Research Article
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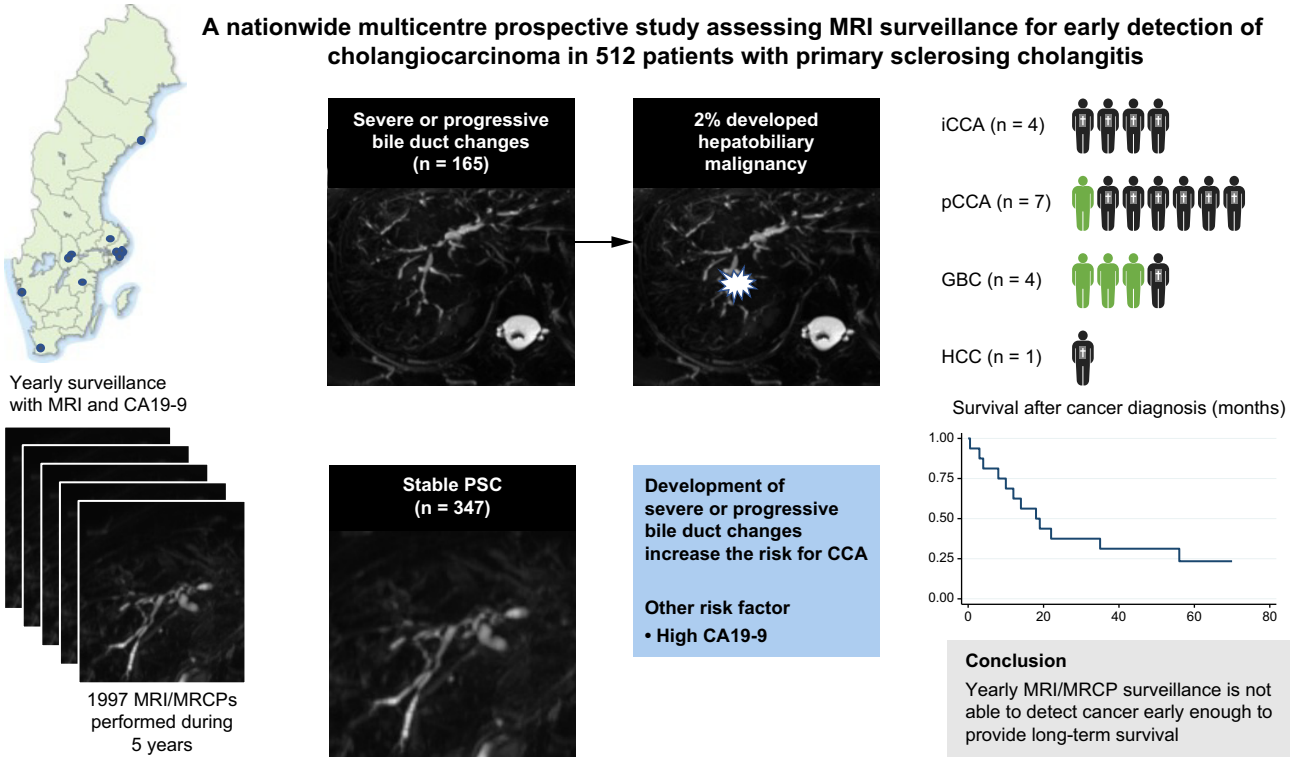
Authors

Christina Villard, Ingalill Friis-Liby, Fredrik Rorsman, …, Therese Hagström, Emma Nilsson, Annika Bergquist

Correspondence

christina.villard@ki.se (C. Villard).

Graphical abstract



Highlights

- CCA was diagnosed in 2% of patients with PSC during a 5-year follow-up.
- The risk of hepatobiliary malignancy was associated with severe biliary strictures.
- Yearly MRI cancer surveillance failed to provide long-term survival.
- Individualised strategies for early diagnosis of CCA in PSC are warranted.

Impact and implications

A prospective nationwide 5-year study was conducted to evaluate yearly cholangiocarcinoma surveillance using MRI and CA19-9 in patients with primary sclerosing cholangitis. Only 2% of the patients were diagnosed with cholangiocarcinoma during follow-up and their prognosis remained poor despite surveillance. This surveillance strategy failed to detect cancer early enough to support long-term survival. Therefore, individualised strategies and improved diagnostic methods will be required to improve the early detection of cholangiocarcinoma in patients with primary sclerosing cholangitis.

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Prospective surveillance for cholangiocarcinoma in unselected individuals with primary sclerosing cholangitis

Christina Villard[1,2,*], Ingalill Friis-Liby[3], Fredrik Rorsman[4], Karouk Said[2,5], Anna Warnqvist[6], Martin Cornillet[2], Stergios Kechagias[7], Nils Nyhlin[8], Mårten Werner[9], Izabella Janczewska[10], Therese Hagström[11], Emma Nilsson[12], Annika Bergquist[2,5]

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Background & Aims: The evidence for hepatobiliary tumour surveillance in patients with primary sclerosing cholangitis (PSC) is scarce. In this study, we aimed to prospectively evaluate cholangiocarcinoma (CCA) surveillance with yearly MRI with cholangiopancreatography (MRI/MRCP) in a nationwide cohort.

Methods: In total, 512 patients with PSC from 11 Swedish hospitals were recruited. The study protocol included yearly clinical follow-ups, liver function tests and contrast-enhanced MRI/MRCP and carbohydrate antigen (CA) 19-9. Patients with severe/progressive bile duct changes on MRI/MRCP were further investigated with endoscopic retrograde cholangiopancreatography. Patients were followed for 5 years or until a diagnosis of CCA, liver transplantation (LT) and/or death. Risk factors associated with CCA were analysed with Cox regression.

Results: Eleven patients (2%) were diagnosed with CCA, and two (0.5%) with high-grade bile duct dysplasia. Severe/progressive bile duct changes on MRI/MRCP were detected in 122 patients (24%), of whom 10% had an underlying malignancy. The primary indication for LT (n = 54) was biliary dysplasia in nine patients (17%) and end-stage liver disease in 45 patients (83%), of whom three patients (7%) had unexpected malignancy in the explants. The median survival for patients with CCA was 13 months (3-22 months). Time to diagnosis of high-grade dysplasia and/or hepatobiliary malignancy was significantly associated with severe/progressive bile duct changes on MRI/MRCP (hazard ratio 10.50; 95% CI 2.49-44.31) and increased levels of CA19-9 (hazard ratio 1.00; 95% CI 1.00-1.01).

Conclusion: In an unselected cohort of patients with PSC, yearly CA19-9 and MRI/MRCP surveillance followed by ERCP was ineffective in detecting cancer early enough to support long-term survival. Given the low occurrence of CCA, studies on individualised strategies for follow-up and improved diagnostic methods for PSC-related CCA are warranted.

