Role of endoscopy in primary sclerosing cholangitis: ESGE/EASL clinical guidelines

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic bile duct disease with an estimated prevalence in the range of 1 to 16 per 100 000 with significant regional differences across Europe. The prevalence of PSC is increased in patients with ulcerative colitis and estimated in the range of 1-5% (1) MRI studies have showed that the prevalence of imaging changes compatible with PSC in ulcerative colitis is almost 4-fold higher than that detected based on clinical assessments (2). PSC is more common in men (comprising 60-70% of the patients) and most patients present with pancolitis often with a right-sided predominance (3-5). A major challenge in the clinical management of the patients is a highly increased and unpredictable risk of biliary and colonic malignancies.

The diagnosis of PSC is based on the combination of clinical, laboratory imaging and histological findings. Briefly, a diagnostic work-up for PSC should be performed in all patients with inflammatory bowel disease (IBD) and abnormal liver biochemistry tests, especially elevated ALP and gGT values, as well as non-IBD patients with elevated cholestatic liver enzymes not otherwise explained. A proposed algorithm for PSC diagnosis has already been proposed by prior European Association for the Study of the Liver (EASL) guidelines (6), and comprehensive discussion of issues unrelated to the use of endoscopy in PSC will not be addressed in the present Guideline.

Endoscopic retrograde cholangio-pancreatography (ERCP) plays a significant role in the handling of PSC due to its high accuracy, prognostic value as well as its sampling and therapeutic possibilities. However, ERCP must be integrated in well defined clinical algorithms together with less or non invasive imaging and biochemical tests. In particular, the widespread implementation of MR cholangiography (MRC) has led to an increasing restriction of the the use of ERCP to cases where the diagnosis is equivocal, or when sampling or endoscopic treatment are required.

The aim of this evidence- and consensus-based Guidelines, commissioned by the European Society of Gastrointestinal Endoscopy (ESGE) and the EASL, is to provide practical advice on how to utilize ERCP and colonoscopy in PSC patients, in order to maximize its benefit and minimize its burden and adverse events.

Methods

The ESGE and the EASL commissioned this Guideline and appointed panel representatives from both societies to participate in the project development. The Guideline development process included meetings and online discussions among members of the Guideline committee during January April 2015 and July 2016. Key questions were prepared by the coordinating team. A systematic literature search in PubMed/MEDLINE and the Cochrane Library was conducted using at minimun the search terms “Primary Sclerosing Cholangitis” and “Endoscopy”, and “Colonoscopy” for the part related with the diagnosis and surveillance of IBD in PSC. Articles were first selected by title, their relevance was then assessed by reviewing full-text articles, and publications with content that was considered irrelevant were excluded. Aspects related to endoscopy in PSC patients after liver transplantation were omitted. Evidence tables were generated for each key question, summarizing the quality evidence of the

available studies. The entire process was performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (7). Draft proposals were presented to the entire group for general discussion and voting during a plenary meeting held in November 2015.

In May 2016, a compiled manuscript prepared by L.A. and T.H.K. was sent to all group members. After revisions and agreement on a final version, the manuscript was submitted for peer review. The revised manuscript was approved by all authors and the governing boards of ESGE and EASL and was subsequentely forwarded to Endoscopy and Journal of Hepatology for publication.

Endoscopic diagnosis and surveillance of PSC

Diagnosis of PSC

1. ESGE/EASL recommend that, as the primary diagnostic modality for PSC, MRC should be preferred over ERCP (moderate quality evidence, strong recommendation).

Although ERCP has been regarded as the standard of reference in diagnosing PSC, MRC is now recommended as first line non-invasive imaging method for patients with suspected PSC, offering comparable accuracy (except in in early stage of PSC restricted into intrahepatic bile ducts and the rare cases of contraindications to MRC) (8-12). A meta-analysis based on six studies using ERCP as a reference method concluded that MRC has high sensitivity and specificity (0.86 and 0.94, respectively) for the diagnosis of PSC (13). According to a decision model comparing different approaches in the work-up of patients with suspected PSC (14), the strategy of initial MRC, followed by ERCP only in selected cases (e.g. ambiguous MRC findings), is the most cost-effective approach (14, 15).

The ductographic features defining PSC are described below but a number of other diseases of the biliary tree may present similar features (table 1). The specificity of the cholangiographic features of PSC without the additional diagnostic clinical and biochemical clues is poor (16).

Table 1: Classification of secondary sclerosing cholangitis and conditions that may mimic primary sclerosing cholangitis on cholangiography

Infection	Bacterial / parasitic cholangitis
	Recurrent pyogenic cholangitis
Immunodeficiency related (infections)	Congenital immunodeficiency
	Acquired immunodeficiency (e.g. HIV)
	Combined immunodeficiencies
	Angioimmunoblastic lymphadenopathy

Mechanic/toxic	Cholelithiasis/choledocholithiasis
	Surgical bile duct trauma
	Intra-arterial chemotherapy
	Drug-induced sclerosing cholangitis
Ischaemic	Vascular trauma
	Hepatic allograft arterial insufficiency
	Paroxysmal nocturnal haemoglobinuria
Other pancreaticobiliary disease	Cystic fibrosis
	Sclerosing cholangitis of critical illness
	ABCB4 associated cholangiopathy
	Chronic pancreatitis
Systemic inflammatory diseases	IgG4-associated systemic disease
	Hypereosinophilic syndrome
	Sarcoidosis
	Graft-versus-host disease
Potentially mimicking on cholangiography	Langerhans cell histiocytosis
	Systemic mastocytosis
	Caroli's disease
	Congenital hepatic fibrosis
	Other types of ductal plate abnormalities
	Hodgkin's disease
	Cholangitis glandularis proliferans
	Neoplastic/metastatic disease

	Amyloidosis
	Hepatic allograft rejection

Of note, the visualization of the distal common bile duct and the peripheral intrahepatic ducts is still suboptimal using MRC (10, 12). One study has suggested that a numerical score calculated based on three-dimensional MRC may predict progression of bile duct changes but the study lacked ERCP reference (17). A diagnostic MRC, because of its very high specificity for the diagnosis of PSC when diagnostic clinical and biochemical clues are present, obviates a confirmatory ERCP unless therapeutic procedures or ductal sampling are indicated (13, 18).

2. ESGE/EASL suggest that ERCP can be considered if MRC and liver biopsy is equivocal or contraindicated in patients with persisting clinical suspicion of PSC. The risks of ERCP have to be weighed against the potential benefit with regard to surveillance and treatment recommendations (low quality evidence, weak recommendation).

Whether or not to perform ERCP in patients with normal high–quality MRC depends on the level of clinical suspicion for PSC and impact of the diagnosis on patients management and prognosis. ERCP is regarded unnecessary in patients with a low level of clinical suspicion, but it could be considered in patients with intermediate or high level of clinical suspicion as suggested by a meta-analysis of MRC diagnostic performance (13). However, this meta-analysis included only studies performed prior to 2007. The continuous improvement in MRC quality due to use of higher magnetic fields, as exemplified by the ability to visualize third- and fourth-order intrahepatic ducts as well as the availability of 3-dimensional image acquisition, is likely to further decrease the probability of abnormal ERCP in patients with normal MRC. In addition, as detailed reports including clinical, biochemical and histological characteristics and outcome of these patients with negative MRC but positive ERCP are lacking, the clinical benefit of ERCP can be questioned in this setting. If high-quality MRC images are not available or in equivocal cases, it is reasonable to consider patient referral to centers with known technical expertise with MRC as a first step(19) , followed by liver biopsy. If high-quality MRC images and liver biopsy still cannot definitely exclude or confirm the presence of PSC, ERCP can be considered in patients with persisting clinical suspicion for the diagnosis to take advantage of the filling pressure obtained by the balloon occlusion, and slight superiority as to visualization of the extrahepatic bile ducts.

