern in the parenchyma after administering Gd-EOB-DTPA, which specifically reveals functionally excluded areas of the liver segments. Gd-EOB-DPTA is a liver-specific magnetic resonance contrast medium transported into the hepatocytes and excreted into the bile in a much higher proportion than gadobenate dimeglumine (Gd-BOTPA) (26).

It was first registered in Sweden in 2004, which is why our study only concerns patients diagnosed with PSC after 2004. We correlated the prognostic score with the patients' biochemical profile, Mayo risk score, TE values, and clinical history over a ten-year follow-up. We found a positive correlation between an MRC score >III and higher serum alkaline phosphatase levels (median 1.63). This is consistent with the claim advanced by de Vries et al (27) that AP can be used to discriminate between PSC patients with a good versus a poor prognosis, suggesting that AP can serve as a patient stratifier, and potentially as a surrogate endpoint in clinical trials on the PSC.

Patients with a score >III also had significantly higher TE values. This result confirms the data obtained by Coperchot et al in a prospective study in 73 consecutive patients with PSC (25). They found that TE was able to differentiate severe from milder liver fibrosis with high levels of confidence in patients with PSC (25). The applicability and prognostic role of TE in PSC is currently undergoing validation by means of the International PSC Study Group Consensus Process (28). In our series, a high MRC score also correlated significantly with the occurrence of bacterial cholangitis and other biliary complications (dominant strictures, pancreatitis, and intrahepatic biliary stones). Although no statistically significant difference was found, all patients who underwent LT or were placed on the waiting list for LT had an MRC score >III.

Our 2-year follow-up analysis showed that an MRC score >III correlated significantly with high serum transaminases, GGT and AP levels, suggesting that this score has a potential role in establishing which PSC patients have a severe prognosis at the baseline and during their follow-up. A French group performed a retrospective analysis of the MRC images obtained with gadoterate dimeglumine (Gd-DOTA) contrast medium in 64 patients with PSC (16). The authors constructed an MRI progression risk score, with and without gadolinium, based on intrahepatic bile duct dilations, parenchymal dysmorphia, portal hypertension and heterogeneity of parenchymal enhancement: a cut-off MRC score of 3 and 2 (without and with gadolinium, respectively) revealed a good accuracy in predicting radiological progression. No clinical or biochemical correlations were performed, however. In our series, a non-homogeneous contrast enhancement pattern after Gd-EOB-DTPA (indicative of the presence of functionally excluded liver parenchymal segments) was found correlated with an increase in baseline liver transaminases, and an increase in transaminases and cholestatic enzymes after 2 years. No significant correlation with high parenchymal scores and biliary complications was apparent after 2 years of follow-up, however. From the comparison of data, the MRC score predicted the occurrence of clinical events, such as recurrent bacterial cholangitis and biliary complications, whereas the contrast enhancement pattern was more predictive of altered parenchymal function. In our experience, Gd-EOB-DTPA provides a good picture of the biliary tree and may add functional information on patients with PSC.

Our study has some limitations, the first of which is the lack of images relating to CCA, which is due to the low prevalence of hepatobiliary malignancies observed in our series. PSC is the main risk factor for the onset of CCA, but we identified only two cases (3.8%): one patient developed a gallbladder carcinoma, the other a hepatocellular carcinoma, which was resected when the patient reached the cirrhotic stage, and he is now on the waiting list for LT. This prevalence is lower than the 10.9% reported by the International PSC Study group (7) – though the same group has reported a 2.1% prevalence of CCA in Southern Europe. Five patients (9.6%) revealed dominant strictures on MRC, and subsequently underwent ERCP with brushing, which revealed no neoplastic cells in any of these cases, and no evidence of malignancy emerged in their follow-up either.

Another limitation of our study concerns the lack of a validation of our MRC score in another series of PSC patients. This demands further investigations in larger series of patients, using the same diagnostic protocol and the same contrast medium, which is specific for hepatocytes, and can provide information on the presence of functionally excluded liver segments. The design of our study was prospective, a point in its favor, but the fact that PSC is a rare disease means that it will be at least 4 years before we can expect to replicate our results.

