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Primary Sclerosing Cholangitis: Current and Future Management Strategies

John E. Eaton¹ and Jayant A. Talwalkar^{§,1}

¹Cholestatic Liver Diseases Study Group, Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine

Abstract

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease. The etiology of this disorder is unknown and there are no effective medical therapies. PSC is associated with inflammatory bowel disease and an increased risk for hepatobiliary and colorectal malignancies. The aim of this review is to highlight the clinical features and diagnostic approach to patients with suspected PSC, characterize associated comorbidities, review screening strategies for PSC associated malignancies and review contemporary and future therapies.

Keywords

Primary sclerosing cholangitis; Management; Diagnosis

Introduction

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterized by inflammation and fibrosis of the intra and extrahepatic ducts [1]. Small duct PSC is a variant that does not involve the large ducts [2].

PSC can have an insidious onset, mimic other forms of cholangitis, or may overlap with other conditions. Therefore, the diagnosis can be challenging to confirm. Furthermore, the surveillance and management of patients with established PSC requires a systematic approach to screen for known complications of this disorder which includes malignancy. Liver transplantation remains the only effective therapy for end-stage liver disease as medical therapy has not conclusively been shown to prevent disease progression.

Clinical Features & Diagnostic Approach

PSC is typically a slowly progressive cholestatic liver disease that often is associated with inflammatory bowel disease [3]. Many patients are asymptomatic at the time of diagnosis; however, others can have fatigue or symptoms consistent with biliary obstruction including: fever, jaundice, pruritus, and weight loss [5, 6]. Secondary sclerosing cholangitis (SSC) has a clinical presentation similar to PSC. However, SSC results from a known process such as recurrent pyogenic cholangitis, trauma, ischemia, portal hypertensive biliopathy,

[§]Correspondence: Jayant A. Talwalkar, Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905, talwalkar.jayant@mayo.edu.

¹John E. Eaton, Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905, eaton.john@mayo.edu

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medications and congenital abnormalities [3, 6]. It should be noted that patients with SSC may have worse long-term outcomes including a shortened life-expectancy as compared to patients with PSC [6].

Serum liver tests typically indicate cholestasis with a predominant elevation in alkaline phosphatase being observed [3]. However, the level of alkaline phosphatase can wax and wane through the disease course and in some cases may be normal [7••]. Persistent normalization of alkaline phosphatase levels may be associated with a better prognosis [7••]. Serum aminotransaminase elevations are typically within 2–3 times the upper limit of normal while serum total bilirubin values are often normal at initial presentation unless high grade biliary obstruction is present [3].

Transabdominal ultrasound is not sufficient to establish a radiographic diagnosis of PSC. However, it can reveal nonspecific findings such as bile duct thickening with or without dilation and gallbladder abnormalities that are common in this population [3, 8]. Magnetic resonance cholangiopancreatography (MRCP) has become the cornerstone for imaging the liver and biliary tree when PSC is suspected. It is noninvasive, avoids radiation exposure, and can be cost effective when compared to endoscopic retrograde cholangiopancreatography (ERCP) [9–11]. Pooled data across multiple studies reveals the sensitivity and specificity for MRCP for diagnosing PSC is 86% and 94%, respectively [11]. Diagnostic ERCP is still required if early changes of PSC are not detected by MRCP or if MRCP images are not optimal [3]. Furthermore, ERCP is the most effective tool for evaluating strictures to exclude malignancy and to provide therapeutic relief of biliary obstruction. ERCP-related complications can occur in 3–11% of patients with PSC [12–14]. Predictors of post-ERCP complications include the presence of cirrhosis, autoimmune hepatitis, Crohn's disease, endoscopists' experience, and the performance of biliary dilation or sphincterotomy [15].

Liver biopsy is usually not required for diagnosing typical PSC unless small-duct PSC or an overlap syndrome with autoimmune hepatitis (AIH) is suspected. In turn, noninvasive measurements of fibrosis which have been increasingly employed to assess the extent of liver fibrosis in other conditions may be useful for PSC [16–17]. Liver stiffness measurement by transient elastography has been studied in patients with PSC and was comparable in performance when used in patients with hepatitis C [16–18]. Magnetic resonance elastography has also been shown to correlate well with liver histology in PSC [unpublished data from Talwalkar and colleagues with permission].