Ductographic criteria for PSC

The first ERCP criteria for ductographic changes in PSC were published in 1984 by Li-Yeng (20). Typical changes seen in PSC consist of minor irregularities of duct contour and local narrowing with prestenotic dilatation (type I), threadlike narrowings alternating with normal caliber of bile ducts or slight dilatation (type II), multiple strictures with saccular dilatations (type III), and the most advanced changes consisting of advanced ductal narrowing with resultant lack of filling of the peripheral ducts (type IV). The classification has later been modified by Majojie et al (21) and Ponsioen et al (22, 23). The classification of Ponsioen et al (23) has been validated and shown to correlate with patient prognosis

(Table 2). Another type of classification is based on evaluation of the grade, length, and extent of strictures, the degree of bile duct dilatation, and the distribution of lesions (24). None of the ductographic criteria published are specific for PSC and the findings must be interpreted in the context of patient demographics and the clinical context. Review by teams with an expertise in complex biliary disease is often useful, as multiple secondary causes of sclerosing cholangitis must be considered (25) (Table 3).

Table 2. Amsterdam classification of cholangiographic changes in PSC (23)

Type	Intrahepatic	Extrahepatic
0	No visible abnormalities	No visible abnormalities
I	Multiple caliber changes; minimal dilatation	Slight irregularities of duct contour; no stricture
II	Multiple strictures; saccular dilatations, decreased arborization	Segmental strictures
III	Only central branches filled despite adequate filling pressure; severe pruining	Strictures of almost entire length of duct
IV	-	Extremely irregular margins; diverticulum like outpoutchings

Table 3 : Characteristic cholangiographic features in primary sclerosing cholangitis (PSC) and other ductal diseases

Diagnosis	**Main Cholangiographic features**
PSC	Multifocal intra- and extra-hepatic bile duct strictures ("beaded" appearance), slight biliary dilatation, diverticular outpouchings, pruned-tree appearance at chronic stage
Ascending cholangitis	Multiple intrahepatic bile duct strictures, stones, biliary abscesses
Ischaemic cholangitis	Proximal intrahepatic bile duct strictures, bile duct necrosis, biliomas, abscesses, biliary cast
Caustic cholangitis	Localized intrahepatic bile duct strictures, irregularities of bile duct wall
AIDS related cholangitis	Stricture of the distal common bile duct, papillitis, acalculous cholecystitis
IgG4 related cholangitis	Multifocal central bile duct strictures, bile duct wall thickening with visible lumen, pancreatic abnormalities compatible with autoimmune pancreatitis
Portal biliopathy	Central and extrahepatic bile duct irregularities

Unusual cholangiographic features

Some PSC patients may present with cystic dilatations of intrahepatic bile ducts simulating Caroli's disease (10). Of note, the fusiform and small cystic dilatations of intrahepatic (mostly peripheral) bile ducts as observed in patients with congenital hepatic fibrosis and autosomal recessive polycystic kidney disease should not be misdiagnosed as PSC (11). Another differential diagnosis is the peculiar cholangiographic phenotype of adult forms of ABCB4/MDR3 deficency which may be characterized by large uni- or multifocal spindle-shaped intra-hepatic bile duct dilatations with or without apparent bile duct stenosis (12, 26). Diagnosis should be suspected on familial clustering of excessive gallstone disease and a history often with prior cholecystectomy at age < 40 years and associated intrahepatic cholestasis of pregnancy and is confirmed by *ABCB4* genotyping.

3. ESGE/EASL do not suggest routine use of other endoscopic techniques (i.e. EUS including IDUS, cholangioscopy, confocal endomicroscopy) than ERC for the *diagnosis* of PSC (weak recommendation, low quality evidence)

In the diagnosis of PSC there is no established role for endoscopic techniques beyond ERCP, e.g. brush cytology, ductal biopsy, cholangioscopy or confocal laser microscopy. In selected cases with suspected extrahepatic disease and inconclusive MRC findings, endoscopic ultrasound (including intraductal ultrasound, IDUS) and elastography may add information on common bile duct strictures, wall thickening and liver fibrosis stage (27-30).

ERCP in established PSC

4. ESGE/EASL suggest to define a dominant stricture (DS) at ERC as a stenosis with a diameter of ≤1.5 mm of the common bile duct and/or ≤1.0 mm of a hepatic duct within 2 cm of the main hepatic confluence (weak recommendation, low quality evidence).

Deciding on the clinical impact of a bile duct stricture may be challenging. The DS denomination arose alongside the term "major stricture" early in the history of endoscopic management of PSC (31). The "major" or "dominant" stricture terms were initially used more broadly pertaining to strictures of the common bile duct and right and left bifurcation of the hepatic ducts (extrahepatic PSC lesions), since these were found to be more prone to clinical events than intrahepatic strictures (31, 32). The precise definition of a DS was introduced by Stiehl et al. for the use in endoscopic studies as a severity measure in 2002 (33, 34), although is somewhat arbitrary set, depending on e.g. filling pressure. A number of endoscopic studies both before and after 2002 do not apply the diameter criterion strictly when determining DS (35, 36), and focus on suspected clinical relevance. Determining the clinical significance and potential benefit from endoscopic interventions should therefore not be based on this definition alone and the decision for intervention rather considered a compound clinical decision. Multiple DS can be found in the same patient (12% in the study by Bjornsson et al) (34). Of note, the ERCP definition of DS is usually considered as not applicable to MRC, in particular in the extrahepatic ducts, given the insufficient spatial resolution of MRC (37, 38) and the lack of hydrostatic pressure as provided by ERCP.

A complete occlusion cholangiogram should generally be obtained if an ERCP is performed because it adds little risk to the ERCP, decreases variability, and may reveal that a DS suspected at MRC is indeed not a stricture (39).

5. ESGE/EASL suggest ERCP and ductal sampling (brush cytology, endobiliary biopsies) should be considered in established PSC in the case of (i) clinically relevant or worsening symptoms (jaundice, cholangitis, pruritus) (ii) rapid increase of cholestatic enzymes levels or (iii) new or progression of existing dominant strictures in ERC in the context of appropriate clinical findings (weak recommendation, low quality evidence).

ERCP can be indicated in patients with a confirmed diagnosis of PSC when changes in clinical, laboratory and radiological findings occur during the course of the disease. The purpose is to make an assessment of the likelihood of the presence of biliary dysplasia as a risk factor for cholangiocarcinoma (CCA) and to determine biliary strictures amenable to intervention.

a) Clinical events.
   In the early stage of PSC dominant biliary strictures are usually asymptomatic. Exacerbation of jaundice (not related to liver failure), episodes of fever and chills suggestive of cholangitis or worsening of pruritus are indications for ERCP for the treatment of dominant strictures and to perform ductal brush sampling to exclude malignancy (40, 41). Worsening pain in the right upper abdominal quadrant, fatigue and weight loss also need careful evaluation.
b) Laboratory results.
   Serum laboratory tests are neither sensitive nor specific enough to evaluate PSC progression (41), but in case of rapid increase of serum bilirubin levels and/or cholestatic liver enzymes (serum alkaline phosphatase, serum gamma glutamyl transferase) ERCP is indicated (6), especially in patients with a diagnosis of clinically significant hilar or extrahepatic strictures on MRC. Elevation of serum CA19-9 in PSC patients has an unsatisfactory sensitivity (14%) and positive predictive value (67%) for the diagnosis of CCA (36, 41, 42), and is not helpful in selecting patients for ERCP.
c) Progression/new onset clinically significant strictures on MRC.
   Progressive intra- or extra-hepatic bile duct dilatation on imaging studies (ultrasound or MRC) is an indication for ERCP with ductal sampling (6). A careful evaluation of new onset dominant strictures in PSC is recommended, due to the increased risk of CCA in this situation.
   In detail, a stricture disproportionately severe relative to others, concomitant biliary filling defects, marked biliary dilation [≥ 2 cm for the common bile duct, ≥1 cm for the right or left intrahepatic ducts, ≥ 5 mm for other intrahepatic ducts]) suggests CCA (43). Conversely, this risk was absent in patients without dominant strictures according to a 25 year experience (44). Abnormal cytological findings, such as suspicion of malignancy or aneuploid DNA findings need a close follow-up by ERCP with repeated sampling, unless urgent liver transplantation is considered warranted.
   The utility of ERCP in handling DS was shown in a prospective study (45) on 171 PSC patients followed for 20 years: repeated endoscopic therapy was associated with a transplant free

survival of 81% at 5 years and 52% at 10 years after initial endoscopic therapy. In this population, a 6% CCA rate was found in patients with dominant strictures.