Introduction

Cholangiocarcinoma (CCA) is the most frequently occurring malignancy in patients with primary sclerosing cholangitis (PSC), with a reported lifetime prevalence ranging from 6-13%.[1–4] The incidence of CCA in patients with PSC is at its highest in the first year after PSC diagnosis, followed by a yearly incidence rate of 0.5-1.5%.[1,2] Radical liver resection or liver transplantation (LT) are the potentially curative therapeutic options for CCA in patients with PSC in the absence of metastatic or locally advanced disease.[5,6]

The potential survival benefit of early cancer detection has warranted CCA surveillance in patients with PSC, but there is at present limited evidence of its efficacy.[7] Recently, a retrospective report from a tertiary centre described a survival benefit in patients previously exposed to regular surveillance and in another population-based registry study, annual imaging was associated with a two-fold risk reduction of hepatobiliary cancer-related death.[8,9] Prospective studies are lacking. Proposed surveillance strategies include imaging by ultrasound or MRI with magnetic resonance cholangiopancreatography (MRI/MRCP), with or without contrast and/or regular measurements of serum carbohydrate antigen 19-9 (CA19-9).[7,10,11] The clinical practice of current surveillance programmes varies considerably across centres.[12]

MRI/MRCP performs well in diagnosing mass lesions but is less accurate in the presence of multiple strictures.[13] Tissue sampling via endoscopic retrograde cholangiopancreatography (ERCP) improves the identification of malignant strictures but is limited by poor sensitivity and invasiveness.[14–17] Ultrasound is less expensive and often more attainable, although its diagnostic performance to detect early-stage CCA is inferior to that of MRI.[18,19] The tumour biomarker CA19-9 has limited

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* Corresponding author. Address: Department of Transplantation, F82 Karolinska University Hospital, 141 57 Huddinge, Stockholm, Sweden. Tel.: +46 704930750.
E-mail address: christina.villard@ki.se (C. Villard).
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value but can be used as a diagnostic marker when CCA is suspected on imaging.[11,18]

This study aimed to prospectively evaluate a surveillance programme with yearly MRI/MRCP and analysis of CA19-9 for early detection of CCA in an unselected PSC population.

Materials and methods

Participants and settings

A prospective cohort study was conducted on 512 consecutive patients with PSC under treatment at 11 Swedish hospitals (Table S1). Patients were enrolled between 1st November 2011 and 1st April 2016 in a 5-year surveillance programme, which included yearly contrast-enhanced MRI/MRCP, clinical examinations, liver function tests and analysis of the tumour marker CA19-9. Inclusion criteria were a diagnosis of PSC, based on cholestatic liver biochemistry with typical cholangiographic features on MRCP and/or a liver biopsy,[20] age older than 18 years and an MRI/MRCP at baseline. Exclusion criteria were expected listing for LT within 1 year after inclusion, previous LT and the presence of a hepatobiliary malignancy. Small-duct PSC and features of autoimmune hepatitis (AIH) were not considered reasons for exclusion if all other conditions were fulfilled. Diagnosis of cirrhosis at the time of inclusion was based on previous histology or clinical/radiological features of portal hypertension.

At the time of inclusion, data on age, sex, comorbidities, previous medical history, inflammatory bowel disease (IBD), medications, liver function tests, CA19-9 and data from a baseline MRI/MRCP were collected. IBD was defined according to the treating physician using accepted diagnostic criteria.[21] To exclude viral hepatitis all patients were screened for hepatitis B and C. Data were registered by the treating physician in an electronic clinical report form (supplementary CTAT table). At yearly follow-ups, clinical data including symptoms, medication, endoscopic interventions, and results of MRI/MRCPs were registered. Yearly blood sample collections included liver function tests and CA19-9. The patients were followed for 5 years or at the latest to the 1st November 2020. All patients with hepatobiliary malignancy were followed until the 1st November 2020. After study completion, the participating patients were continuously followed with yearly MRI/MRCP and liver function tests as part of the clinical routine.

Imaging

The study protocol specified that MRI should be performed with liver-specific contrast gadoxetic acid (Primovist®) and include MRCP (Table S2). MRI/MRCP was used instead of annual ultrasound.[22] The MRI/MRCPs were evaluated by the local radiologists describing the number, location, and severity of biliary strictures, and if present, mass lesions. The radiologist described the severity of biliary strictures according to the existing standards of the time.[22,23] Tight strictures, in which an underlying malignancy could not be excluded, or progression with increased stricturing with pre-stenotic dilatation were considered severe/progressive bile duct changes (Fig. S1). The results of the radiology report were interpreted and evaluated by the treating hepatologist, categorising the radiology report as either benign with stable disease or with severe/progressive bile duct changes defined as the presence of severe stricturing, progression of stricturing and/or lesions raising concern of underlying malignancy. Ultrasound examination was performed to complement the MRI/MRCP if a suspected wall thickening of the gallbladder was detected or if the gallbladder could not be visualized properly, at the physician's discretion. In case of an MRI/MRCP with severe/progressive bile duct changes, the patient was managed through a predefined study management algorithm presented in Fig. S2, which included consideration of tumour diagnostics with ERCP, with brush cytology as the first step. Referral to an experienced centre (*i.e.*, the closest university hospital) was encouraged when an ERCP was indicated. Fluorescent *in situ* hybridisation (FISH) was used, as part of the clinical routine, mainly in biliary brush samples with equivocal cytology results.[24,25] Cytology results were classified as benign, atypic, dysplastic or cancerous and FISH results were categorised into positive and negative. Data on the ERCP procedures were reported in patients with severe or progressive bile duct changes by the treating physician. In addition, data on ERCP procedures in all patients were collected from the nationwide and well-validated Swedish Registry of Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (GallRiks).[26] Indications for LT were end-stage liver disease or perihilar high-grade dysplasia (pHGD). Patients with suspected or confirmed CCA were evaluated at a regional multidisciplinary team conference, in which liver resection or LT, with or without neoadjuvant chemoradiotherapy, was considered in patients eligible for curative treatment and palliative chemotherapy was considered for unresectable cases, according to current guidelines.[5,6] Liver resection including resection of four or more liver segments was considered major liver resection.[27]

Statistical analysis

Descriptive information at baseline for the whole cohort is presented as median (IQR) for continuous variables and n (%) for categorical variables. A descriptive comparison between patients with and without hepatobiliary malignancy was performed using an independent *t* test for comparisons of normally distributed data and the Mann-Whitney *U* test for data that failed the normality test. The Chi-square test and Fischer's exact test were used for categorical variables. Patients were followed from inclusion until completion of the study, *i.e.*, 5 years, date of death, or 1st of November 2020, whichever came first. Survival and cumulative incidence were estimated using the Kaplan-Meier product-limit method. Cox proportional hazards regression analysis was used to determine factors, included in the surveillance programme, associated with time to the diagnosis of hepatobiliary malignancy and/or HGD. Clinicopathological characteristics of patients with PSC underwent a backward stepwise regression analysis. All baseline variables were initially analysed in a univariate regression analysis. Any variable with a p value <0.1 was included in a multivariable regression model. The MRI/MRCPs were treated as time-varying in the Cox regression analysis, allowing several observational periods per patient. The result from each surveillance visit was a predictive factor for outcome during that year, *e.g.* until the next visit or outcome, whichever came first. Clustered robust standard errors were used to adjust for the intra-person correlation caused by having several observed time intervals per participant. The hazard ratio (HR) for being

diagnosed with CCA after the event of an MRI/MRCP with severe/progressive bile duct changes *vs.* no severe/progressive bile duct changes was assessed by the illness-death model. The model was estimated using parametric Weibull proportional hazards regression.