Variant Presentations of PSC

AIH/PSC Overlap

There are no standard diagnostic criteria for the AIH/PSC overlap syndrome and the diagnosis can be challenging. The simplified International Autoimmune Hepatitis Group criteria aid is a diagnostic tool with good sensitivity and specificity for pure AIH [19]. However, this system has a low sensitivity for defining overlap syndromes and should not be used to diagnose these distinct subgroups [20, 21]. Consequently, individuals should be characterized by the dominant disease processes. AIH/PSC should be suspected when there is cholangiographic or histologic evidence of PSC along with biochemical features of AIH (disproportionately elevated transaminases >5 times the upper limit of normal, elevated antibody titers suggestive of AIH) or histologic features of AIH [22]. AIH/PSC should also be suspected if an individual with AIH becomes refractory to immunosuppressive therapy [3, 22]. Patients with features of AIH should be carefully considered for immunosuppressive therapy [3, 22].

IgG4 Associated Cholangitis

IgG4 associated cholangitis can mimic PSC. It is typically characterized as an entity with biliary strictures, lymphoplasmacytic tissue infiltration and elevated serum IgG4 levels [23]. IgG4 elevations have been reported in 12% of patients with PSC [24]. However, elevated IgG4 levels in bile may be a more specific method of distinguishing between IgG4 associated cholangitis and PSC [25]. Cholangiography cannot reliably distinguish between PSC and IgG-4 associated cholangitis [26]. Therefore, assessing serum IgG-4 levels and pancreatic anatomy on cross-sectional imaging is important to aid in distinguishing between the two entities particularly since IgG-4 can be responsive to steroids [3].

Small Duct PSC

Small duct PSC is a variant where the bile ducts are normal on cholangiography but have the same cholestatic and histologic evidence as large duct PSC [2]. Small duct PSC may be prevalent in patients with AIH/PSC [27]. It is associated with an improved long term prognosis compared to large duct PSC. However, progression to large duct PSC can occur in selected individuals [2].

Inflammatory Bowel Disease in PSC

Nearly 60%–80% of PSC patients will have concurrent inflammatory bowel disease (IBD) with ulcerative colitis (UC) being most common [3]. IBD can be diagnosed at any point in the natural history of PSC, even after liver transplantation [28]. A unique IBD phenotype has been described in association with PSC where an increased prevalence of rectal sparing, backwash ileitis and pancolitis is observed. While the clinical course of PSC-IBD is typically mild or quiescent, the long-term risk for colorectal neoplasia is higher when compared to patients with IBD alone [28–30]. Following a diagnosis of PSC, patients should undergo a colonoscopy with surveillance biopsies (a minimum of 32) to exclude the presence of neoplasia [3]. Conversely, patients with IBD and cholestatic liver test elevations should be assessed for PSC, and this is typically done by performing MRCP when subjects have no liver-related symptoms. In a population-based study, patients with PSC-IBD were more likely to have adverse outcomes such as death and transplantation compared to those with PSC alone [31]. Further studies are needed to verify this observation. Interestingly, the severity of UC and PSC may be inversely related. In a single center, retrospective study, Marelli et al noted that severe, progressive PSC requiring a liver transplant was associated with a more mild UC activity on histology and fewer developed neoplasia [32]. Whether these findings can raise new questions about the pathogenesis of PSC and IBD remains to be seen.

For patients with PSC-IBD who require a colectomy, an Ileal pouch anal anastomosis (IPAA) is considered safe and efficacious in selected patients [33]. In one experience, 100 patients underwent an IPAA before or after liver transplant for PSC due to IBD related complications. Complications occurred in 39% of patients within 30 days of surgery and were primarily related to infection. After nearly 6 years of follow up, only 3% of patients had failure of their pouch due to either refractory pouchitis, adenocarcinoma of the pouch, or fistula formation [33]. Although patients with PSC are at an increased risk of pouchitis, the IPAA can afford long-term satisfactory pouch function in patients [3, 33]. However, patients with PSC who undergo a proctocolectomy with ileostomy are at a higher risk of peristomal varices which can be difficult to manage [34].