6. EAGE/EASL suggest that, in patients with an established diagnosis of PSC, MRC should be considered before therapeutic ERCP (weak recommendation, low quality evidence).

MRC may be useful to confirm the indication, exclude focal parenchymal changes and to give clinicians performing ERCP imaging based guidance to minimize the risk of complications. Regarding MRC in established PSC, a single retrospective centre study reported a 76% accuracy of MR with MRC in the diagnosis of CCA complicating PSC (43). For these reasons, patients with an established diagnosis of PSC should have an MRC exam in his/her clinical records (13, 46).

7. ESGE/EASL suggest performing endoscopic treatment with concomitant ductal sampling (brush cytology, endobiliary biopsies) of suspected significant stricture at MRC in PSC patients who present with symptoms likely to improve following endoscopic treatment (strong recommendation, low quality evidence).

Selected series reporting on the endoscopic treatment in PSC patients are summarized in Table 4; none of these compared performance vs no performance of endoscopic treatment for DS. The benefits reported following DS dilation included short-term improvement of symptoms and of liver biochemical tests as well as a longer liver transplantation (LT)-free survival compared to that predicted using the Mayo clinical risk model. Similar findings have also been reported in several smaller case series (47-51).

The main criticisms made to these studies are as follows:

a) The Mayo clinical risk model was not designed to evaluate patients with DS; specifically, many patients underwent therapeutic ERCP because of elevated bilirubin, which is part of the Mayo risk score, and went down in most patients after the intervention. Hence, baseline Mayo risk score was not determined in a steady state situation;
b) Serum tests for cholestasis may spontaneously fluctuate in patients with PSC complicated or not with a DS. Bjornsson et al reported in 125 PSC patients changes in s-ALP and s-bilirubin from baseline up to 12 months following ERCP. As patients with DS received no stricture dilation, the authors stated that “If our patients had been consequently dilated or stented the decrease in bilirubin and clinical features at follow-up would have been attributed to endoscopic therapy” (34). However, in that study, the variations reported in ALP and in total serum bilirubin after vs before ERCP were not significant, in contrast with various studies listed in Table 4 that used DS dilation/stenting. Also, it was not clear on what basis these patients were treated conservatively, while others did receive endoscopic therapy.

Other limitations of most studies listed in Table 4 include a retrospective design, selection bias, reporting of results mixed for dilation ± stenting of DS as well as treatment with ursodeoxycholic acid started during follow-up in a minority of patients.

A critical issue is to weigh potential benefits vs. the certain risks of therapeutic ERCP in patients with no other therapeutic option except LT. Symptoms likely to improve following DS treatment generally include pruritus, pain, cholangitis and jaundice in patients with a significant (≥20%) increase in cholestasis while in patients with end-stage liver disease, only cholangitis is expected to improve.

Finally, patients with advanced liver disease with cirrhosis may not benefit from endoscopic treatment. Ahrendt et al. reported no change in serum bilirubin at one year following endoscopic and/or percutaneous stricture dilation in 10 patients with cirrhosis and a baseline serum bilirubin ≥5 mg/dl (52). Death following endoscopic balloon dilation of DS has been reported in a patient with PSC and end-stage liver disease (53). Diagnostic ERCP was followed by deterioration of cholestasis in 7 of 8 vs. one of 7 patients with more (Ludwig stage III or IV) vs. less (Ludwig stage I or II) advanced PSC at biopsy (54).

Balloon dilation vs. stent therapy

8. EASGE/EASL suggest that the choice between stenting and balloon dilation should be left at the endoscopist's discretion (weak recommendation, low quality evidence).

Results from selected series reporting on endoscopic treatment of dominant strictures in PSC are summarized in Table 4. Of note, (i) in the majority of studies that reported on balloon dilation for DS, stents were inserted in a minority of patients, (ii) a significant improvement in LT-free survival compared with the Mayo model has been reported only with balloon dilation and (iii) the perforation rate has been higher with stenting compared with balloon dilation.

A single, retrospective, study compared balloon dilation vs. balloon dilation combined with stenting for DS in PSC patients (n=34 and n=37, respectively) (53). The "balloon dilation alone group" was treated by endoscopic means only while 23 (62%) patients in the "stenting" group underwent percutaneous treatment due to failed endoscopic access and/or DS dilation. Serum bilirubin similarly decreased in both groups of patients but more procedures and more complications were recorded in the stent vs. the balloon dilation group (median number of procedures per patient, 5.0 vs. 2.1, respectively; patients with complications, 54% vs. 15%, respectively). Complications included bile duct perforation in 7 (10%) patients, 5 of whom were in the stent group. However, conclusions are difficult to draw due to the different access routes used (percutaneous in 62% vs. 0 in the stent vs. balloon dilation group, respectively), a selection bias due to more severe stricture in the stent groupand the long stenting duration used (mean, 3 months) putting the patient at high risk for stent clogging and cholangitis. A short stenting duration (see recommendation 13) is currently the standard of care.
The European multicenter randomized DILSTENT trial comparing single balloon dilatation versus short-term stenting was prematurely stopped recently after a planned interim analysis. Preliminary results show no differences in outcome, but a significantly higher serious adverse event rate in the stent group, mainly consisting of PEP and suppurative cholangitis (ref. pending).

Role of sphincterotomy

9. ESGE/EASL recommend weighing the anticipated benefits of biliary papilllotomy/sphincterotomy against its risks on a case-by-case basis (strong recommendation, moderate quality evidence). Biliary papillotomy/sphincterotomy should be considered especially after difficult cannulation (strong recommendation, low quality evidence).

Biliary sphincterotomy was performed routinely as part of the endoscopic treatment of DS in some studies (53) while its use was restricted to specific cases such as stone extraction and difficulties in stent insertion in other studies. For example, in 32 PSC patients treated with stents for DS, sphincterotomy was performed in 12 (38%) patients (55) while in another study of DS dilation±stenting, sphincterotomy was performed in 63% of 63 patients (56).

Generally, biliary sphincterotomy is not recommended as a routine procedure prior to biliary stenting because of the associated risks as demonstrated in RCTs (57). However, if cannulation is difficult, biliary sphincterotomy is advised, when considering that these patients are likely to require multiple procedures. Many endoscopists prefer a small sphinterotomy in PSC in order to avoid ascending cholangitis.

Specifically in PSC, biliary sphincterotomy was independently associated with an increased risk of short-term adverse events in two retrospective studies (odds ratios [OR] 4.7 and 5.0) (58, 59) while previous biliary papillotomy/sphincterotomy was protective for subsequent ERCPs (58); therefore experienced endoscopists perform biliary sphincterotomy in patients with difficult cannulation in whom ERCP is likely to be repeated during follow-up.

Balloon dilation

10. ESGE/EASL suggest selecting the balloon calibre of up to the the maximum caliber of the ducts delimiting the stricture (weak recommendation, low quality evidence).

11. ESGE/EASL suggest repeating dilation of relapsing DS if (i) the DS is regarded as the cause of recurrent symptoms (cholangitis, pruritus) or of significant increase in cholestasis and (ii) patient's response to previous dilations has been satisfactory (weak recommendation, very low evidence).

There are no comparative data on the optimal dilation scheme or balloon diameter for treating DS. In the largest prospective study (500 endoscopic balloon dilations in 96 patients), the authors performed stepwise DS dilation up to diameters of 8 mm and 6-8 mm in the common bile duct and the hepatic ducts, respectively (60). Bile duct diameter upstream and downstream of the DS should be taken into account for selecting the balloon diameter to avoid dilating to more than the duct diameter. Balloon dilations are usually repeated at intervals of one to four weeks up to technical success, for an average of 2-3 balloon dilations (33, 51, 60). Technical success has been defined as complete balloon inflation within the DS with no waist observed fluoroscopically followed by the unobstructed passage of contrast medium through the dilated biliary segment to the duodenum (51, 60). Using this technique, bile duct perforation was reported in 0.2% of DS dilations (1% of patients) (60). In contrast, another study that

used 4-12 mm in-diameter balloons for dilation reported dilation-related biliary perforations in 3.5% of procedures (56).

Repeat balloon dilation during follow-up after initial treatment (usually consisting of several ERCPs) has been mentioned in some studies but no results of the repeat dilation in terms of clinical or biochemical improvement has been reported (33, 51).