Fluctuations of CA19-9 were assessed using a mixed model with person-specific random intercept. Each timepoint was treated as a separate row, allowing all information to be included in the model. Statistical significance was assumed for p values <0.05. Statistical analysis was performed using STATA 17.

The regional Ethics Committee in Stockholm approved the study (Dnr 2011/824-31/2), clinicaltrials.gov NCT03041662. All patients included provided written informed consent. Due to the nature of this research, participants in this study did not agree for their data to be shared publicly, so supporting data is not available.

Results

Study cohort

Out of 512 patients included, 345 patients (68%) were males and the median age at time of inclusion was 38 years (IQR 19 years). Four hundred and twenty-two patients (82%) had IBD, 322 patients (76%) had ulcerative colitis and 75 patients (17%) had Crohn's disease. The median duration of PSC and IBD at time of inclusion was 7 years (IQR 11 years) and 15 years (IQR 16 years), respectively. Thirty-two patients (6%) had small duct PSC and 57 patients (11%) had PSC with features of AIH. At baseline MRI/MRCP, 59 patients (12%) had cirrhosis and 43 patients (8%) had an MRI/MRCP with severe/progressive bile duct changes. None of the 43 patients with severe/progressive bile duct changes at baseline MRI/MRCP had small duct PSC or PSC with features of AIH. Clinical characteristics of the study population are provided in Table 1.

Table 1. Baseline clinical characteristics of patients with PSC.

	Patients with PSC, N = 512
Male sex	345 (67)
Age	38 [19]
BMI	24 [4]
PSC	
Small duct PSC	32 (6)
Features of AIH	57 (11)
Duration of PSC	7 [11]
PSC <1 years	35 (7)
PSC 1-5 years	164 (32)
PSC 6-10 years	118 (23)
PSC >11 years	194 (38)
Cirrhosis	59 (12)
Ascites	4 (1)
Treatment for bacterial cholangitis in the last 12 months	33 (6)
ERCP in the last 12 months	25 (5)
History of variceal bleeding	6 (1)
History of encephalopathy	3 (.5)
MRI/MRCP with severe/progressive bile duct changes	43 (8)
IBD	422 (82)
Ulcerative colitis	322 (63)
Mb Crohn	75 (15)
Duration of IBD (years)	15 [16]
Previous colectomy	79 (15)
Medications	
Ursodeoxycholic acid	326 (64)
5-aminosalicylic acid	344 (67)

Data presented in median [interquartile range, IQR] for continuous variables and frequency (%) for categorical variables.
AIH, autoimmune hepatitis; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

Adherence to surveillance study programme

Data on the causes for non-adherence was not systematically collected. The reasons for not completing the 5-year surveillance programme were patients' moving (n = 17), study closure before the fifth year of surveillance was completed (n = 14), pregnancy (n = 3), repeated colon surgery interfering with the MRI/MRCPs (n = 2) and other medical conditions (n = 1). In addition, MRI/MRCPs were delayed for various reasons such as re-scheduling due to patients' wishes and, later in the study, due to the COVID-19 pandemic. Altogether, 1,997 MRI/MRCPs were performed during the 5-year follow-up, out of which 1,786 MRIs (89%) were performed with liver-specific contrast (gadoxetic acid) including MRCP, according to the study protocol. In some centres there was a deviation from the protocol and 184 MRIs (9%) were performed without contrast and 27 examinations (1%) were performed with extracellular contrast.

Newly diagnosed PSC

Thirty-five patients (7%) were diagnosed with PSC less than a year before the time of inclusion. The median age of patients with newly-diagnosed PSC was 40 years. Twenty-three patients (66%) were men and 28 patients (80%) had IBD. None of the newly-diagnosed patients had small duct PSC and three patients (9%) had PSC with features of AIH. Two out of five patients with newly-diagnosed PSC, who presented with severe/progressive bile duct changes at the baseline MRI/MRCP, were diagnosed with perihilar CCA (pCCA).

Hepatobiliary malignancy during follow-up

During the 5-year study period, 11 patients (2%) were diagnosed with CCA, of whom four were diagnosed with intrahepatic CCA (iCCA) and seven with pCCA. In addition, pHGD was detected in two patients. Four patients (0.5%) were diagnosed with gallbladder carcinoma (GBC), one with HGD in the gallbladder and one with hepatocellular carcinoma (HCC). The diagnosis of CCA was verified by either a tumour biopsy and/or by the pathology report from either liver resection or LT describing adenocarcinoma originating from cholangiocytes. The cumulative incidence of hepatobiliary malignancies in the cohort is shown in Fig. 1A.

Seven patients were diagnosed with pCCA at a mean time of 20 months from inclusion. All but one patient were symptomatic at the time of cancer diagnosis (Table 2). Three patients had metastatic disease at the time of diagnosis and in four patients the cancer diagnosis was an unexpected finding at the time of LT (Table 2). One patient with pCCA underwent LT according to the Mayo protocol.[28] All but one patient with pCCA suffered recurrence and died within 5 years (Table 2). Survival following a diagnosis of hepatobiliary malignancy is illustrated in Fig. 1B,C. Four patients were diagnosed with iCCA at a mean time of 33 months from inclusion. All four patients

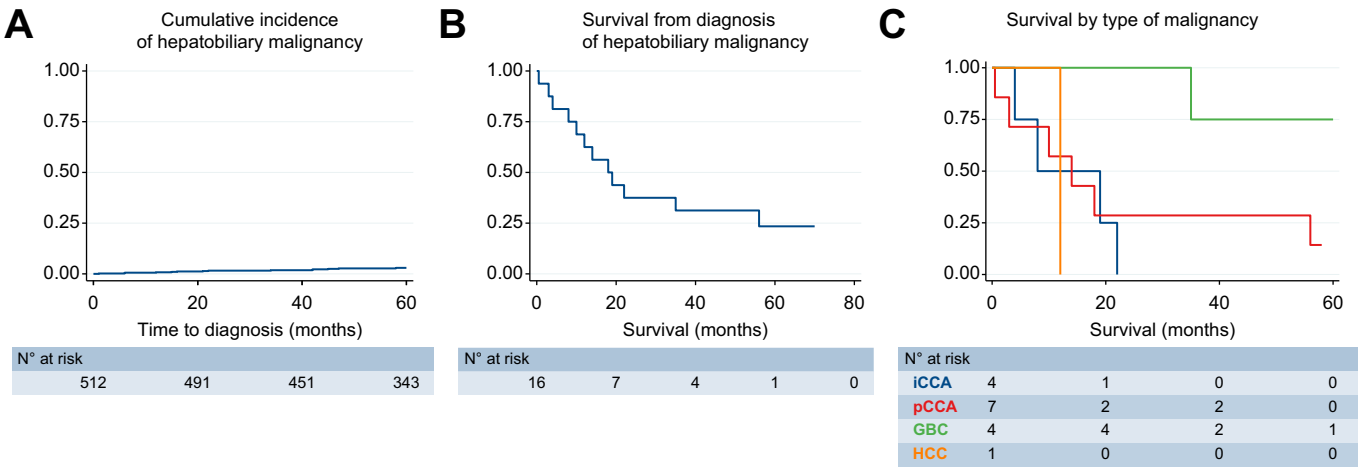

Fig. 1. Cumulative incidence of hepatobiliary malignancy and related death during study. (A) Cumulative incidence of hepatobiliary malignancy during the 5-year follow-up (the Kaplan-Meier product-limit method). (B) Hepatobiliary malignancy-related death during the study period (the Kaplan-Meier product-limit method). (C) Survival in months following diagnosis of iCCA, pCCA, GBC and HCC, $p = 132$ (the Kaplan-Meier product-limit method). GBC, gallbladder cancer; HCC, hepatocellular carcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma. (This figure appears in color on the web.)