In conclusion, our findings indicate that the proposed MRC score, based on cholangiographic features and the contrast enhancement pattern was seen after administering Gd-EOB-DTPA, can provide prognostic information in patients with PSC. Further studies on a larger series of patients are therefore warranted to validate the prognostic value of our MRC score.

Table 1. Score for presence and severity of intra- and extrahepatic biliary tree strictures and dilations

Intrahepatic bile ducts		Extrahepatic bile ducts	
1	no strictures + no dilations	**1**	no strictures + no dilations
2	mild strictures + no or mild dilations	**2**	mild strictures + no or mild dilations
3	severe strictures + no or mild dilations	**3**	severe strictures + no or mild dilations
4	severe strictures + marked dilations	**4**	severe strictures + marked dilations

Table 2. Final MRC score by the grade of intra- and extrahepatic biliary alterations

		Intrahepatic			
		1	**2**	**3**	**4**
Extrahepatic	**1**	I	II	III	III
	2	II	III	III	IV
	3	III	III	IV	V
	4	III	III	IV	V

Table 3. Comparison between patients with final MRC scores ≤III and >III in terms of their baseline laboratory parameters and development of clinical complications during the follow-up

	MRC score ≤III (n=23)	**MRC score >III (n=29)**	**P**
Males, n(%)	6 (26.09%)	17 (58.62%)	0.123
Association with IBD, n(%)	11 (47.83%)	20 (68.97%)	0.200
AST (xULN) mean ± SD [median]	1.41 ± 1.37 [0.98]	1.57 ± 0.77 [1.38]	0.0651
ALT (xULN) mean ± SD [median]	1.93 ± 2.45 [1.22]	2. 07 ± 1.46 [1.70]	0.0835
GGT (xULN) mean ± SD [median]	2.74 ± 2.61 [2.04]	5.02 ± 4.48 [3.56]	0.0651
AP (xULN) mean ± SD [median]	1.28 ± 0.93 [0.87]	1.87 ± 1.12 [1.63]	0.0458
Total bilirubin (mg/dl) mean ± SD [median]	0.89 ± 0.55 [0.65]	2.09 ± 4.12 [1.10]	0.1616
Albumin (g/dl) mean ± SD [median]	4.11 ± 0.36 [4.02]	4.16 ± 0.32 [4.10]	0.8332
CA 19-9 (U/ml) mean ± SD [median]	9.53 ± 8.73 [6.0]	19.07 ± 20.12 [10.4]	0.2272
Mayo risk score mean ± SD [median]	-0.73 ± 0.72 [-0.72]	-0.39 ± 0.73 [-0.38]	0.1831
Stiffness (kPa) mean ± SD [median]	11.74 ± 18.24 [5.85]	11.25 ± 6.05 [9.95]	0.0495
Recurrent bacterial cholangitis, n(%)	4 (17.39%)	13 (44.83%)	0.043
Total biliary complications, n(%)	11 (47.83%)	19 (65.52%)	0.019
Hepatobiliary malignancy, n(%)	1 (4.35%)	1 (3.45%)	1.000
Portal hypertension, n(%)	2 (8.7%)	5 (17.25%)	0.444
LT/waiting list, n(%)	0	4 (13.8%)	0.088

Table 4. Comparison at baseline between patients with parenchymal contrast enhancement patterns after Gd-EOB-DTPA administration graded as 0-1 versus 2-3