Stent therapy

12. ESGE/EASL suggest selecting a single 10-Fr stent or two 7-Fr stents for, respectively, for DS in the extrahepatic ducts or hilar strictures extending into the left or right hepatic duct (final stent diameters in the case of stepwise stenting) (weak recommendation, very low quality evidence).

In all large studies of endoscopic treatment for DS, plastic stents measuring 7 to 10-Fr in diameter were used, with no comparison of the results obtained with various stent diameters reported. Specifically, the Amsterdam group aimed at inserting a single 10-Fr stent, and if this was not possible at first attempt, it was preceded by 1-week stenting with a 7-Fr stent or insertion of a nasobiliary catheter (55, 61). The Mayo group used 7–10-Fr stents at the endoscopist's discretion (53). The Indianapolis group did not mention the diameter of stents used (56). Two 7-Fr stents have typically been used in patients with multiple bilateral DS and in patients with a hilar stricture extending into the left or right hepatic duct in order to avoid temporary obstruction of the contralateral biliary system. In general, the stent caliber and length must be adapted to the specific biliary tree configuration.

In other diseases, studies have shown that polyethylene stents provide better short-term (one-month) patency than Teflon models and that, at long-term, 10-Fr models provide longer biliary patency compared with thinner ones (11.5-Fr models do not provide longer patency) (57).

With respect to balloon dilation prior to stenting, it is currently unclear whether a balloon dilation is beneficial before stent placement.

Duration of stenting

13. ESGE/EASL suggest that stents used for treating DS should be removed 1-2 weeks following insertion (weak recommendation, low quality evidence).

No comparison of various stenting durations has been identified in studies reporting on stenting for DS. A short stenting duration is currently favored because stents tend to clog rapidly in PSC patients and similar efficacy results have been reported with short (1-2 weeks) vs. standard (8-12 weeks) stenting duration. Specifically, a retrospective study of short-term stenting (mean duration, 11 days) in 32 symptomatic PSC patients with DS showed, at two months, a symptomatic improvement in 83% of the patients as well as a significant improvement of cholestasis tests; at one and three years, actuarial analysis showed that 80% and 60% of patients, respectively, would not require reintervention (55). Stent dysfunction was not reported in this study but two patients treated by stent removal developed hydrops of the gallbladder. The same group of authors had previously reported similar efficacy results with 3-month stenting in 25 patients with symptomatic DS but, in that study, unscheduled stent exchange had to be performed on 32 occasions due to suspected stent clogging (cholangitis, n=23; jaundice, n=9) (62).

All studies mentioned focused on clinical and serum liver tests, not radiological data, to assess the short-term effect of therapeutic ERCP (53, 55, 61, 62). Endoscopic treatment has been repeated in a sizeable proportion of patients: for example, with long median stenting periods (3 months), the median number of repeated ERCPs per patients ranged between 3 and 5 during follow-up periods of 29 and 22 months in two studies (53, 62) while following a short stenting period (mean, 11 days) repeat ERCP rates at one and three years after treatment were estimated at 20% and 40%, respectively (55). Other details about repeated treatments were not reported.

In many centers, stents are removed during an esophagogastroduodenoscopy without biliary opacification in PSC patients.

Table 4: Selected series reporting on endoscopic treatment of dominant strictures in primary sclerosing cholangitis

First author, Year	Study design	N	Intervention	Outcomes	Results
1. Dilation ± stenting					
Gotthardt, 2010 (extension of Stiehl 2002 study (33)) (60)	Pro-spective	96 (AP>2xULN)	Balloon dilation (8 mm in CBD, 6-8 mm for IHBD), plus stent in 5 patients with severe cholestasis and bacterial cholangitis	Short-term improvement in cholestasis; transplant-free survival; complications	- At 2 weeks, mean bilirubin level significantly decreased (by 56%) - Change in symptoms and LT-free survival - Comparison with Mayo model not reported (5-and 10-year LT-free survival, 81% and 52%) - Overall complication rate, 3.8%
Gluck, 2008 (35)	Retro-spective	84, symptom-matic patients	Balloon dilation and stenting (70% and 51% of patients, respectively)	LT-free survival	- Higher proportion of patients alive with no LT at 3 and 4 years than predicted using Mayo model ($P < 0.05$); at 1 and 2 years similar survival

					- Adverse events in 21 therapeutic ERCPs (7.2% of 291 procedures, 25% of patients)
Stiehl, 2002 (33)	Pro-spective	52 (AP>2xULN)	Balloon dilation (8 mm in CBD, 6-8 mm for IHBD), plus stent in 5 patients with severe cholestasis and bacterial cholangitis	Bilirubin and liver enzymes 2 weeks after dilation, symptoms, LT-free survival	- At 2 weeks, significant decrease in liver enzymes and bilirubin - Improvement of jaundice in 24/24 and of pruritus in 12/13 patients - Longer LT-free survival than predicted using 1992 Mayo model (P < 0.0001)
Baluyut, 2001 (56)	Retro-spective	56 with and 7 without symptoms	Balloon dilation (4-12 mm, N=61) 1x/year, with stent if no significant radiological improvement following dilation (N=33)	LT-free survival, complication rate	- Longer LT-free survival than predicted using 1999 Mayo model (P=0.027) - 12% complications
2. Stenting					
Ponsioen, 1999 (55)	Retro-spective	32 symptom-matic patients with successful stenting for DS	One-week stenting (10 Fr stent) with no balloon dilation	Two-month symptomatic and biochemical improvement, actuarial curve of reintervention-free patients	- Improvement of symptoms in 83% - Significant decrease in bilirubin (44% had increased conjugated bilirubin at baseline) and cholestasis enzymes - Reintervention-free patients (actuarial): 60% at 3 years

van Milligen de Wit, 1996 (62)	Retro-spective	25 with symptoms or progression of serum tests for cholestasis	Stenting for a median of 3 months (plus 8-mm dilation in 3 patients)	Change in symptoms and biochemical tests within 6 months following stent insertion; Adverse vents	- Improvement of symptoms in 76% - Significant decrease in bilirubin (52% had increased bilirubin at baseline) and serum tests for cholestasis; - 32 episodes of cholangitis/jaundice related to stent clogging
3. Dilation v. stenting					
Kaya, 2001 (53)	Retro-spective	71 with symptoms	Balloon dilatation (4-8 mm, N=34) vs balloon dilation with 3-4-month stenting (N=37). Intervention via PTBD in 0/34 vs 23/37 patients in balloon vs stent group	Biochemical course up to 24 months	- Both strategies improved liver biochemistry, fever resolved only in the dilatation without stent group. No additional benefit of stenting after balloon dilatation - More complications in stent vs dilation alone group (P=0.001) as well as in PTBD vs ERCP group (P<0.001) (no multivariate analysis)

AP, alkaline phosphatases; DS, dominant stricture; ULN, upper limit of normal values; CBD, common bile duct ; IHBD, intrahepatic bile ducts ; UDCA, ursodeoxycholic acid ; LT, liver transplantation ; SAE, serious adverse events ; PTBD percutaneous transhepatic biliary drainage.

Complications of endoscopic therapy

14. ESGE/EASL suggest that ERCP in PSC patients should be undertaken by experienced pancreaticobiliary endoscopists (strong recommendation, very low quality evidence).

Several studies have evaluated the risk of complications in PSC patients undergoing ERCP (63-74). ERCP carries an increased risk for complications in the context of PSC, especially pancreatitis, cholangitis and extravasation of contrast, although not all the studies were documented such an increased risk in PSC (69, 74). In the systematic survey (75) of post-ERCP complications on various indications for ERCP including 21 prospective studies and 16,855 patients the number of total complications was 6.85% (CI 6.46-7.24%). Pancreatitis occurred in 585 subjects (3.47%, CI 3.19-3.75%). In another large retrospective single center study (76) with 11,497 procedures over 12 years the total complication rate was 4.0 % and pancreatitis occurred in 3.6%. The overall risk of adverse events in patients with PSC has varied in different, much smaller, studies from 1.8 % to 18.4 % (63-74), which is higher than reported in other indications (75, 76).

