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The Role of Cholangioscopy in the Management of Primary Sclerosing Cholangitis

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Abstract

Purpose of Review Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the biliary ducts associated with a high risk for hepatobiliary malignancies. Up to 50% of PSC patients develop dominant strictures (DS) and warrant investigations to exclude cholangiocarcinoma (CCA). Most patients undergo endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, but diagnostic accuracy is suboptimal, with sensitivity varying between 8 and 43% for the detection of CCA. Negative brush cytology often results in repeat ERCPs and need for heightened surveillance.

Recent Findings The relatively recent introduction of per oral single operator cholangioscopy (SOC) as a safe and efficient complementary tool to ERCP allows for visual characterization and direct targeted forceps biopsy acquisition, with some studies showing sensitivity of up to 90% for overall diagnostic performance. However, most of the data for SOC in PSC comes from retrospective single-center studies.

Summary SOC allows visual characterization and direct targeted biopsies, with some studies demonstrating superior diagnostic performance for CCA detection in PSC. In addition, SOC may have potential benefit in characterization of different phenotypes of DS in PSC.

Keywords Primary sclerosing cholangitis · Cholangioscopy · Cirrhosis · Dominant stricture · Cholangiocarcinoma

Introduction

Primary sclerosing cholangitis (PSC) is a sporadic, inflammatory condition described by multifocal biliary duct strictures that can lead to chronic liver disease. PSC has a male preponderance and a substantial proportion of affected patients has concomitant inflammatory bowel disease (IBD), either ulcerative colitis or Crohn's disease [1, 2]. PSC is considered an autoimmune disease; however, the pathogenesis of PSC has not been entirely elucidated and is assumed to be related to a blend of genetic risk factors and environmental triggers [1, 2].

The prevalence is approximately 4–16/100,000 people, and distribution varies according to the geographic area, with the highest frequency described in northern Europe and the lowest in Asia [3–5].

Unfortunately, no effective treatment for PSC exists, and the reported median time from diagnosis until the need for liver transplantation (LT) or liver-related death is approximately 13 and 21 years in transplant and community centers, respectively [6]. Several clinical factors have been associated with prognosis. In the largest global cohort of PSC patients, diagnosis at older age was related to a lower LT-free survival, while female sex, presence of Crohn's disease compared to ulcerative colitis, and small duct PSC compared to classical PSC were associated with a better outcome [7].

As PSC is a heterogeneous disease and its natural history is not similar to other chronic liver diseases, detailed prognostic models have been established. In 2000, the Mayo Clinic established a score integrating bilirubin, age, AST, and albumin as well as variceal bleeding history and patients were classified into three groups as low, intermediate, and high risk for disease progression [8].

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More recently, risk estimation tools have been developed using machine learning that demonstrated accurate prediction for decompensation, including the PSC estimate tool (PREsTo) and the United Kingdom (UK-PSC) Risk Scores [9, 10].

Dominant Strictures and Cholangiocarcinoma in PSC

More than half of the patients with PSC develop high-grade or dominant strictures (DS) of the bile ducts during the course of their disease. DS can either represent worsening of the underlying inflammatory response or the progression to malignancy. Development of a DS, therefore, significantly complicates the management of this disease, since precise diagnosis of these indeterminate biliary strictures becomes a difficult clinical task.

Dominant strictures are characterized as a stenosis with a diameter of ≤ 1.5 mm in the common bile duct and/or ≤ 1.0 mm in the right or left hepatic duct within 2 cm of the main hepatic confluence. The investigation for the etiology of DS is pivotal, as PSC is related to 400-fold higher risk of cholangiocarcinoma (CCA) in comparison to the general population [6]. In fact, the yearly risk for CCA in PSC is estimated at 2%, with a cumulative incidence from 6 to 11% at 10 years, and up to 20% at 30 years [6]. Interestingly, the cancer risk in PSC seems to be variable over time, as 27–37% of all the hepatobiliary cancers are detected in the first year of PSC diagnosis [11].