Medical Therapy & Liver Transplantation

Medical Therapy

Currently, there is no effective medical therapy for halting disease progression in PSC. Finding an effective medical therapy for PSC has been challenging for several reasons. As a rare disease, the ability to execute study designs of sufficient power creates logistical difficulties in terms of enrollment. Secondly, the pathogenesis of PSC remains poorly understood, and thus the ability to identify therapeutic targets at a molecular level has not been successful. Finally, PSC is a chronic condition that often takes years to progress making it difficult to capture enough relevant clinical endpoints such as death or need for liver transplantation to determine the efficacy of novel therapies.

Numerous agents have been investigated in an attempt to reduce adverse clinical events related to PSC. Ursodeoxycholic acid (UDCA) at varying doses has been studied the most extensively. Studies utilizing doses between 10–15 mg/kg/day were associated with biochemical and histologic improvement [35,36]. However, no important survival difference was observed between active and placebo treated groups. Subsequent attempts were made to study higher doses of UDCA. A 5-year randomized controlled study examined the effect of UDCA 17–23 mg/kg/day and found no differences in mortality or liver transplant and quality of life between the treatment groups. However, this study was limited by a lack of power [37]. When UDCA at 28–30 mg/kg/day was studied versus placebo, an unexpected two-fold increased risk of adverse events was observed with active therapy compared to placebo despite improvements in liver biochemistries. Subjects with early stage (Stage 1–2) disease were more often observed to have faster progression of disease with high-dose UDCA as compared to placebo, while subjects with advanced (stage 3–4) disease progressed equally in both treatment arms [38,39]. A recent meta-analysis found no difference in fatigue, mortality, histologic progression or development of cholangiocarcinoma for standard or high dose UDCA [40]. In turn, high dose UDCA has not been recommended for use in clinical practice [3].

In recent years, there have been several animal or pilot studies examining unique mechanisms of action that may play a role in disease pathogenesis for PSC. Cystic fibrosis transmembrane conductance regulators (CFTR) abnormalities have been detected in some patients with PSC [41,42]. CFTR dysfunction may lead to fatty acid alterations including a decrease in docosahexaenoic acid (DHA) [43,44]. Martin et al examined the effects of DHA supplementation on serum alkaline phosphatase levels in 23 patients with PSC over a 12 month period. Results were noted for significant reductions in mean alkaline phosphatase levels after treatment, and there were no reported adverse events. Larger, multicenter, randomized studies are needed to further clarify the role of DHA in the treatment of PSC [45]. 24-norUrsodeoxycholic acid (norUDCA) is a side chain modified derivative of UDCA [46]. In an experimental animal model, norUDCA was associated with significantly improved liver tests and histology when compared to UDCA treatment [47]. The authors postulated that these findings may be related to norUDCA's ability to increase bile acid hydrophilicity and flow while inducing the detoxification and elimination of bile acids. Human phase 2 clinical studies with norUDCA are currently underway in Europe.

Liver Transplantation

Liver transplantation (LT) is the only known effective therapy for PSC. Five year post transplant survival exceeds 80% [48]. Unique indications for LT in PSC are intractable pruritus, recurrent bacterial cholangitis, and perihilar cholangiocarcinoma [3]. Patients with these complications, however, may have disproportionately lower MELD scores that prevents them from receiving a deceased donor LT [49]. In turn, a number of patients with

PSC have undergone living donor LT. Goldberg et al examined the United Network for Organ Sharing database and determined that PSC patients were more likely to obtain a living donor LT compared to non-PSC patients [49].

Recurrent PSC can occur in 20–25% of patients after 5–10 years post transplant [3]. Multiple risk factors for recurrence have been suggested. Pre-transplant colectomy in patients with IBD may be protective against recurrence; whereas prolonged use of steroids and the presence of UC has been shown to be associated with the development of recurrent PSC [50,51]. Acute cellular rejection may also increase the risk of PSC [52].

Recent studies have also suggested that UC disease activity may improve after LT [53, 54]. However, more than half of patients with concurrent IBD will have continued or worsened disease activity despite immunosuppression following LT [28]. To date, management strategies for IBD after LT remain ill defined. Recent case series describe the safety of anti-TNF therapies for treating IBD after LT, [55–57]. In the largest case series of 8 patients, nearly 88% of patients started on anti-TNF therapy had a clinical response. Infections occurred in 3 of 8 patients, and post transplant lymphoproliferative disorder was detected in 1 patient after 4 months of anti-TNF therapy [55]. Therefore, anti-TNF agents may be an option in highly selected patients but additional data is needed to understand the short and long term safety of these agents after LT.