Retraction of the papilla and an altered, more difficult, position of the endoscope due to hypertrophy of the left liver lobe may be encountered during ERCP in PSC patients. Whether this actually influences cannulation success rates has not been investigated by specific studies. Cohort studies describing PSC patients provide only limited details on cannulation difficulties with failure rates of 0% to 6% (36, 44, 64-66, 74, 77-80). Furthermore, there is likely a selection bias since most retrospective series describing the results of endoscopic treatment have the initiation of therapy as prerequisite, therefore potentially excluding cannulation failures.

The largest series is the study by Ismail et al (71). In this retrospective review of 441 ERCP procedures over a three-year time period, primary cannulation success was 88.2%. Of note, in 137 patients (37.8%) a previous biliary sphincterotomy had been performed. Pancreatic sphincterotomy as an access technique was used in 11.8% and freehand needle knife sphincterotomy in a further 2.5%. Primary failure rate was 0.5%. These figures suggest that cannulation in PSC patients may indeed be more difficult than in other types of patients.

Post-ERCP pancreatitis

15. ESGE/EASL recommends routine rectal administration of 100mg of diclofenac or indomethacin immediately before or after ERCP in all patients without contraindication. In addition to this, in the case of high risk for post-ERCP pancreatitis, the placement of a 5-Fr prophylactic pancreatic stent should be considered (strong recommendation, high quality evidence).

Post ERCP-pancreatitis (PEP) is the most common and feared complication associated with ERCP. The risk for PEP in PSC vary from 1 to 7 %, although the diagnostic criteria vary between studies (81). Although the quality of the evidence is low, risk factors increasing the risk for PEP are probably not different in PSC patients from the general population: female sex (odds ratio [OR] 2.6, P= 0.015) and a guide wire in the pancreatic duct (OR 8.2, P<0.01). Native papilla increases whereas previous sphincterotomy decreases the risk (71), suggesting that preemptive EPT might be warranted in PSC patients where repeat procedures might be anticipated. This has however yet to be proven.

Prolonged papilla contact time as well as therapeutic procedures such as biliary brush cytology, sphincterotomy, stenting and dilatation are associated with increased risk of PEP. Precut biliary and pancreatic sphincterotomy is markedly associated with PEP (71), possibly reflecting the difficult cannulation and prolonged procedure time. The recent Cochrane analysis comparing the contrast-assisted technique with the guidewire-assisted cannulation technique showed that guidewire technique both increased the primary cannulation rate and reduced the risk of PEP, and it appears to be the most appropriate first-line cannulation technique (82).

Rectal NSAIDs. In its 2014 update to the Guideline on the prophylaxis of post-ERCP pancreatitis, the ESGE recommends routine rectal administration of 100mg of diclofenac or indomethacin immediately before or after ERCP in all patients undergoing ERCP without contraindication to NSAIDs (83). The recommendation was supported by the results of six meta-analyses published between 2009 and 2014 that compared NSAIDs vs. placebo administration for prophylaxis of post-ERCP pancreatitis. These meta-analyses concordantly showed the benefit of NSAIDs in preventing either mild or moderate/severe PEP. These results were further supported by subsequent meta-analyses (84, 85) and the cost-efficiency of this approach has been demonstrated (86). This recommendation applies to PSC patients.

Pancreatic stenting: The ESGE 2014 recommendation about prophylactic pancreatic stenting was supported by (i) three meta-analyses of RCTs that showed a significant reduction in the incidence and the severity of PEP when prophylactic pancreatic stenting was used and (ii) a study showing that pancreatic stent placement is cost-effective only in patients/procedures at high risk for post-ERCP pancreatitis.

The following conditions relevant to PSC are considered to represent high risk for PEP: precut biliary sphincterotomy, pancreatic guidewire-assisted biliary cannulation, endoscopic balloon sphincteroplasty, pancreatic sphincterotomy, and presence of more than three of the following risk factors: female gender, previous pancreatitis, younger age, nondilated extrahepatic bile ducts, absence of chronic pancreatitis, normal serum bilirubin, cannulation attempts duration > 10 min, pancreatic guidewire passages > 1, pancreatic injection, failure to clear bile duct stones, intraductal ultrasound.

16.ESGE/EASL suggest routine administration of prophylactic antibiotics before ERCP in patients with PSC (strong recommendation, low quality evidence).

Bacterial cholangitis and bacteriobilia are not an infrequent finding among patients with PSC. In studies evaluating the complications of ERCP in PSC the risk for cholangitis has varied from 0.2 to 8 % (63-74), depending among other items on the criteria used to define cholangitis. The use of prophylactic antibiotics markedly varies between studies in terms of prevalence, type of antibiotic and duration of of administration (from one oral dose before the procedure to one-week dosing afterwards). In a Cochrane meta-analysis (9 RCTs, 1573 patients), the prophylactic use of antibiotics was shown to prevent cholangitis (relative risk (RR) 0.54, 95% CI 0.33 to 0.91), septicemia (RR 0.35, 95% CI 0.11 to 1.11), bacteriemia (RR 0.50, 95% CI 0.33 to 0.78), and pancreatitis (RR 0.54, 95% CI 0.29 to 1.00). It was concluded that prophylactic antibiotics reduce bacteriemia and seem to prevent cholangitis and septicemia in patients undergoing elective ERCP (87). Our recommendation is in line with the ASGE

recommendation to prescribe antibiotic prophylaxis in procedures where drainage achieved at ERCP is incomplete or achieved with difficulty, such as PSC (88). Bile fluid sampling could be considered during ERCP, to guide antibiotic treatment in case cholangitis occurs despite the prophylaxis (89)

Table 5. Complications of ERCP in PSC patients.

First author, year, country	**Study design**	**Patients/ERCPs**	**Complications, %**		
			Total	Pancreatitis	Cholangitis
Lee, 1995, USA (65)	Retrospective	53/175	13.7	7	8
van den Hazel, 2000, The Netherlands (66)	Retrospective	83/106	9	3	2
Baluyut, 2001, USA (56)	Retrospective	63/63	1.8	1.26	0.6
Stiehl 2002, Germany (64)	Retrospective	106/ ERCP yearly, median 5 years	9	5.2	3.3
Enns, 2003, Canada (67)	Retrospective	104	17	5	7.5
Gluck, 2008,USA (68)	Retrospective	106/317	7.3	3.8	0.95
Etzel, 2008, USA (74)	Retrospective	PSC:30/85 Non-PSC:45/70	12.9 8.6	2.4 2.9	5.9 1.4
Bangarulingam 2009, USA (69)	Retrospective	PSC: 168 Non-PSC: 981	11 8	5 4	3.6 0.2
Alkhatib, 2011, USA (70)	Retrospective	75/185	8	5	1
Ismail, 2012 Finland (71)	Retrospective	441/441	9	7	-
Navaneethan 2015, USA (72)	Retrospective	294/697	4.3	1.2	2.4
von Seth,2015, Sweden (73)	Retrospective, national registry study	PSC: 141/141 Non-PSC: 8791	18.4 7.3	7.8 3.2	7.1 2.1

PSC and cholangiocarcinoma

17. EASL/ESGE recommend that CCA should be suspected in any patient with worsening cholestasis, weight loss, raised serum CA19-9 and/or new or progressive DS, particularly with an associated enhancing mass lesion (strong recommendation, moderate quality evidence)

18. A raised serum CA19-9 may support the diagnosis of CCA, but has a poor specificity (weak recommendation, low quality evidence).

PSC is associated with a markedly increased risk for CCA with a lifetime risk of 10%-20% (90, 91), or up to 400-fold compared with the general population (92). CCA represents a common cause of death among PSC patients (93), whereby 27-50% of all CCAs are detected within one year of a PSC diagnosis (44, 94, 95) depending on the indications for ERCP.

CCA should be suspected in PSC patients experiencing rapid deterioration of liver function tests, increasing jaundice, weight loss and abdominal pain. However, the development of such a clinical trend may also suggest an advanced form of CCA. An observational study performed in the U.S. on 230 PSC patients affected by PSC, twenty-three of which had CCA, showed no major differences in the clinical features of the patients with or without CCA when the malignancy is at an earlier stage (43).