A recent retrospective study evaluating almost 2400 cases of CCA in different anatomical locations (1169 intrahepatic, 995 perihilar, and 231 distal) demonstrated a reverse association between the use of aspirin and the risk of all CCA subtypes, with adjusted odds ratios (AORs) ranging from 0.29 to 0.35 for different anatomical locations ($P < 0.001$ for all). Association between PSC and the peri-hilar subtype (AOR = 453, 95% CI 104–999), was stronger than the association with intrahepatic (AOR = 93.4, 95% CI 27.1–322) or distal (AOR = 34.0, 95% CI 3.6–323) CCA [12•].

According to the American Association for Gastroenterology (AGA) practice guidelines, patients with PSC and DS should be investigated for CCA using biliary ductal sampling with endoscopic retrograde cholangiopancreatography (ERCP) and simple brush cytology, possibly with the addition of other procedures such as fluorescence in situ hybridization (FISH), and/or the use of per oral single operator cholangioscopy (SOC) with direct targeted biopsies [13••]. Detection rates for CCA with current techniques are suboptimal and negative brush cytology results in the need for close monitoring of these DS. Routine brush cytology obtained with ERCP has demonstrated a wide range of diagnostic performance, with sensitivities ranging between 8 and 43% for the detection of CCA when suspicious results were considered as positive. On the other hand, the reported specificity has been as high as 97% [14, 15]. The addition of sophisticated techniques, including fluorescence in situ hybridization (FISH) and digital image analysis (DIA), has demonstrated an improvement in the sensitivity of CCA detection by 10–15% [16–19]. However, these techniques are not accessible in many centers, and some patients with negative results will require several ERCPs when CCA suspicion remains high. In fact, up to 20% of DS end up being classified as indeterminate after multiple ERCPs with brush cytology [20].

It should be emphasized that in patients with PSC, the opportune identification of CCA within a biliary stricture is fundamental for management and has a significant impact on clinical outcomes. Prompt identification of CCA is critical in order to enable timely curative surgical resection in patients with preserved liver function but for a majority of patients, the detection of CCA would be a contraindication for LT unless centers have access for special treatment protocols for LT in the setting of perihilar CCA [21].

Effectiveness of Cholangioscopy in PSC

Cholangioscopy is an endoscopic technique used not only for direct visual characterization of the bile duct but also to acquire direct targeted biopsy forceps for diagnostic evaluation of biliary lesions, and if needed, for therapeutic intervention within the bile ducts. Cholangioscopy has recently been transformed by the introduction of a system enabling a single endoscopist to perform the entire procedure. This single-operator cholangioscopy (SOC) system is a significant improvement over the previous 2-endoscopist system using a "mother-daughter" cholangioscope [22, 23]. In SOC, the cholangioscope is attached to the handle of a conventional duodenoscope and the procedure is completed concurrent with ERCP. Improvements in the optical image quality and in the accessories, such as biopsy forceps, that can be used through this system have significantly enhanced the diagnostic capability of ERCP.

Detection of Cholangiocarcinoma with Cholangioscopy

It has been reported that SOC improves the diagnostic precision of ERCP for indeterminate biliary strictures [24, 25]. A systematic review and meta-analysis, including eight studies involving 335 patients, confirmed that the overall diagnostic performance of SOC visual impression had a sensitivity of 90% (95% CI, 73%–97%), and specificity of 87% (95% CI, 76–94%). However, the sensitivity for histological diagnosis

with biopsy forceps was 69% (95% CI, 57–79%) and specificity of 98% (95% CI, 92–99%) [26].

Another systematic review of 10 studies with 456 patients reported sensitivity of 60.1% (95% CI 54.9–65.2%) and specificity of 98.0% (95% CI, 96.0–99.0%) for SOC-guided biopsies [24]. These studies suggest that visual impression might have better diagnostic performance than targeted biopsies, but the concern is that in most centers, surgical/oncologic treatment is difficult to recommend without a corroborating tissue diagnosis.

In the case of PSC, the diagnostic performance of SOC-targeted biopsies has been inconstant, with studies indicating sensitivities as low as 33% for the diagnosis of CCA (Table 1) [27, 31, 36]. In a systematic review and meta-analysis of 49 studies, the overall estimated accuracy of SOC for a visual diagnosis was 89% (95% CI 84–93%) while it was 79% (95% CI 74–84%) for a histological diagnosis, with the estimated overall adverse event rate of 7% (95% CI 6–9%) [37]. Nonetheless, there is evidence to suggest that SOC is still the most precise diagnostic procedure for the diagnosis of CCA in PSC [31•]. Furthermore, Arnelo et al. demonstrated the ability of SOC to acquire targeted biopsies from biliary strictures not accessible with conventional ERCP [31]. Even though some centers suggest a step-up approach for the detection of CCA in PSC [32••], we feel that SOC should be considered earlier in this diagnostic algorithm as having a diagnosis in a timely manner is critical for management (Fig. 1).