PSC-Associated Malignancy

The development of either hepatobiliary or colorectal neoplasia (CRN) is one of the most feared complications of PSC with as many as 44% of deaths being attributed to cancer [58]. Consequently, there have been recent publications discussing strategies for surveillance of hepatocellular carcinoma, cholangiocarcinoma (CCA), gallbladder neoplasia (GBN), and CRN [3,59]. For the purposes of this review, we will focus on the diagnosis, surveillance and chemoprevention for the latter three malignancies.

Cholangiocarcinoma

Perihilar cholangiocarcinoma (CCA) is often detected within 2 years from an initial diagnosis of PSC. Thereafter, the annual risk is about 1% per year with a lifetime prevalence of 5–10% [58]. Unfortunately, subjects with CCA continue to have poor 5 year survival rates (less than 10%) despite advances in diagnosis and management. Of note, some individuals with PSC develop intrahepatic CCA which contributes to the increased mortality rate. [58, 60–64].

Developing an evidence-based, cost effective, screening program to detect early CCA in PSC remains of great interest. Current practices include the use of serum carbohydrate antigen 19-9 (CA 19-9) and/or cross-sectional imaging tests for detecting early or localized CCA.[65]. In turn, the presence of significant interval changes in one or both test results may warrant ERCP and brush cytology/biopsy to rule out CCA even in the absence of worsening cholestasis or suspected cholangitis.

The ability to determine whether dominant strictures (typically defined as less than or equal to 1.5 mm in the common bile duct or less than or equal to 1 mm in the hepatic duct) are inflammatory or malignant also remains challenging [3]. Obtaining adequate tissue or cellular material for excluding malignancy is difficult partly because CCA is a desmoplastic malignancy. Thus, conventional biliary cytology has a low sensitivity for the detection of cholangiocarcinoma [65]. In contrast, fluorescence *in situ* hybridization (FISH) utilizes labeled DNA probes to detect abnormal loss or gain of chromosomes involving several loci [66]. The majority of the studies examining FISH in PSC utilized centromeric probe against

chromosomes 3, 7, and 17 and a locus-specific probe (9p21) [66–67]. In a large series of 235 patients with PSC with at least one FISH cytology analysis from ERCP, patients with trisomy or tetrasomy had similar outcomes to those with a negative FISH [66]. However, the detection of FISH polysomy was associated with a sensitivity of 46% and specificity of 88% for CCA in PSC. Patients with a positive FISH polysomy and no CCA were more likely to have a lower CA-19-9, lower Mayo risk score, lower bilirubin, and lower occurrence of dominant strictures compared to those with CCA [66]. The detection of serial FISH polysomy is more likely to be associated with developing CCA when compared to individuals without reoccurrence of polysomy (69% versus 18%, $p=0.008$). In this study, CCA developed after 1 year from the initial polysomy result in 46% of patients and in 75% of patients after 3 years [67]. These findings support the practice of close follow up of patients with FISH polysomy who do not otherwise meet the criteria for CCA.

Emerging data on novel approaches may potentially add to the clinical armamentarium to help detect CCA among patients with PSC. A recent experience with proteomic analysis of bile aspirated at the time of ERCP was able to distinguish between PSC from CCA with a sensitivity 78% and specificity of 84% [68]. A less invasive approach examined urine specimens and found proteomic analysis distinguished CCA from PSC and benign biliary disorders with a sensitivity and specificity of 83% and 79%, respectively. All patients with CCA and PSC were classified correctly based on this model [69]. Serologic markers, offer another noninvasive approach for monitoring this high risk population for CCA [70–72]. Sandanayake et al, examined the role of serum leucine-rich α -2-glycoprotein (LGRI), CA19-9, and interleukin-6 (IL-6) to distinguish biliary tract cancers from benign strictures. The sensitivity, specificity and area under the curve (AUC) for elevated levels of LGRI, CA19-9 and IL-6 was 83%, 92%, and 0.87 versus 83%, 67%, 0.84 versus 92%, 92%, and 0.93 respectively. Combining the receiving operator curves for all three tests resulted in an improved AUC of 0.98 [72]. Validation of these findings in a PSC cohort for CCA surveillance would be of great interest.