Increased s-CA19-9 have been reported to indicate the development of CCA in PSC patients. Employing 129 or 100 U/mL cut-off levels detected CCA with high sensitivity (nearly 80%) and specificity (nearly 100%) (96), but only in advanced cases of CCA. These data are in contrast with other observations, which showed that one third of PSC patients with high CA19-9 levels did not have CCA.(97, 98) In a recent study performed on 433 PSC patients, 41 of whom had biliary malignancy, the use of *FUT2/3* genotype-dependent cut-off values for CA19-9 improved sensitivity and reduced the number of false positive results (99). In a study screening for biliary dysplasia using ERCP and brush cytology, serum CA19-9 had no prognostic value for biliary dysplasia or CCA (39). Currently, there are no definite radiologic features that indicate CCA in a PSC patient, although the detection of a DS by MRCP may be suggestive for CCA. However, 50% of PSC patients experience a DS and its absence does not rule out CCA. In a cohort of 230 patients, US, CT and MRCP were found to have high specificity but low sensitivity (10-32%).(43)

ERCP findings indicative of CCA

DSs are frequent in PSC (60) and do not per se indicate development of a malignancy. In a large single center study, CCA was seen in 6/95 DSs (6%). In general it could be inferred that the chance of any DS of harbouring a CCA is around 5%. Most CCAs develop in perihilar region or in extrahepatic bile ducts, and are reachable with cytological brush. In a large series of patients with CCA (100), 50% had perihilar CC (pCC), 42% had distal CC, and only 8% of the CCA's were intrahepatic CCA. No specific imaging features have been found to differentiate benign strictures from malignant ones. Based on ERCP findings only it is not possible to exclude CCA from benign strictures caused by PSC, and the diagnosis requires always additional techniques such as biliary cytology or histology.

19. ESGE/EASL recommend ductal sampling (brush cytology, endobiliary biopsies) as part of the initial investigation for the diagnosis and staging of suspected CCA in patients with PSC (strong recommendation, high quality evidence).

20. ESGE/EASL suggest that fluorescence in situ hybridization (FISH) or equivalent chromosomal assessments are considered in patients with suspected CCA when brush cytology results are equivocal (weak recommendation, low quality evidence)

21 ESGE/EASL suggest that additional investigations such as cholangioscopy, endoscopic ultrasound and probe-based confocal laser endomicroscopy (pCLE) may be useful in selected cases (weak recommendation, low quality evidence).

Brush cytology

Bile duct brushing is the most common method for tissue sampling in patients with PSC for detecting inflammation, biliary dysplasia or CCA. In a recent meta-analysis (11 studies, 747 patients) (101), the pooled sensitivity, specificity, positive predictive value and negative predictive value of bile duct brushings for diagnosis of CCA in patients with PSC were 43% (95%CI, 35%-52%), 97% (95% CI, 95%-98%), 78.2% (95% CI, 63.6%-86.7%), and 87.2% (95% CI, 85.4%-89.1%), respectively. The authors concluded that bile duct brushing is a simple and highly specific technique for detecting CCA in patients with PSC. However, the modest sensitivity from bile duct brushing precludes its utility as a diagnostic tool for early detection of CCA in patients with PSC. In a recent study of 261 mostly (81%) asymptomatic patients with PSC referred for their first ERC to confirm diagnosis and screen for biliary dysplasia with systematic bile duct brushings, 43% were found to have advanced disease, and malignant/suspicious cytology was present in 6.9% (39).

Addition of FISH analysis of cytology specimens enhanced the sensitivity for detecting CCA in patients with PSC in several patient series (42, 43, 102, 103). The ideal methodology (e.g. FISH vs. digital image analysis [DIA] vs. flow-cytometri) and appropriate threshold values for markers assessed by each of these methodologies have not been robustly established and this makes meta-analysis of available data challenging (104). For this reason, chromosomal assessments can so far only be recommended in equivocal cases (104). As DNA technologies evolve, new markers are likely to emerge.

Ductal biopsy

Ductal biopsy has shown to improve the sensitivity, specificity and accuracy to diagnose CCA compared to brush cytology alone (105). Since the sampling area for ductal biopsies is limited, complementary biliary brushings should be considered in all patients. The sensitivity and specificity for the detection of CCA by ductal biopsy in published studies varies from 30-88%, and 97-100%, respectively (106). Combining brush cytology and biopsy has a sensitivity varying from 47-86% and specificity of 97-100%. A study (106) assessing the accuracy of triple modality: brush cytology, biopsy and FISH or their combination demonstrated that brush cytology alone had a sensitivity of 42%, specificity of 100%, positive predictive value of 100% and negative predictive value of 88%. Triple sample assessment modality markedly improved the overall sensitivity (82%), specificity (100%), positive predictive value (100%), and negative predictive value (87%).

Cholangioscopy

Peroral cholangioscopy (POCS) allows a direct visualization of extrahepatic bile duct strictures. The recent development of video-based systems offers better image resolution and offers clearer views than fiberoptic cholangioscopy. Compared to ERC and tissue sampling POCS was shown to improve the diagnostic accuracy (107, 108) (109). However, these studies were not focused on CCA in PSC-patients.

Single-operator cholangioscopy (SpyGlass) is gaining popularity, primarily for stone treatment and assessment of indeterminate strictures. The utility in PSC was studied in a recent case series (110) with visual assessment and targeted biopsies of 64 strictures in 47 patients. Only 1 of 3 patients with CCA were diagnosed by the ERCP procedure. It is likely that newer digital versions of this instrument (e.g. SpyGlass DS) will perform better, at least in terms of visual diagnostics.

Other techniques

Other techniques such as intraductal ultrasonography and confocal laser endomicroscopy have shown potential utility in the diagnosis of CCA in PSC, but are not established in routine clinical practice. Regular endoscopic ultrasonography with sampling of detectable masses or locoregional lymph nodes is advocated by some, but such sampling is also regarded as a contraindication to LT in some centers, thus any such sampling should be discussed locally.

Table 6. Detection of biliary malignancy in PSC with brush cytology (BC)

First author, year	Study design	Intervention	Participants	Outcomes	Results: Sens, Spec, PPV, NPV
Ponsioen, 1999, (111)	Prospective	ERC with BC from dominant strictures	43	Detection of malignancy/CC	60%, 89%, 59%, 89%
Lindberg, 2002, (112)	Prospective	BC + DNA flow cytometry from biliary strictures	57	Detection of malignancy/CC	71% ,100 %, NA, NA
Siqueira, 2002, (113)	Retrospective	BC from bile ducts	151	Detection of malignancy/C	46.4%, 100%, NA,NA
Lal, 2004, (114)	Retrospective	BC from bile ducts	21	Detection of malignancy/CC	67%,94%,NA,NA
Furmanczyk, 2005, (115)	Retrospective	BC from bile ducts	51	Detection of malignancy/CC	62.5%, 100%,NA,NA
Boberg 2006, (116)	Prospective	BC from biliary strictures	61	Detection of malignancy/CC	100%, 84%, 68%, 100%
Moff, 2006, (117)	Retrospective	BC from bile ducts	47	Detection of malignancy/CC	50%,91%,NA,NA
Moreno Luna, 2006 (102)	Prospective	BC from biliary strictures	86 PSC	Detection of malignancy/CC	18%, 100%, 100%, 83%
Charatcharoen-witthaya,2008, (43)	Prospective	BC from biliary strictures	230	Detection of malignancy/CC	8 %, 100%,100%, 89%,89%
Levy, 2010, (42)	Prospective	BC from biliary strictures	32 PSC	Detection of malignancy/CC	7%,100%,NA,NA

Halme, 2012, (103)	Retrospective	BC from bile ducts	102	Detection of dysplasia/CC	46%,88%,86%,52%

Table 7. Detection of biliary malignancy in PSC with brush cytology – metaanalysis and reviews.