A more recent study evaluating the performance features of SOC-guided biopsies and transpapillary biopsies with regular sampling methods for the diagnosis of CCA demonstrated that sensitivity for the detection of CCA was improved using SOC-guided and transpapillary biopsies in combination with other ERCP-based procedures when compared to only brush cytology alone. Although SOC was harmless, these procedures do not considerably increase the sensitivity for the diagnosis of malignancy in PSC [34].

Similar results were reported in a single-center retrospective of patients who received SOC for the assessment of

Table 1 Main studies evaluating the use of cholangioscopy in PSC

Author/year	Number	Design	Main findings
Tischendorf JJ, et al. [27]/2006	53 with PSC	Prospective	• SOC was superior to ERCP for identifying malignancy • Sensitivity (92% vs. 66%; $P = 0.25$), specificity (93% vs. 51%; $P < 0.001$), accuracy (93% vs. 55%; $P < 0.001$), PPV (79% vs. 29%; $P < 0.001$), and NPV (97% vs. 84%; $P < 0.001$)
Siiki A, et al. [28]/2014	11 consecutive PSC patients	Prospective	• Samples adequate for cytological diagnosis in 82% • Histological diagnosis in 91%
Liu R, et al. [29]/2014	25/18 with PSC	Retrospective	• Detection of CCA in PSC, sensitivity of 75%, specificity of 55%, and a positive predictive value (PPV) of 23%, and a negative predictive value of 92%
Rey JW, et al. [30]/2014	35/19 with PSC	Prospective	• A greater yield was obtained by SOC-directed biopsies diagnostic compared to brush cytology. • Biopsy method resulted in greater tissue yield than brush cytology method ($P = 0.021$). • Inflammatory characteristics and activity were higher in biopsies than cytology ($P = 0.014$).
Arnelo U, et al. [31]/2015	47 PSC patients	Prospective	• 98% (62/63) of the cytology brushings and 95% (21/22) of the mini-forceps biopsies yielded adequate sample quality. • 3 patients had final diagnosis of CCA, 1 was detected at the time of the investigation. • Sensitivity of 33%, specificity of 100%, accuracy of 96%, and NPV of 95%, was observed.
Njei B, et al. [32•]/2016	128 PSC patients	Meta-analysis	• SOC pooled sensitivity for CCA in PSC was 65% (95% CI, 35–87%) and the specificity was 97% (95% CI, 87–99%). • Pooled diagnostic odds ratio for CCA identification was 59 (95% CI, 10–341).
Majeed A, et al. [33••]/2018	225 consecutive PSC patients	Retrospective analysis diagnosis Prospective follow-up after liver transplant	• SOC for targeted examination at the 2nd· ERCP improved sensitivity (100%) and specificity (97%)
Kaura K, et al. [34]. 2019	92/36 with PSC	Retrospective cohort study	• Brush cytology showed sensitivity of 44.7% in overall cohort which increased with adding FISH (56.8%; $P = 0.12$), and FISH with SOC-guided biopsy (71.4%; $P = 0.03$), and FISH with transpapillary biopsy (64.5%; $P = 0.01$). • In PSC, no significant enhancement in sensitivity was noticed by adding SOC-guided biopsy or transpapillary biopsy in addition to FISH compared to brush cytology.