	Contrast enhancement pattern 0-1 (n=39)	Contrast enhancement pattern 2-3 (n=13)	p
Males, n(%)	23 (58.97%)	8 (61.54%)	0.8700
Association with IBD, n(%)	22 (56.41%)	8 (61,54%)	0.7460
AST (xULN) mean ± SD [median]	1.38 ± 1.14 [1.02]	1.86 ± 0.72 [2.04]	0.0129
ALT (xULN) mean ± SD [median]	1.95 ± 2.19 [1.23]	2. 17 ± 0.77 [1.94]	0.0267
GGT (xULN) mean ± SD [median]	3.87 ± 4.23 [2.32]	4.53 ± 2.95 [3.84]	0.1146
AP (xULN) mean ± SD [median]	1.41 ± 0.97 [0.99]	2.22 ± 1.16 [1.63]	0.0196
Total bilirubin (mg/dl) mean ± SD [median]	1.75 ± 3.65 [0.82]	1.08 ± 045 [1.10]	0.3866
Albumin (g/dl) mean ± SD [median]	4.16 ± 0.35 [4.07]	4.07 ± 0.29 [4.07]	0.3065
CA 19-9 (U/ml) mean ± SD [median]	18.73 ± 21.06 [11.0]	12.20 ± 10.83 [8.00]	0.4558
Mayo risk score mean ± SD [median]	-0.62 ± 0.70 [-0.61]	-0.32 ± 0.73 [-0.34]	0.1097
Stiffness (kPa) mean ± SD [median]	10.86 ± 13.10 [7.0]	12.51 ± 6.94 [11.45]	0.0965
Recurrent bacterial cholangitis, n(%)	12 (30.77%)	5 (38.46%)	0.6090
Total biliary complications, n(%)	17 (43.59%)	6 (46.15%)	0.8720
Hepatobiliary malignancy, n(%)	2 (5.13%)	0	1.000
Portal hypertension, n(%)	4 (10.26%)	3 (23.08%)	0.3470
LT/waiting list, n(%)	3 (7.69%)	1 (7.69%)	0.6960