First author, year	Study design	Inter-vention	N	Outcomes	Results: Sens, Spec, PLR, NLR	Comments
Trikudanathal, 2014 (101)	Meta-analysis including 11 studies (prospective and retrospective)	bile duct brushing	827	Diagnostic yield of bile duct brushing in diagnosing CC in PSC strictures	43%. 97%. 8.87, 0.56	The moderate sensitivity in detecting CC, precludes its utility as a surveillance tool for early diagnosis of CC.
Navaneethan, 2014 (104)	Meta-analysis including 4 studies (prospective and retrospective)	FISH	629	Diagnostic yield of FISH in diagnosing CC in PSC strictures	31%. 71% 1.19, 0.95	FISH positivity has reasonable diagnostic accuracy. However, the specificity is poor.
	Meta-analysis including 6 studies (prospective and retrospective)	FISH polysom y	690	Diagnostic yield of FISH polysomy in diagnosing CC in PSC strictures	51%. 93% 6.81, 0.56	FISH polysomy is highly specific; however, it has limited sensitivity.
Navaneethan, 2014 (118)	Meta-analysis including 9 studies (prospective and retrospective)	Intraduc tal biopsy	730	Diagnostic yield of intraductal biopsies performed during ERCP	48%, 99% 18.9, 0.54	Limited sensitivity.
	Meta-analysis including 9 studies (prospective and retrospective)	Brush cytology	730	Diagnostic yield of brush cytology performed during ERCP	45%, 99% 15.7, 0,54	Limited sensitivity.
	Meta-analysis including 6 studies (prospective and retrospective)	Intraduc tal biopsy AND Brush cytology	628	Diagnostic yield of both brush cytology and intraductal biopsies	59%, 100% 53.8, 0.42	Both brushings and biopsy are comparable and have limited sensitivity.

				performed during ERCP		
Walker, 2007 (119)	Systematic review	MRI	na	Diagnosing cholangiocarcinoma in primary sclerosing cholangitis	N/A	Lack of evidence
	Systematic review	CT	45	Diagnosing cholangiocarcinoma in primary sclerosing cholangitis	82%, 80% 4.10, 0.25	CT provides good Se and Sp in detecting biliary tract carcinoma complicating primary sclerosing cholangitis

Endoscopic surveillance of PSC-associated IBD

The relationship between PSC and IBD is well established (120). The prevalence of IBD in patients with established PSC varies widely, but is reported at 80% in Scandinavian countries (121). The often asymptomatic phenotype of IBD means that prevalence data are strongly influenced by the level of proactive search for the disease. The typical scenario was for IBD to precede the presentation of PSC. However, the clinical presentation of IBD is variable, and the disease may be subclinical or asymptomatic for years (122) and is nowadays often diagnosed after the recognition of the liver disease. Notably, IBD may have been present for an unknown period of time when PSC is diagnosed. The increased risk of colon cancer in PSC-associated IBD, (123, 124), hence makes it crucial to perform a full ileocolonoscopy already at the time of PSC diagnosis in patients. As to the diagnosis of IBD per se, complete ileocolonoscopy is critical since rectal sparing, as well as right-sided involvement is frequent in these patients (40).

Timing of screening

22. ESGE/EASL recommend screening ileocolonoscopy at the time of PSC diagnosis (strong quality evidence, strong recommendation). If IBD is documented endoscopically or histologically, annual surveillance colonoscopies are warranted (strong recommendation, low quality evidence).

23. ESGE/EASL suggest that if no IBD is documented, next ileocolonoscopy should be considered at 5 years or whenever bowel complaints suggestive of IBD occur (weak recommendation, low quality evidence)

Based on initial screening subsequent surveillance can be planned. If IBD is documented, annual colonoscopies are warranted (6, 125), since it has been shown that PSC/IBD patients whose CRC is detected in a surveillance program have a significantly lower risk of CRC-related mortality as compared to non-surveilled patients (95). If not, repeat colonoscopy should be done with the occurrence of symptoms suggestive of IBD, or elevated F-calprotectin, otherwise at 3-5 years (126), although this recommendation lacks any scientific evidence beyond extrapolation from general IBD recommendations (127).

Endoscopic modality

24. EASL/ESGE recommend ileocolonoscopy with four-quadrant biopsies from all colonic segments and the terminal ileum *for screening for the presence of IBD* (strong recommendation, low quality evidence)

25. EASL/ESGE recommends ileocolonoscopy with dye-based chromoendoscopy with targeted biopsies *for dysplasia surveillance* of PSC-associated IBD (strong recommendation, low quality evidence)

PSC-associated colitis seems to be distinctive from other IBD: Colitis is predominant in the right colon (128), and colon cancer is typically right-sided (129). Lack of inflammation in the rectum ('rectal sparing') is reported in some studies but less frequently observed in others (3). Endoscopic surveillance of PSC-associated colitis is presumed to increase the chance of early detection of dysplasia or malignancy (130).

Screening for IBD at diagnosis of PSC is best performed by high-definition ileo-colonoscopy with four quadrant biopsies from all colonic segments and the terminal ileum. Biopsies should be taken at the index-endoscopy even without macroscopic signs of inflammation (126, 131, 132).

In established PSC-IBD, ileocolonoscopy with dye-based chromoendoscopy (0.1% methylene blue or 0.1% – 0.5% indigo carmine) with targeted biopsies is required for neoplasia surveillance of PSC-associated IBD. In appropriately trained hands, in the situation of quiescent disease activity and adequate bowel preparation, nontargeted four-quadrant biopsies can be abandoned (133). This procedure is also endorsed by the ECCO (127). It should be noted that there are no studies on colonic neoplasia surveillance specifically in the setting of PSC-associated IBD.

Routine use of pancolonic chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing colitis (disease duration of >8 years) increased the proportion of patients found with dysplasia by a factor of 2.1–3.3 compared to standard definition video-colonoscopy. The pooled incremental yield of conventional chromoendoscopy with random biopsies over SD-WLE with random biopsies for the detection of patients with neoplasia was 7% (95%CI 3.2%–11.3%) (134). Benefit of conventional chromoendoscopy over WLE with latest-generation HD-WLE colonoscopes is unknown to date.

Handling of polyps and colorectal dysplasia

26. ESGE/EASL recommend endoscopic resection of any visible lesions and assessment of the surrounding mucosa. We recommend procto-colectomy in case of dysplasia in the surrounding mucosa, or when the lesion cannot be completely resected. Otherwise, repeat colonoscopy and close follow-up is warranted (strong recommendation, low quality evidence)
27. In the case of invisible lesions with HGD confirmed by two expert pathologists, procto-colectomy should be advised (strong recommendation, low quality evidence)
28. In the case of invisible lesions with LGD confirmed by two expert pathologists, repeat colonoscopy after 3 months with chromo-endoscopy is recommended (strong recommendation, low quality evidence).

Colorectal cancer (CRC) risk is significantly increased in patients with co-existing IBD and PSC. A meta-analysis of 11 studies concluded that patients with UC-PSC were at increased risk of developing CRC compared to patients with UC alone (OR: 4.09; 95%CI 2.89-5.76) (124). A recent large population-based study in the Netherlands found a 9-fold increased risk of developing CRC in PSC-UC patients, compared to the age- and gender-matched population (SIR, 8.6; 95% CI: 3.5-17.7), and a 10-fold increased risk, compared to UC controls (ratio of SIRs: 9.8; 95% CI: 1.9-96.6) (95).

Most dysplasia is visible at colonoscopy (135, 136). On the other hand, invisible dysplastic lesions can also be diagnosed by random biopsies during surveillance. According to the IBD-Dysplasia Morphology Study Group (137), dysplasia is subdivided in low grade (LGD) and high grade dysplasia (HGD). According to the recent ECCO guidelines, a visible lesion with dysplasia should be completely resected endoscopically irrespective of the grade of dysplasia or the localisation relative to the inflamed mucosal areas (127). Subsequently, the surrounding mucosa (around the visible lesion) should be examined (with chromo-endoscopy-guided targeted biopsies or random biopsies if chromo-endoscopy not available). If endoscopic resection is incomplete or impossible, or if dysplasia is detected in the surrounding mucosa, total procto-colectomy is recommended. In the case of

invisible lesions with LGD, urgent repeat chromoendoscopy should be performed, to eventually identify a well-circumscribed lesion and/or perform additional random biopsies. If the presence of LGD is confirmed, there is no clear consensus regarding management; proctocolectomy or surveillance could be recommended. Actually, two studies revealed a significant 5-year progression rate (33%-54%) of LGD to HGD (138, 139), whereas others showed low progression rates (140, 141). Finally, in the case of invisible lesions with HGD or adenocarcinoma, total procto-colectomy is indicated.