CCA cholangiocarcinoma, *ERCP* endoscopic retrograde cholangiopancreatography, *PPV* positive predictive value, *NPV* negative predictive value; primary sclerosing cholangitis, *SOC* single-operator cholangioscopy

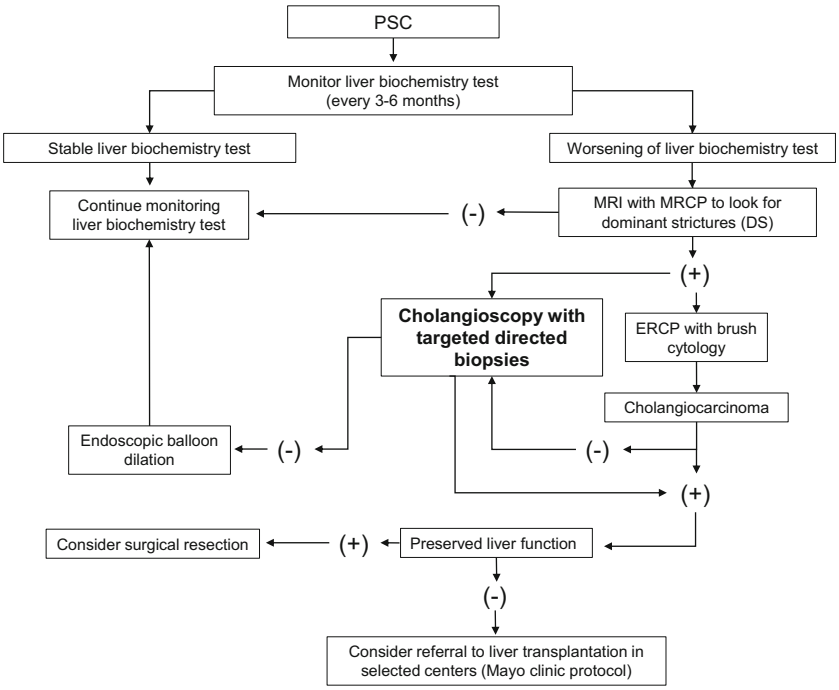


Fig. 1 Algorithm suggesting role of cholangioscopy in management of patients with PSC and a dominant stricture. Abbreviations. ERCP endoscopic retrograde cholangiopancreatography; MRI magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography

indeterminate biliary strictures. Eighty patients were evaluated and 40% had PSC, and more than 80% had prior ERCP. Sensitivity and specificity for visual impression was 64 and 62% and for targeted biopsies was 15 and 65% respectively [38]. In addition, for 32% of patients, SOC results did not change management; in 51%, results confirmed the previous diagnosis; and in 17%, SOC results changed the management plan [38].

Newly, high-resolution per-oral video cholangioscopy allowed to visualize tumor margins in CCA in comparison with traditional fluoroscopy-based ERCP, with 48% increase in dubious lesions biopsied with narrow band imaging compared with white-light imaging; however, an enhancement in dysplasia detection in PSC was not established [39]. An additional advantage of SOC, however, is its ability to distinguish PSC from other stricturing biliary diseases such as IgG4-associatied cholangitis [40].

There are also some limitations with SOC. Despite similar accuracy for cancer diagnosis in PSC and patients with single biliary strictures, the inability to traverse strictures with the cholangioscope and incidence of cholangitis post-SOC seems to be more prevalent in patients with PSC (15 versus 2%; $P = 0.051$) [41].

We acknowledge limitations and discrepancies in the evidence behind current guidelines and recommend that additional data are required to elucidate the role of SOC in PSC.

Endoscopic Treatment of Dominant Strictures

The development of DS in PSC patients has been related to worse long-term outcomes, mainly related to the fact that a substantial percentage of DS has an underlying CCA [42]. Chapman et al. describe their 25-year experience in 128 patients with PSC and found that there was a 26% risk of developing CCA only in those with a DS, and a shorter survival was observed in this group compared to those without a DS (14 versus 23 years) [43].

In the presence of DS not related to CCA, treatment with endoscopic balloon dilatation is recommended, preferably without plastic stent insertion [44–46]. Baluyut et al. demonstrated that the 5-year survival rate of patients with a DS who underwent endoscopic balloon dilatation was superior to the prediction by the Mayo Risk Score (83% versus 65%, $P = 0.027$) [47]. Gluck et al. presenting their 20-year practice with endoscopic therapy for 84 symptomatic PSC patients also found that survival was higher than expected [48].

Short-term stenting was compared to the balloon dilatation for a DS in a more recent multicentre randomized trial and no differences in outcome measures between the 2 groups, but adverse events, consisting primarily of post-ERCP pancreatitis and suppurative cholangitis, were more common in patients that underwent short-term stenting (42 versus 10%, OR 6.4, 95% CI 1.6–25.4) [44].