with iCCA were symptomatic at the time of cancer diagnosis and three out of four patients were diagnosed with locally advanced/metastasised disease (Table 3). GBC was diagnosed in four patients at a mean time of 31 months from inclusion. Three of them (75%) were asymptomatic at diagnosis (Table 4). None of the patients with GBC undergoing cholecystectomy with or without liver resection suffered from tumour recurrence and all patients were alive at the end of the study (Table 4, Fig. 1C).

None of the patients with small duct PSC was later diagnosed with CCA, whereas two patients with PSC with features of AIH were diagnosed with hepatobiliary malignancy during the study period, one with iCCA and one with GBC. Baseline characteristics of patients with and without hepatobiliary malignancies were similar, with the exceptions of previously treated cholangitis, endoscopic interventions, and severe/progressive bile duct changes on MRI/MRCP, which were more prevalent in patients with hepatobiliary malignancies (Table S3).

Levels of CA19-9

Four patients diagnosed with pCCA (67%) and three with iCCA (75%) had increased CA19-9 levels of >100 kilounits per litre (kU/L), reference level, <35 kU/L (Tables 2 and 3). The inter-patient variability of repeated CA19-9 measurements during surveillance in all patients is illustrated in Fig. 2A. The levels of CA19-9 were quite stable throughout the study period in benign PSC, whereas for patients diagnosed with CCA the levels fluctuated markedly prior to the cancer diagnosis. The CA19-9 levels taken during surveillance correlated significantly with the presence of severe/progressive bile duct changes on MRI/MRCP (odds ratio 1.00; 95% CI 1.00-1.01; p <0.001). In patients with severe/progressive bile duct changes, the inter-patient variability of repeated CA19-9 measurements during surveillance overlapped between patients with benign disease and those who were later diagnosed with CCA/GBC (Fig. 2B). None of the patients without severe/progressive bile duct changes had levels of CA19-9 >100 kU/L. Eighty-five patients (24%) without severe/progressive bile duct changes had levels of CA19-9 greater than the reference level (35 kU/L) on at least one occasion. The levels of CA19-9 at time of diagnosis of CCA are presented in Tables 2 and 3.

Severe/progressive bile duct changes at MRI/MRCP

Altogether, 1,997 MRI/MRCPs were performed during the 5-year follow-up. One hundred and twenty-two patients (24%) developed severe/progressive bile duct changes on MRI/MRCP, in addition to the 43 patients presenting with such changes at inclusion. Out of the 43 patients that presented with severe/progressive bile duct changes at baseline MRI/MRCP, six patients were later diagnosed with CCA and/or GBC. The cumulative incidence of CCA and/or GBC in patients with and without severe/progressive bile duct changes at inclusion is presented in Fig. 3A. The positive predictive value for CCA in the event of an MRI/MRCP with severe/progressive bile duct changes was 10% (95% CI 7-13%) and the negative predictive value was 99% (95% CI 98-100%). The HR of being diagnosed with CCA in the event of an MRI/MRCP with severe/progressive biliary strictures during the study was 3.44 (95% CI 0.42-28.15), $p = 0.248$, Fig. 3B.

ERCP during follow-up; outcome and complications

As a consequence of MRI/MRCP findings, 91 patients (75%) underwent 168 ERCPs during follow-up. The most common reasons for not performing an ERCP following an MRI/MRCP with severe/progressive biliary duct changes were either that the patients had undergone a recent ERCP or that the strictures on MRI/MRCP were considered stable and previously investigated with ERCP. Altogether, 427 ERCPs in 153 patients were performed during the study period, registered in the national registry GallRiks. Forty-five patients had one ERCP, 41 patients two ERCPs, 23 patients three ERCPs and 40 patients four or more ERCPs. Data on findings, sampling, and complications after ERCP reported in GallRiks are summarized in Table S4. Complications after ERCP occurred in 57 procedures (13%). The most common postoperative complications were pancreatitis (8%) and cholangitis (4%). Brush cytology was performed

Table 2. Clinicopathological characteristics of patients with pHGD and pCCA.

Pt #	Type of lesion	Age	Years with PSC	Symptoms	Mode of diagnosis	ERCP	CA19-9*	Surgical treatment	Tumour size (cm)	Chemotherapy	Recurrence	Survival, months after dx**
1	pHGD	34	10	None	MRI/MRCP	Atypia + pos. FISH	3	LT	—	No	No	Alive-103
2	pHGD	72	32	None	MRI/MRCP	Dysplasia + pos. FISH		Liver resection	—	No	No	Alive-22
3	pCCA	45	7	Fatigue	HGD detected in explant	Atypia + neg. FISH	5	LT	—	No	Yes	14
4	pCCA	44	1	Cholangitis	MRI/MRCP	Dysplasia + neg. FISH	140	LT	2.0	Mayo protocol	Yes	54
5	pCCA	33	15	Jaundice	CT + ERCP	Malignant	471	None	3.0+2.0+1.0	Best supportive care	—	0
6	pCCA	51	11	Cholangitis	Malignancy detected in explant	Benign	—	LT	1.8x1.2	No	No	Alive-58
7	pCCA	66	16	None	MRI/MRCP	Dysplasia + neg. FISH	245	Major resection	2.2x1.7	No	Yes	10
8	pCCA	31	13	Weight loss	Metastasised malignancy detected at LT	Benign	1,916	Explorative laparotomy		Best supportive care	—	3
9	pCCA + intrahepatic spread	58	2	Jaundice/weight loss	Malignancy detected at LT	Benign	5	LT	0.7	No	Yes	13

CA19-9, carbohydrate antigen 19-9; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence *in situ* hybridisation; LT, liver transplantation; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; pCCA, perihilar CCA; pHGD, perihilar high-grade dysplasia.

*At time of tumour diagnosis.

**Extended follow-up until 1st November 2020.

Table 3. Clinicopathological characteristics of patients with iCCA.

Pt #	Type of lesion	Age	Years with PSC	Symptoms	Mode of diagnosis	ERCP	CA19-9*	Surgical treatment	Tumour size (cm)	Chemotherapy	Recurrence	Survival, months after dx**
1	iCCA	57	26	Jaundice	MRI/MRCP	—	98	None	4.0	Palliative (FOLFOX/Panit)	—	22
2	iCCA	74	36	Weight loss	MRI/MRCP	Benign	8,970	Major resection	6.0x6.0+1.8x2.0 +0.4x0.4	Adjuvant (gemzar)	Yes	19
3	iCCA	42	15	Jaundice	MRI/MRCP	—	426	None	5.5x6.0	Palliative (gemzar/oxaliplatin)	—	8
4	iCCA	34	10	Abdominal pain	CT	—	515	None	5.5	Palliative (gemzar/cisplatin)	—	4

CA19-9, carbohydrate antigen 19-9; ERCP, endoscopic retrograde cholangiopancreatography; iCCA, intrahepatic cholangiocarcinoma; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

*At time of tumour diagnosis.