A proposed rational approach to screening for CCA is outlined in Figure 1 [59]. As more data becomes available, new methods will likely be incorporated into this algorithm to enhance the diagnostic accuracy of this challenging problem.

After CCA is diagnosed, therapeutic options are limited. Unfortunately, CCA is often detected at a late stage where the lesion is unresectable. A multimodal approach culminating in liver transplantation in selected patients with unresectable perihilar CCA has been available. This approach involves highly selected group of patients with early stage, unresectable perihilar CCA who then undergo radiotherapy with radiosensitizing chemotherapy, brachytherapy, maintenance chemotherapy with oral capecitabine, staging surgery to exclude metastases and finally liver transplantation. Five year recurrence free survival was determined to be near 70% [73–78]. Consequently, a model of end-stage liver disease (MELD) exception pathway (analogous to hepatocellular carcinoma) was approved. Recently, Murad et al examined the success of this approach across 12 centers utilizing this protocol. The five year recurrence free survival across all centers was 65% with similar rates at all 12 sites. A larger proportion of patients with PSC remained free of recurrence compared to those without PSC (62% versus 51%); however this was not statistically significant ($p=0.06$). Lastly, there was a 11.5% drop-out rate after 3.5 months which indicates the use of the current MELD exception (expects a 10% increase in wait list mortality after 10 months) is appropriate [79]. This multicenter study provides additional justification for use of liver transplantation in a highly select group of patients for this devastating disease.

Gallbladder Neoplasia

PSC is associated with gallbladder disease including gallbladder neoplasia [8, 80–81]. Because of this heightened risk, an annual ultrasound is recommended to screen for gallbladder polyps with subsequent cholecystectomy if a polyp is detected regardless of size [3]. If other abdominal imaging which visualized the gallbladder adequately (ultrasound, MRCP, etc) has been performed in the past year we do not repeat an ultrasound that year for the purposes of gallbladder neoplasia screening. It has been established that in patients without PSC, polyp size can be a predictor for the presence of underlying dysplasia or cancer. For example, polyps less than 1.0 cm in the absence of PSC are unlikely to be malignant [82–84]. The natural history and malignant potential of small polyps in PSC, however, is less clear. This is primarily due to a limited number of published cases of small polyps and prospective studies. A single center retrospective study examined 57 patients with PSC who underwent a cholecystectomy. Polyps less than 0.8 cm did not have dysplasia or cancer. In addition, the morbidity associated with cholecystectomy in patients with PSC was 40% with increased Child-Pugh scores associated with higher post-operative complications [85]. Until more data are available, the performance of cholecystectomy for small polyps less than 0.8 cm (without other high risk features) versus close observation should be carefully considered in patients who are at a high risk of post operative complications.

Colorectal Neoplasia

Patients with PSC and concurrent UC have a 4-fold higher risk of colorectal neoplasia (CRN) compared to those with UC alone [30]. PSC may also be a risk factor for CRN development in Crohn's disease, and individuals with PSC and Crohn's should also undergo surveillance although this association is less clear [3, 86–87]. The risk of neoplasia in PSC-IBD is present soon after both conditions are discovered [88]. Therefore, it is recommended that screening for IBD occur at the time of the initial diagnosis of PSC and every 5 years thereafter until IBD is detected. In the setting of IBD, colonoscopic screening with surveillance biopsies every year is recommended [3]. This risk does not dissipate following liver transplant and thus annual screening should continue [3,89]. Furthermore, patients who undergo IPAA for disease activity or colorectal neoplasia may be at risk for adenocarcinoma in the pouch [90]. In one series of 65 patients, followed for 6 years, with PSC-UC plus an IPAA only 5% had pouch neoplasia (1 patient had adenocarcinoma) [unpublished data from Talwalkar and colleagues with permission]. The optimal pouch surveillance strategy remains unclear.

As a result of this heightened surveillance, practitioners and patients may frequently encounter indefinite (IND) and low grade (LGD) dysplasia. A retrospective study followed 47 patients with PSC-UC patients diagnosed with IND dysplasia for 2 years with nearly 13% of individuals ultimately developing high grade dysplasia (HGD) or cancer [unpublished data from Talwalkar and colleagues with permission]. When 16 individuals diagnosed with either endoscopically flat or raised LGD found in an area of colitis were followed for 1 year, an estimated 19% were subsequently found to have HGD or cancer [unpublished data from Talwalkar and colleagues with permission]. Additional outcomes studies for patients with IND and LGD with PSC are required to delineate the optimal management. The presence of HGD, cancer or unresectable LGD are clear indications for colectomy.