Recently, a large retrospective study evaluated 286 patients of whom 133 (47.5%) underwent arranged ERCP and the rest received on-demand ERCP. At 10 years follow-up, higher rate of LT-free survival was observed in patients who underwent scheduled ERCP (51 versus 29.3%; $P < 0.001$). Results of this study recommend that regular ERCP with balloon dilatation considerably benefits PSC patients with a DS, detected both

at early presentation and throughout surveillance, even if patients are asymptomatic [49].

For those patients with a failed ERCP, percutaneous transhepatic biliary access is an alternative treatment option [2].

Detection and Removal of Stones

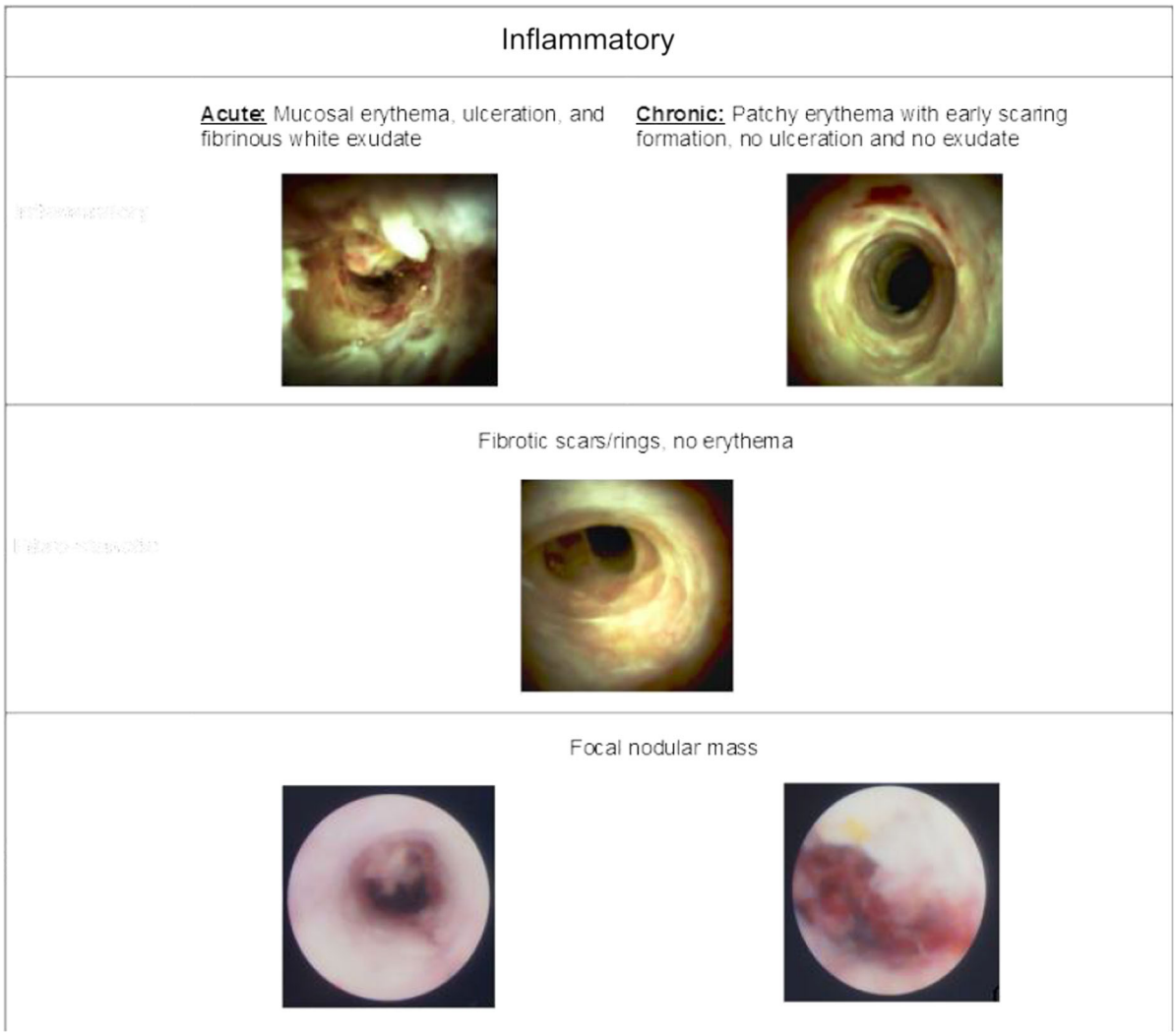
Biliary stones constitute another indication for endoscopic biliary intervention in PSC patients. In a retrospective study of more than 100 patients with PSC, approximately 50% of patients who received ERCP had biliary stones [48]. Extrahepatic bile duct stones are fairly frequent in the general population, whereas intrahepatic bile duct stones are unusual. In patients with PSC, both occur relatively frequently [50].