**Extended follow-up until 1st November 2020.

in 70% (298/427). Data on FISH were not available for all ERCPs. Brush samples were taken in 94% (162/168) of the performed ERCPs following an MRI/MRCP with severe/progressive bile duct changes and FISH results were available in 76% (129/168). All patients diagnosed with pCCA underwent ERCP prior to cancer diagnosis.

Risk factors associated with hepatobiliary malignancy and high-grade dysplasia

In a multivariable regression analysis, time to diagnosis of hepatobiliary malignancy and HGD during surveillance were significantly associated with severe/progressive bile duct changes on MRI/MRCP (HR 10.50; 95% CI 2.49-44.31) and levels of CA19-9 (HR 1.00; 95% CI 1.00-1.01) (Table 5).

Liver transplantation during follow-up

Fifty-four patients (11%) underwent LT during the 5-year follow-up. The primary indication for LT was end-stage liver disease in 83% (n = 45) and biliary dysplasia in 17% (n = 9). One patient had confirmed pCCA, by brush cytology, and received treatment according to the Mayo protocol.[28] In 78% (7/9) of the patients transplanted primarily due to biliary dysplasia, the pathology report described fibrosis/cirrhosis without malignancy. In addition, CCA/GBC was unexpectedly found in the explants of three patients primarily transplanted for end-stage liver disease.

Mortality during follow-up

Twenty-five patients died during the 5-year follow-up. Biliary tract malignancy was the cause of death in eight of the 25 patients (32%). The only patient with pCCA alive at the end of the study (1st November 2020) at 58 months, was a patient in whom the CCA was an unexpected finding in the explant (Table 2). Other causes of death were metastatic colorectal cancer (n = 2), ovarian cancer (n = 3), liver failure following LT (n = 1), septicaemia (n = 2), complications due to end-stage liver disease (n = 1), stroke (n = 1), heart failure (n = 2) and unknown cause (n = 5).

Discussion

In this prospective observational cohort study of 512 unselected patients with PSC, followed in a 5-year surveillance programme with MRI/MRCP, 2% were diagnosed with CCA. Although 62% of the patients with CCA were eligible for treatment with curative intent (LT or surgical resection) all but one patient suffered from tumour recurrence and died during the 5-year follow-up. The results suggest that a surveillance strategy with yearly CA19-9 and MRI/MRCP followed by diagnostic ERCP in the event of severe/progressive bile duct changes fails to detect CCA early enough for long-term survival in an unselected cohort of patients with PSC.

Previous studies report a survival benefit in patients under surveillance for PSC-associated hepatobiliary malignancies. One population-based registry study reported that annual imaging was associated with a two-fold risk reduction of hepatobiliary cancer-related death.[8] Another retrospective study from a tertiary care centre showed that patients with PSC developing hepatobiliary malignancies

Table 4. Clinicopathological characteristics of patients with HGD in the gallbladder, GBC and HCC.

Pt #	Type of lesion	Age	Years with PSC	Symptoms	Mode of diagnosis	ERCP	CA19-9*	Surgical treatment	Tumour size (cm)	Chemo therapy	Recurrence	Survival, months after dx**
1	HGD gallbladder	70	19	None	MRI/MRCP	–	3	Minor resection	1.5	No	No	Alive-70
2	GBC	45	7	None	MRI/MRCP	–	1	Minor resection	2.5x1.5	No	No	Alive-70
3	GBC	42	9	None	Malignancy detected in explant	Benign		LT	7.0	No	Yes	35
4	GBC	52	11	None	MRI/MRCP	Benign	–	Minor resection	1.2x0.6	Adjuvant	No	Alive-58
5	GBC	71	7	Jaundice	MRI/MRCP	–	–	Chole cystectomy	–	No	No	Alive-39
6	HCC	51	19	None	MRI/MRCP	–	42	Ablation	2.5 +1.0	No	Yes	12

CA19-9, carbohydrate antigen 19-9; ERCP, endoscopic retrograde cholangiopancreatography; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; HGD, high-grade dysplasia; LT, liver transplantation; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.
*At time of tumour diagnosis.
**Extended follow-up until 1st November 2020.

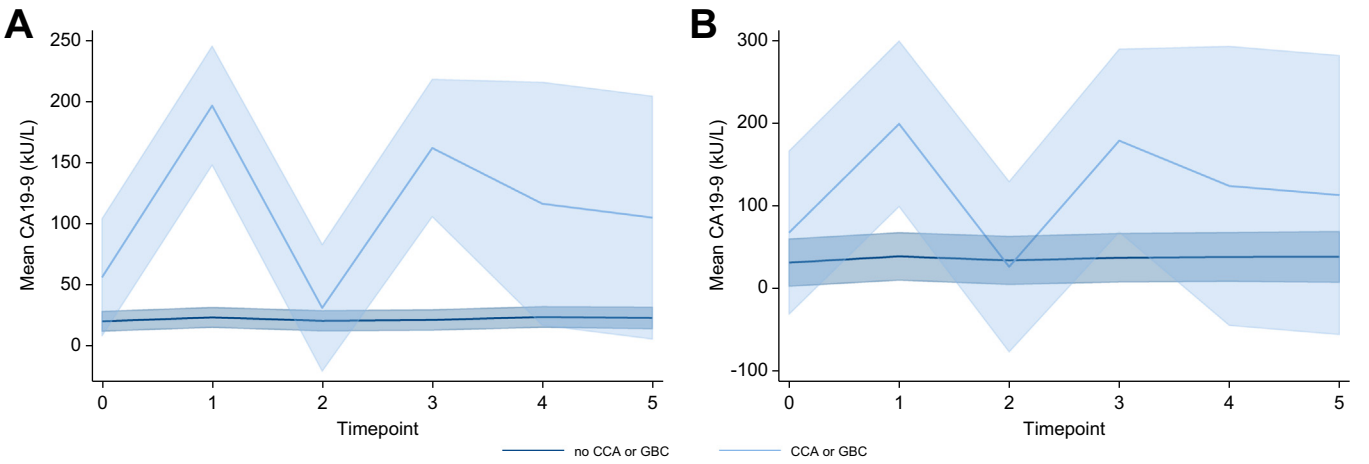

Fig. 2. Fluctuations in yearly measurements of CA19-9 levels. (A) Fluctuations in yearly measurements of CA19-9 levels, mean (95% CI), during 5-year surveillance in patients with and without later diagnosis of CCA or GBC, p <0.001 (the mixed model). (B) Fluctuations in yearly measurements of CA19-9 levels, mean (95% CI), during 5-year surveillance in patients with severe/progressive bile duct changes with and without a later diagnosis of CCA or GBC p = 0.737, (the mixed model). CA19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; GBC, gallbladder cancer.