The elevated risk of CRN in this population has led many to investigate the efficacy of chemopreventative agents. UDCA has been most extensively studied in PSC-IBD with six principal studies published on the subject (Table 1) [91–96]. All have been retrospective. Using standard dosing, two studies showed a potential benefit. However, high dose UDCA

was associated with an increased risk of neoplasia development (predominately LGD) [95]. UDCA was also shown to increase the risk of developing CRN following liver transplantation [96]. At this time, the AASLD recommendation does not support the use of UDCA for CRN prevention while the European Association for the Study of the Liver guidelines are in favor of its use [3,97].

5-aminosalicylate agents (5-ASA) may have a role in chemoprevention for patients with UC [98]. Of concern, one study suggested the use of 5-ASA in patients with PSC was associated with worse outcomes [96]. However, this has not been observed in other studies [91–95]. In fact, the use of 5-ASA medications following a diagnosis of IND among patients with PSC-UC was associated with a decreased risk of progression to more advanced neoplasia [unpublished data from Talwalkar and colleagues with permission]. The contemporary literature is limited to retrospective, observational studies and the data remains insufficient to recommend 5-ASA agents for CRN prevention in this population. Future, prospective studies should confirm the protective role of 5-ASA and determine if there is a relationship between dose, duration, and type of preparation used in CRN prevention.

Conclusion

Presently, the cornerstone to the management of patients with PSC lies in the prompt recognition of the disorder, followed by close monitoring to identify comorbid conditions and complications such as malignancy. A better understanding of the natural history and pathogenesis of PSC and related conditions is needed to drive the development of effective medical therapies.

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Abbreviations

PSC	primary sclerosing cholangitis
SSC	secondary sclerosing cholangitis
MRCP	Magnetic resonance cholangiopancreatography
ERCP	endoscopic retrograde cholangiopancreatography
AIH	autoimmune hepatitis
IBD	inflammatory bowel disease
UC	ulcerative colitis
IPAA	Ileal pouch anal anastomosis
MELD	model for end-stage liver disease
UDCA	ursodeoxycholic acid
AASLD	American Association for the Study of Liver Disease
CFTR	Cystic fibrosis transmembrane conductance regulators
DHA	docosahexaenoic acid
norUDCA	24-norUrsodeoxycholic acid
anti-TNF	anti-tumor necrosis factor

CCA	cholangiocarcinoma
GBN	gallbladder neoplasia
CRN	colorectal neoplasia
CA 19-9	carbohydrate antigen 19-9
FISH	Fluorescence <i>in situ</i> hybridization
LGRI	leucine-rich α -2-glycoprotein
IL-6	interleukin-6
AUC	area under the curve
IND	indefinite for dysplasia
LGD	low grade dysplasia
HGD	high grade dysplasia
5-ASA	5-aminosalicylate agents

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Fig. 1.

Proposed cholangiocarcinoma surveillance algorithm for patients with primary sclerosing cholangitis. Abbreviations: PSC (primary sclerosing cholangitis); MRI (magnetic resonance imaging); MRCP (magnetic resonance cholangiopancreatography); CA19-9 (carbohydrate antigen 19-9); ERCP (endoscopic retrograde cholangiopancreatography); FISH (fluorescence *in situ* hybridization); CCA (cholangiocarcinoma). Adapted from [59], with permission

Table 1

Studies examining UDCA for colorectal neoplasia prevention in inflammatory bowel disease associated with primary sclerosing cholangitis.

Ref	Agent	Number of Patients	Outcome in treatment Group
[91]	UDCA (9–10 mg/kg/day)	59	Reduction in HGD
[92]	UDCA (13–15 mg/kg/day)	52	Reduction in neoplasia
[93]	UDCA (dose unknown)	120	No change in neoplasia
[94]	UDCA (17–23 mg/kg/day)	98	No change in neoplasia
[95]	UDCA (28–30 mg/kg/day)	56	Increased risk of neoplasia
[96**]	UDCA (dose unknown)	353	Increased risk of neoplasia

Abbreviations: Ref (reference); UDCA (ursodeoxycholic acid); HGD (high grade dysplasia)