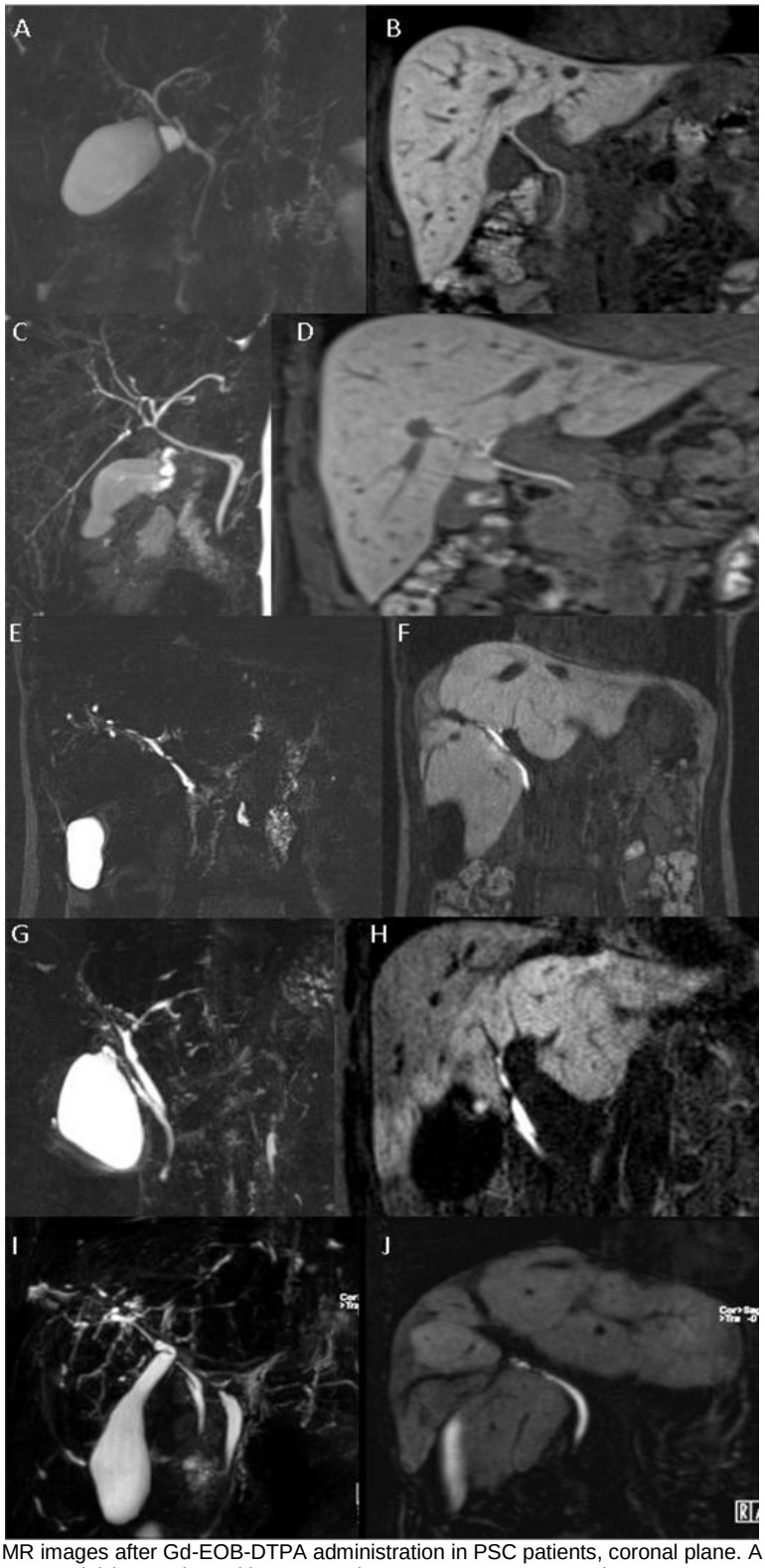

Fig. 1. Cholangiographic images and MR images after Gd-EOB-DTPA administration in PSC patients, coronal plane. A and B: normal biliary tree (A) and homogeneous contrast enhancement pattern (B) in a patient with SD-PSC (MRC score 1, contrast enhancement pattern 0). C and D: MRC images from a PSC patient with MRC score 2 (mild intrahepatic strictures without dilations and contrast enhancement pattern 0). E: diffuse and severe biliary strictures with beaded appearance; F: after Gd-EOB-DTPA administration, showing hypotrophic and functionally excluded segment on the right lobe (MRC score 6, contrast enhancement pattern 1). G and I: cholangiographic images with: severe strictures and mild dilations, both intra- and extrahepatic (MRC score 5) in the former; and severe intra- and extrahepatic strictures with severe intrahepatic and mild extrahepatic dilations (MRC score 6) in the latter; H and J, acquired after Gd-EOB-DTPA administration: non-homogeneous contrast enhancement with functional exclusion of more than 75% of liver parenchyma (grade 3).