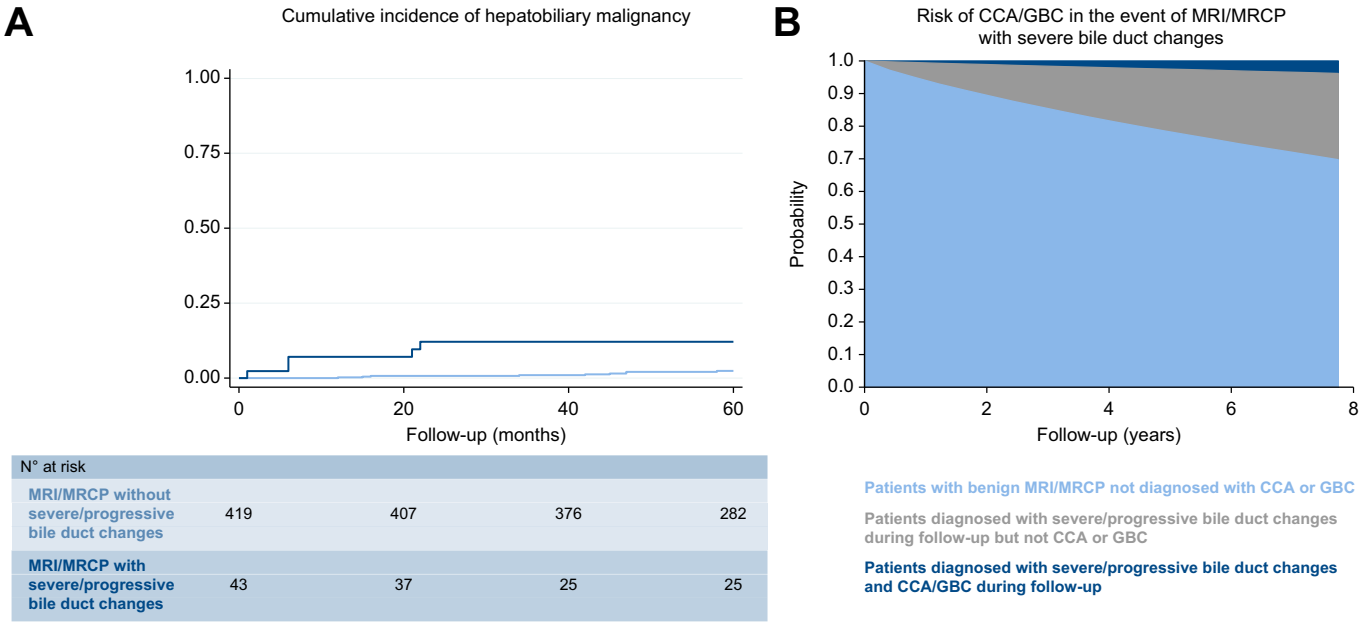

Fig. 3. Incidence and risk of CCA or GBC. (A) Cumulative incidence of CCA or GBC in patients with and without severe bile duct changes at baseline MRI/MRCP, p <0.001 (the Kaplan-Meier product-limit method). (B) Risk of CCA/GBC diagnosis in the event of severe bile duct changes on MRI/MRCP during follow-up, p = 0.248 (the illness-death model). CCA, cholangiocarcinoma; GBC, gallbladder cancer; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography.

had a survival benefit if surveillance had been performed.[9] The latter study showed only a trend and no significant survival benefit in the subgroup of patients with extrahepatic or intrahepatic CCA. This is in line with the data presented here, where only one patient with CCA survived the 5-year follow-up. In this study, long-term survival was observed in patients with GBC and HGD. Whether the presented surveillance programme had an impact on survival is unknown and not possible to determine. The reported survival benefit associated with annual imaging surveillance could potentially be ascribed to lead-time bias and the potential benefit of surveillance still remains unclear.[8,9]

The characterisation of new or progressive biliary strictures found at MRI/MRCP is important, as they might indicate an underlying CCA.[29,30] In this study, severe bile duct changes raising concern of a potential underlying malignancy, had a very low positive predictive value and only a minority of patients with these suspicious strictures had an underlying CCA. The cost-effectiveness of an MRI/MRCP-based surveillance programme can therefore be questioned. Nearly 2,000 MRI/MRCPs were performed during the study and only one patient with CCA (diagnosed unexpectedly after LT) showed long-term survival without recurrence. Altogether these are disappointing results, suggesting that a surveillance strategy with MRI/MRCP

Table 5. Features associated with diagnosis of CCA, GBC, HCC and HGD during 5-year surveillance, assessed by cox proportional hazards regression (cox regression analysis).

	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Male sex	1.21 (0.44-3.34)	0.719		
Age	1.04 (1.00-1.07)	**0.013**	1.03 (0.93-1.13)	0.575
BMI	0.98 (0.86-1.09)	0.582		
Severity of liver disease				
Small duct PSC	#			
PSC with autoimmune features	0.98 (0.22-4.29)	0.974		
Duration of PSC	1.03 (0.98-1.09)	0.277		
Ascites	5.61 (0.70-45.28)	0.105		
Treatment of cholangitis	3.93 (1.14-13.60)	**0.031**	2.70 (0.31-22.59)	0.369
Jaundice intervention	1.98 (0.25-15.50)	0.513		
MRI/MRCP with severe/progressive bile duct changes	14.85 (5.52-39.91)	**<0 .001**	10.50 (2.49-44.31)	**0.001**
Inflammatory bowel disease				
Diagnosis of IBD	3.49 (0.46-26.70)	0.228		
Duration of IBD	1.05 (1.02-1.09)	**0.006**	1.04 (0.95-1.14)	0.433
Medications				
Ursodeoxycholic acid*	1.25 (0.44-3.51)	0.676		
5-aminosalicylic acid*	0.72 (0.27-1.95)	0.519		
Tumor marker				
Carbohydrate antigen 19-9	1.00 (1.00-1.01)	**<0.001**	1.00 (1.00-1.01)	**0.022**
Liver function tests				
Bilirubin	1.01 (1.00-1.03)	0.077	0.99 (0.96-1.02)	0.435
Alkaline phosphatase	1.11 (1.00-1.24)	0.068	1.07 (0.90-1.27)	0.421
Aspartate aminotransferase	1.02 (0.98-1.05)	0.288		
Alanine aminotransferase	1.02 (0.98-1.05)	0.310		
Albumin	0.88 (0.81-0.96	**0.004**	1.01 (0.89-1.15)	0.858
International normalized ratio	1.46 (0.40-5.40)	0.569		
Thrombocytes	1.00 (0.99-1.01)	0.931		
Immunoglobulin total*	1.02 (0.94-1.11)	0.639		
Immunoglobulin G4*	1.16 (0.53-2.52)	0.716		
Immunoglobulin A*	1.00 (0.98-1.02)	0.701		

Values in bold denote significance.

GBC, gallbladder cancer; HCC, hepatocellular carcinoma; HGD, high-grade dysplasia; HR, hazard ratio; IBD, inflammatory bowel disease; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

*At inclusion.