One of the earlier experiences of SOC in PSC demonstrated that stones identified by cholangioscopy were not detected by cholangiography in 30% of patients, and SOC-directed lithotripsy might be better than conventional ERCP for reaching comprehensive stone clearance [36]. A more recent study similarly demonstrated that residual biliary stones could be found with SOC in 34% of cases missed by occlusion cholangiography in patients with dilated bile ducts and in those receiving lithotripsy [51]. In a systematic review and meta-analysis that comprised 49 studies, the overall predicted stone clearance rate was 88% (95% CI 85–91%) [37].

Adverse Events Associated with SOC

The use of SOC has been linked to the elevated risk of cholangitis and bacteremia, possibly related to longer procedure time, increased intraluminal pressure from irrigation, and insufflation within the bile duct causing bacterial translocation [52]. In a prospective experience, SOC was associated with a

Table 2 Edmonton Classification of dominant strictures in PSC by cholangioscopic findings. (Adapted from Sandha G, et al. 2018 [35])



bacteremia and cholangitis rate of 8.8% and 7.0%, respectively [53].

Prior to the cholangioscopy, pre-procedural antibiotics may be used particularly if tissue harvesting with biopsy sampling is required [54]. Antibiotics recommended are ciprofloxacin 500 mg orally given within 60 to 90 min before procedure (or 400 mg IV over 60 min beginning within 120 min before procedure), or amoxicillin-clavulanate 1750 mg orally within 60 min prior to procedure, or ampicillin-sulbactam 3 g IV within 60 min prior to procedure [55].

Cholangioscopy Classification of PSC and Potential Prognostic Significance

PSC is a diverse disease, with an extensive variety of disease phenotypes. A cholangiography-based classification has been demonstrated to correlate with clinical outcomes in PSC [56]. A recent classification, not specific for PSC, proposed a system using a new set of descriptions which, in a single-centered non-randomized study, seemed to advance performance for malignancy detection, with a sensitivity of 96%, specificity of 92%, with a PPV and NPV of 93% and 96%, respectively [57]. Edmonton Classification has been proposed by our group to stratify PSC patients with extrahepatic dominant strictures according to the phenotypic expression differences seen on cholangioscopy (Table 2) [35]. However, the clinical efficacy of these classification systems needs to be identified. Similar to patients with IBD, it is tempting to consider that SOC could benefit from routine screening strategies and early detection of premalignant biliary lesion that might indicate surgical resection or LT [58]; nevertheless, the feasibility of such strategies has yet to be established.

Conclusions

In summary, up to 50% of PSC patients develop DS during the evaluation of their disease. All DS should be investigated as PSC carries a significant risk for CCA. ERCP with brushing cytology is performed in most centers, but diagnostic accuracy is suboptimal despite inclusion of techniques such as FISH or DIA. SOC is a safe and efficient adjunctive tool with ERCP that allows for visual characterization and direct targeted biopsies, with studies demonstrating superior diagnostic performance. In addition, SOC could be useful for potential characterization of different phenotypes and treatment of residual bile duct stones in PSC. Most of the data for SOC in PSC comes from retrospective single-center studies analyzing heterogeneous cohorts without standardized protocols. As we still have an unmet need for appropriate diagnosis of CCA in PSC, additional prospective and multicenter studies are warranted to clarify the role of SOC in PSC.

Compliance with Ethical Standards

Conflict of Interest A Montano-Loza and M Ebadi declares no conflict of interest.

G Sandha is a consultant for Boston Scientific Corporation and has received honoraria for speaking commitments and advisory board meetings.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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