REFERENCES

1.Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. Lancet 2013;382:1587-1599.
2.Maggs JR, Chapman RW. An update on primary sclerosing cholangitis. Curr Opin Gastroenterol 2008;24:377-383.
3.Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol 1998; 33:99-103.
4.Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. J Hepatol 2012;56:1181-1188.
5.Molodecky NA, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, Kaplan GG. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. Hepatology 2011;53:1590-1599.
6.European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009; 51:237-267.
7.Weismüller TJ, Talwalkar JA, Ponsioen CY, Gotthardt DN, Marschall HU, Naess S, et al. Primary sclerosing cholangitis from a global perspective. A multicenter, retrospective, observational study of the International PSC Study Group. J Hepatol 2014;60:S3.
8.Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, van Nieuwkerk KM, Drenth JP, Witteman BJ, Tuynman HA, Naber AH, Kingma PJ, van Buuren HR, van Hoek B, Vleggaar FP, van Geloven N, Beuers U, Ponsioen CY, Epi PSG. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013;58:2045-2055.
9.Khaderi SA, Sussman NL. Screening for malignancy in primary sclerosing cholangitis (PSC). Curr Gastroenterol Rep 2015;17:17.
10.Craig DA, MacCarty RL, Wiesner RH, Grambsch PM, LaRusso NF. Primary sclerosing cholangitis: value of cholangiography in determining the prognosis. AJR Am J Roentgenol 1991;157:959-964.
11.Majoie CB, Reeders JW, Sanders JB, Huibregtse K, Jansen PL. Primary sclerosing cholangitis: a modified classification of cholangiographic findings. AJR Am J Roentgenol 1991;157:495-497.
12.Rajaram R, Ponsioen CY, Majoie CB, Reeders JW, Lameris JS. Evaluation of a modified cholangiographic classification system for primary sclerosing cholangitis. Abdom Imaging 2001;26:43-47.
13.Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, Rajaram R, Rauws EA, Mulder CJ, Reitsma JB, Heisterkamp SH, Tytgat GN. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. Gut 2002;51:562-566.
14.Ponsioen CY, Reitsma JB, Boberg KM, Aabakken L, Rauws EA, Schrumpf E. Validation of a cholangiographic prognostic model in primary sclerosing cholangitis. Endoscopy 2010;42:742-747.
15.Dave M, Elmunzer BJ, Dwamena BA, et al. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. Radiology 2010;256:387-96.
16.Ruiz A, Lemoinne S, Carrat F, Corpechot C, Chazouilleres O, Arrive L. Radiologic course of primary sclerosing cholangitis: assessment by three-dimensional magnetic resonance cholangiography and predictive features of progression. Hepatology 2014; 59: 242-250.
17.Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of sclerosing cholangitis, detected by magnetic resonance cholangiography, in patients with long-term inflammatory bowel disease. Gastroenterology, 2016 in press
18.Ringe KI, Husarik DB, Sirlin CB, Merkle EM. Gadoxetate disodium-enhanced MRI of the liver: part 1, protocol optimization and lesion appearance in the noncirrhotic liver. AJR Am J Roentgenol 2010;195:13-28.
19.Tschirch FT, Struwe A, Petrowsky H, Kakales I, Marincek B, Weishaupt D. Contrast-enhanced MR cholangiography with Gd-EOB-DTPA in patients with liver cirrhosis: visualization of the biliary ducts in comparison with patients with normal liver parenchyma. Eur Radiol 2008;18:1577-1586.
20.Frydrychowicz A, Jedynak AR, Kelcz F, Nagle SK, Reeder SB. Gadoxetic acid-enhanced T1-weighted MR cholangiography in primary sclerosing cholangitis. J Magn Reson Imaging 2012;36:632-640.
21.Nilsson H, Blomqvist L, Douglas L, Nordell A, Jacobsson H, Hagen K, et al. Dynamic gadoxetate-enhanced MRI for the assessment of total and segmental liver function and volume in primary sclerosing cholangitis. J Magn Res Imaging 2014; 39: 879-886.
22.Hinrichs H, Hinrichs JB, Gutberlet M, Lenzen H, Raatschen H-J, Wacker F, et al. Functional gadoxetate disodium-enhanced MRI in patients with primary sclerosing cholangitis (PSC). Eur Radiol 2016; 26: 1116-1124.
23.Franceschet I, Cazzagon N, Del Ross T, D'Incà R, Buja A, Floreani A. Primary sclerosing cholangitis associated with inflammatory bowel disease: an observational study in a Southern Europe population focusing on new therapeutic options. Eur J Gastroenterol Hepatol 2016; 28: 508-513.
24.Rudolph G, Gotthardt D, Kloeters-Platchky P, Rost D, Kulaksis H, Stiehl A. In PSC with dominant bile duct stenosis, IBD is associated with an increase of carcinomas and reduced survival. J Hepatol 2010; 53: 313-317.
25.Corpechot C, Gaouar F, Naggar AE, Kemgang A, Wendum D, Poupon R, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology 2014; 146: 970-979.
26.Van Beers BE, Pastor CM, Hussain HK. Primovist-Eovist: What to expect? J Hepatol 2012; 57: 421-429.
27.De Vries EM, Wang J, Leeflang MM, Boonstra K, Weersma RK, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and one year later: evaluation of prognostic value. Liver Int 2016; DOI: 10.1111/liv.1311
28.Ponsioen CY, Chapman RW, Chazouillères O, Hischfield GM, Karlsen TH, Lohse AW, et al. Surrogate endpoints for clinical trials in primary sclerosing cholangitis: review and results from an International PSC Study Group Consensus Process. Hepatology 2016; 63: 1357-1367.