#Not measured due to limited number of events in the group.

followed by ERCP in unselected patients with PSC fails to reach the main goal of surveillance, *i.e.* early detection of malignancy to enable cure.

Elevated levels of CA19-9 were found, as expected, in patients with CCA and patients without CCA with severe bile duct changes. High levels of CA19-9 were associated with a cancer diagnosis in line with previous studies.[31] Elevated CA19-9 levels, in the absence of bacterial cholangitis, strengthen tumour suspicion but as known from longitudinal series, measurements of CA19-9 are of limited value to predict CCA.[32,33] In this study, the interpatient variability of repeated CA19-9 measurements in patients with severe/progressive bile duct changes, with and without a later cancer diagnosis, overlapped and the results of this study are in line with previous reports and do not support measurements of CA19-9 levels as a screening tool.[32,33]

Treatment options for advanced CCA are scarce.[1,5,6] The curative treatment options for CCA in patients with PSC include LT according to the Mayo protocol and liver resection with adjuvant chemotherapy.[6,28,34] Some centres recommend LT in patients with PSC and pHGD.[35,36] The complication and recurrence rate after a LT is high in patients with PSC and the potential risks should be weighed against the potential for cure.[37] In this study, CCA and/or HGD were confirmed in only 22% (2/9) of patients treated with LT due to suspicion of premalignancy. The high frequency of patients undergoing LT with benign explant pathology reports and four accidentally detected malignancies at time of LT, indeed illustrate the difficulty in determining the indication for LT and its timing in patients with PSC and biliary dysplasia. Before the diagnostics of early-stage CCA have improved, LT solely on the indication of biliary dysplasia remains controversial.

In light of our findings, screening for early tumour detection in all patients with PSC can be questioned. Proposed surveillance strategies include imaging by ultrasound or MRI/MRCP and regular measurements of CA19-9.[7,10,11] Evidence to support one surveillance strategy over another is lacking. Although the numbers were small, the only group of patients with a favourable outcome in this study were those with GBC. These tumours could just as well, or perhaps preferably, have been detected with ultrasound. MRI/MRCP is the best modality for CCA diagnosis but seems not specific enough in the presence of multiple strictures[13,18,19] and no study so far has shown survival benefits with surveillance for pCCA or iCCA. High quality MRI/MRCP may be recommended in patients at the initial diagnosis of PSC, when new symptoms occur, and more regularly in patients with advanced disease with time intervals that remain to be decided.[3] The psychological effect of regular cancer surveillance should also be considered and should not be underestimated. Unfortunately, we did not collect patient-reported data and we can therefore not evaluate the potential

distress associated with the anticipation of an MRI/MRCP result. Studies on the psychological effects of CCA surveillance are warranted.

The strengths of this study are its prospective nature and the unselected group of patients with PSC, representing the heterogeneity of the disease. However, there are many limitations, the major being the limited sample size. The low incidence of hepatobiliary malignancy, and a relatively short follow-up limit the analyses. In addition, data was dependent on evaluations of several physicians, and there was not complete adherence to the study protocol. The MRI/MRCP were reviewed by the local radiologists and interpreted according to the standards of the time during the study period. This may have resulted in different evaluations, both over time, and with a risk of inter-reader variability, which is known to be high in PSC.[38] New guidelines for MRI interpretation were not broadly implemented until after end of the study in 2020, which is the reason for not using the terminology recently suggested.[10,39] Universal use of recommended reporting standards and improved technique may in the future improve the chances of early cancer detection in clinical practice.[39] Our results describe the clinical real-life practice, in which problems with inter-reader disagreement between radiologists, patient adherence and delayed investigations are common.[38] In addition, due to the COVID-19 pandemic, several MRI/MRCPs and appointments in the outpatient clinic were postponed, resulting in a lower attendance than expected. Re-review of all MRIs was unfortunately not possible. Whether a standardized reporting or re-review of the images by expert radiologists would change the detection of CCA in PSC is not known.

In conclusion, a surveillance programme with yearly CA19-9 and MRI/MRCP followed by investigations with ERCP, and cytology/histology, in an unselected cohort of patients with PSC, was ineffective in detecting CCA early enough to benefit survival, although detection of early GBC was successful. The low incidence of CCA and the limited capacity to discriminate between severe/progressive stricturing with or without underlying CCA, questions the value of yearly MRI/MRCP for detection of early CCA in all patients with PSC. Regular imaging for early detection of gallbladder polyps/GBC seems justified, which could probably be done cost-effectively with ultrasound. CCA surveillance with frequent regular MRI/MRCPs may be reserved for selected patient groups, such as those with PSC-related symptoms, high-grade strictures and advanced disease. Studies on individualised strategies for follow-up and improved diagnostic methods for PSC-related CCA are warranted.

Affiliations

[1]Department of Transplantation Surgery, Karolinska University Hospital, Stockholm, Sweden; [2]Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; [3]Department of Hepatology, Sahlgrenska University Hospital, Göteborg, Sweden; [4]Department of Hepatology, Akademiska University Hospital, Uppsala, Sweden; [5]Department of Upper Abdominal Diseases, Karolinska University Hospital, Stockholm, Sweden; [6]Division of Biostatistics, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [7]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; [8]Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; [9]Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [10]Department of Gastroenterology, Ersta Hospital, Stockholm, Sweden; [11]Department of Gastroenterology, Stockholm South General Hospital, Stockholm, Sweden; [12]Gastroenterology Clinic, Skåne University Hospital, Sweden

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AIH, autoimmune hepatitis; CA19-9, serum carbohydrate antigen 19-9; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescent *in situ* hybridisation; GBC, gallbladder carcinoma; HCC, hepatocellular carcinoma; HGD, high-grade dysplasia; HR, hazard ratio; IBD, inflammatory bowel disease; iCCA, intrahepatic CCA; INR, international normalised ratio; kU/L, kilounits per litre; LT, liver transplantation; MRI/MRCP, MRI with magnetic resonance cholangiopancreatography; pCCA, perihilar CCA; pHGD, perihilar high-grade dysplasia; PSC, primary sclerosing cholangitis.

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Conflicts of interest

Described in ICMJE disclosure forms for IJ, NN and AB. All other authors report no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: AB, KS, IFL, FR, SK, NN, MW, EM. Acquisition of data: CV, KS, IFL, FR, SK, NN, MW, EM, IJ, TH, AB. Analysis and interpretation of data: CV, AW, MC, AB. Drafting of the manuscript: CV, AB. Critical revision of the manuscript for important intellectual content: IFL, FR, SK, NN, MW, EM, MC, KS, TH, IJ, AW, CV, AB. Statistical analysis; CV, AW. Obtained funding: AB. Administrative, technical, or material support: AB. Study supervision: AB.

Data availability statement

Data not available due to ethical restrictions. Participants in this study did not agree for their data to be shared publicly.

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Supplementary data

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References

Author names in bold designate shared co-first authorship

[1] Boonstra K, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. Hepatology 2013;58(6):2045–2055.

[2] Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Loof L, Danielsson A, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol 2002;36(3):321–327.

[3] **Weismuller TJ**, **Trivedi PJ**, Bergquist A, Imam M, Lenzen H, Ponsioen CY, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary sclerosing cholangitis. Gastroenterology 2017;152(8):1975–19784 e8.

[4] Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klumpen HJ, et al. Cholangiocarcinoma landscape in Europe: diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. J Hepatol 2022;76(5):1109–1121.

[5] Mansour JC, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. HPB (Oxford) 2015;17(8):691–699.

[6] Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. HPB (Oxford) 2015;17(8):669–680.

[7] Bowlus CL, Lim JK, Lindor KD. AGA clinical practice update on surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis: expert review. Clin Gastroenterol Hepatol 2019;17(12):2416–2422.

[8] Trivedi PJ, Crothers H, Mytton J, Bosch S, Iqbal T, Ferguson J, et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with inflammatory bowel disease, based on sex, race, and age. Gastroenterology 2020;159(3):915–928.

[9] **Ali AH**, **Tabibian JH**, Nasser-Ghodsi N, Lennon RJ, DeLeon T, Borad MJ, et al. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. Hepatology 2018;67(6):2338–2351.

[10] **Schramm C**, **Eaton J**, Ringe KI, Venkatesh S, Yamamura J, IPSCSG MRIwgot. Recommendations on the use of magnetic resonance imaging in PSC-A position statement from the International PSC Study Group. Hepatology 2017;66(5):1675–1688.

[11] Charatcharoenwitthaya P, Enders FB, Halling KC, Lindor KD. Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis. Hepatology 2008;48(4):1106–1117.

[12] Bergquist A, Weismuller TJ, Levy C, Rupp C, Joshi D, Nayagam JS, et al. Impact on follow-up strategies in patients with primary sclerosing cholangitis. Liver Int 2022. 2022 May 10. Online ahead of print.

[13] Lee JJ, Schindera ST, Jang HJ, Fung S, Kim TK. Cholangiocarcinoma and its mimickers in primary sclerosing cholangitis. Abdom Radiol (NY) 2017;42(12):2898–2908.

[14] Kipp BR, Stadheim LM, Halling SA, Pochron NL, Harmsen S, Nagorney DM, et al. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. Am J Gastroenterol 2004;99(9):1675–1681.

[15] Quinn KP, Tabibian JH, Lindor KD. Clinical implications of serial versus isolated biliary fluorescence in situ hybridization (FISH) polysomy in primary sclerosing cholangitis. Scand J Gastroenterol 2017;52(4):377–381.

[16] Majeed A, Castedal M, Arnelo U, Soderdahl G, Bergquist A, Said K. Optimizing the detection of biliary dysplasia in primary sclerosing cholangitis before liver transplantation. Scand J Gastroenterol 2018;53(1):56–63.

[17] von Seth E, Arnelo U, Enochsson L, Bergquist A. Primary sclerosing cholangitis increases the risk for pancreatitis after endoscopic retrograde cholangiopancreatography. Liver Int 2015;35(1):254–262.

[18] Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology 2011;54(5):1842–1852.

[19] Eaton JE, Welle CL, Bakhshi Z, Sheedy SP, Idilman IS, Gores GJ, et al. Early cholangiocarcinoma detection with magnetic resonance imaging versus ultrasound in primary sclerosing cholangitis. Hepatology 2021;73(5):1868–1881.

[20] Chapman MH, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, et al. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. Gut 2019;68(8):1356–1378.

[21] Maaser C, Sturm A, Vavricka SR, Kucharzik T, Fiorino G, Annese V, et al. ECCO-ESGAR Guideline for Diagnostic Assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. J Crohns Colitis 2019;13(2):144–164.

[22] European Association for the Study of the L. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51(2):237–267.

[23] Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 2002;51(Suppl 6):VI1–VI9.

[24] Aabakken L, Karlsen TH, Albert J, Arvanitakis M, Chazouilleres O, Dumonceau JM, et al. Role of endoscopy in primary sclerosing cholangitis: European society of gastrointestinal endoscopy (ESGE) and European association for the study of the liver (EASL) clinical guideline. Endoscopy 2017;49(6):588–608.

[25] von Seth E, Ouchterlony H, Dobra K, Hjerpe A, Arnelo U, Haas S, et al. Diagnostic performance of a stepwise cytological algorithm for biliary malignancy in primary sclerosing cholangitis. Liver Int 2019;39(2):382–388.

[26] Enochsson L, Thulin A, Osterberg J, Sandblom G, Persson G. The Swedish registry of gallstone surgery and endoscopic retrograde cholangiopancreatography (GallRiks): a nationwide registry for quality assurance of gallstone surgery. JAMA Surg 2013;148(5):471–478.

[27] Reddy SK, Barbas AS, Turley RS, Steel JL, Tsung A, Marsh JW, et al. A standard definition of major hepatectomy: resection of four or more liver segments. HPB (Oxford) 2011;13(7):494–502.

[28] Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. Semin Liver Dis 2004;24(2):201–207.

[29] Chapman MH, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. Eur J Gastroenterol Hepatol 2012;24(9):1051–1058.

[30] Rudolph G, Gotthardt D, Kloters-Plachky P, Kulaksiz H, Rost D, Stiehl A. Influence of dominant bile duct stenoses and biliary infections on outcome in primary sclerosing cholangitis. J Hepatol 2009;51(1):149–155.

[31] Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci 2005;50(9):1734–1740.

[32] Hultcrantz R, Olsson R, Danielsson A, Jarnerot G, Loof L, Ryden BO, et al. A 3-year prospective study on serum tumor markers used for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 1999;30(4):669–673.

[33] Wannhoff A, Brune M, Knierim J, Weiss KH, Rupp C, Gotthardt DN. Longitudinal analysis of CA19-9 reveals individualised normal range and early changes before development of biliary tract cancer in patients with primary sclerosing cholangitis. Aliment Pharmacol Ther 2019;49(6):769–778.

[34] Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, et al. Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting treatment paradigms for resectable disease. Ann Surg 2018;267(5):797–805.

[35] **Vannas MJ**, **Boyd S**, Farkkila MA, Arola J, Isoniemi H. Value of brush cytology for optimal timing of liver transplantation in primary sclerosing cholangitis. Liver Int 2017;37(5):735–742.

[36] Boyd S, Vannas M, Jokelainen K, Isoniemi H, Makisalo H, Farkkila MA, et al. Suspicious brush cytology is an indication for liver transplantation evaluation in primary sclerosing cholangitis. World J Gastroenterol 2017;23(33):6147–6154.

[37] Fosby B, Karlsen TH, Melum E. Recurrence and rejection in liver transplantation for primary sclerosing cholangitis. World J Gastroenterol 2012;18(1):1–15.

[38] Zenouzi R, Liwinski T, Yamamura J, Weiler-Normann C, Sebode M, Keller S, et al. Follow-up magnetic resonance imaging/3D-magnetic resonance cholangiopancreatography in patients with primary sclerosing cholangitis: challenging for experts to interpret. Aliment Pharmacol Ther 2018;48(2):169–178.

[39] Venkatesh SK, Welle CL, Miller FH, Jhaveri K, Ringe KI, Eaton JE, et al. Reporting standards for primary sclerosing cholangitis using MRI and MR cholangiopancreatography: guidelines from MR working group of the international primary sclerosing cholangitis study group. Eur Radiol 2022;32(2):923–937.