References

1. Olsson R, Danielsson A, Jarnerot G, Lindstrom E, Loof L, Rolny P, et al. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. Gastroenterology. 1991;100(5 Pt 1):1319-23.
2. Lunder AK, Hov JR, Borthne A, Gleditsch J, Johannesen G, Tveit K, et al. Prevalence of Sclerosing Cholangitis, Detected by Magnetic Resonance Cholangiography, in Patients with Long-term Inflammatory Bowel Disease. Gastroenterology. 2016.
3. Boonstra K, van Erpecum KJ, van Nieuwkerk KM, Drenth JP, Poen AC, Witteman BJ, et al. Primary sclerosing cholangitis is associated with a distinct phenotype of inflammatory bowel disease. Inflammatory bowel diseases. 2012;18(12):2270-6.
4. O'Toole A, Alakkari A, Keegan D, Doherty G, Mulcahy H, O'Donoghue D. Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(4):439-41.
5. Loftus EV, Jr., Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005;54(1):91-6.
6. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. Journal of hepatology. 2009;51(2):237-67.
7. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. 2004;4(1):38.
8. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660-78.
9. Berstad AE, Aabakken L, Smith HJ, Aasen S, Boberg KM, Schrumpf E. Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2006;4(4):514-20.
10. Moff SL, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Kalloo AN, et al. Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. Gastrointestinal endoscopy. 2006;64(2):219-23.
11. Philpott C, Rosenbaum J, Moon A, Bekhit E, Kumbla S. Paediatric MRCP: 10 year experience with 195 patients. European journal of radiology. 2013;82(4):699-706.
12. Rossi G, Sciveres M, Maruzzelli L, Curcio G, Riva S, Traina M, et al. Diagnosis of sclerosing cholangitis in children: blinded, comparative study of magnetic resonance versus endoscopic cholangiography. Clinics and research in hepatology and gastroenterology. 2013;37(6):596-601.
13. Dave M, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. Radiology. 2010;256(2):387-96.
14. Meagher S, Yusoff I, Kennedy W, Martel M, Adam V, Barkun A. The roles of magnetic resonance and endoscopic retrograde cholangiopancreatography (MRCP and ERCP) in the diagnosis of patients with suspected sclerosing cholangitis: a cost-effectiveness analysis. Endoscopy. 2007;39(3):222-8.
15. Talwalkar JA, Angulo P, Johnson CD, Petersen BT, Lindor KD. Cost-minimization analysis of MRC versus ERCP for the diagnosis of primary sclerosing cholangitis. Hepatology. 2004;40(1):39-45.

16. Kalaitzakis E, Levy M, Kamisawa T, Johnson GJ, Baron TH, Topazian MD, et al. Endoscopic retrograde cholangiography does not reliably distinguish IgG4-associated cholangitis from primary sclerosing cholangitis or cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9(9):800-3 e2.
17. Ruiz A, Lemoinne S, Carrat F, Corpechot C, Chazouilleres O, Arrive L. Radiologic course of primary sclerosing cholangitis: assessment by three-dimensional magnetic resonance cholangiography and predictive features of progression. Hepatology. 2014;59(1):242-50.
18. Weber C, Kuhlencordt R, Grotelueschen R, Wedegaertner U, Ang TL, Adam G, et al. Magnetic resonance cholangiopancreatography in the diagnosis of primary sclerosing cholangitis. Endoscopy. 2008;40(9):739-45.
19. Eaton JE, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. Gastroenterology. 2013;145(3):521-36.
20. Li-Yeng C, Goldberg HI. Sclerosing cholangitis: broad spectrum of radiographic features. Gastrointest Radiol. 1984;9:39-47.
21. Majoie CB, Reeders JW, Sanders JB, Huibregtse K, Jansen PL. Primary sclerosing cholangitis: a modified classification of cholangiographic findings. AJR Am J Roentgenol. 1991;157(3):495-7.
22. Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, Rajaram R, Rauws EA, Mulder CJ, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. Gut. 2002;51(4):562-6.
23. Ponsioen CY, Reitsma JB, Boberg KM, Aabakken L, Rauws EA, Schrumpf E. Validation of a cholangiographic prognostic model in primary sclerosing cholangitis. Endoscopy. 2010;42(9):742-7.
24. Craig DA, MacCarty RL, Wiesner RH, Grambsch PM, LaRusso NF. Primary sclerosing cholangitis: value of cholangiography in determining the prognosis. AJR Am J Roentgenol. 1991;157(5):959-64.
25. Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. Hepatology. 2006;44(5):1063-74.
26. Trauner M, Fickert P, Wagner M. MDR3 (ABCB4) defects: a paradigm for the genetics of adult cholestatic syndromes. Semin Liver Dis. 2007;27(1):77-98.
27. Mesenas S, Vu C, Doig L, Meenan J. Duodenal EUS to identify thickening of the extrahepatic biliary tree wall in primary sclerosing cholangitis. Gastrointestinal endoscopy. 2006;63(3):403-8.
28. Rustemovic N, Cukovic-Cavka S, Opacic M, Petrovecki M, Hrstic I, Radic D, et al. Endoscopic ultrasound elastography as a method for screening the patients with suspected primary sclerosing cholangitis. European journal of gastroenterology & hepatology. 2010;22(6):748-53.
29. Lutz HH, Wasmuth HE, Streetz K, Tacke F, Koch A, Luedde T, et al. Endoscopic ultrasound as an early diagnostic tool for primary sclerosing cholangitis: a prospective pilot study. Endoscopy. 2012;44(10):934-9.
30. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of hepatology. 2015;63(1):237-64.
31. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. Semin Liver Dis. 1991;11(1):40-8.
32. Johnson GK, Geenen JE, Venu RP, Schmalz MJ, Hogan WJ. Endoscopic treatment of biliary tract strictures in sclerosing cholangitis: a larger series and recommendations for treatment. Gastrointestinal endoscopy. 1991;37(1):38-43.
33. Stiehl A, Rudolph G, Klöters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. Journal of hepatology. 2002;36(2):151-6.
34. Bjornsson E, Lindqvist-Ottosson J, Asztely M, Olsson R. Dominant strictures in patients with primary sclerosing cholangitis. The American journal of gastroenterology. 2004;99(3):502-8.
35. Gluck M, Cantone NR, Brandabur JJ, Patterson DJ, Bredfeldt JE, Kozarek RA. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. J Clin Gastroenterol. 2008;42(9):1032-9.

36. Ponsioen CY, Lam K, van Milligen de Wit AW, Huibregtse K, Tytgat GN. Four years experience with short term stenting in primary sclerosing cholangitis. The American journal of gastroenterology. 1999;94(9):2403-7.
37. Moff SL, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Kalloo AN, et al. Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. Gastrointestinal Endoscopy. 2006;64(2):219-23.
38. Ruiz A, Lemoinne S, Carrat F, Corpechot C, Chazouillères O, Arrivé L. Radiologic course of primary sclerosing cholangitis: assessment by three-dimensional magnetic resonance cholangiography and predictive features of progression. Hepatology. 2014;59(1):242-50.
39. Boyd S, Tenca A, Jokelainen K, Mustonen H, Krogerus L, Arola J, et al. Screening primary sclerosing cholangitis and biliary dysplasia with endoscopic retrograde cholangiography and brush cytology: risk factors for biliary neoplasia. Endoscopy. 2016.
40. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660-78.
41. Aljiffry M, Renfrew PD, Walsh MJ, Laryea M, Molinari M. Analytical review of diagnosis and treatment strategies for dominant bile duct strictures in patients with primary sclerosing cholangitis. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2011;13(2):79-90.
42. Levy MJ, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, et al. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. The American journal of gastroenterology. 2008;103(5):1263-73.
43. 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):1106-17.
44. 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. European journal of gastroenterology & hepatology. 2012;24(9):1051-8.
45. Gotthardt DN, Rudolph G, Kloters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. Gastrointestinal endoscopy. 2010;71(3):527-34.
46. Kaltenthaler E, Vergel YB, Chilcott J, Thomas S, Blakeborough T, Walters SJ, et al. A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography. Health technology assessment. 2004;8(10):iii, 1-89.
47. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointestinal endoscopy. 2009;70(1):80-8.
48. Johnson GK, Geenen JE, Venu RP, Schmalz MJ, Hogan WJ. Endoscopic treatment of biliary tract strictures in sclerosing cholangitis: a larger series and recommendations for treatment. Gastrointestinal endoscopy. 1991;37(1):38-43.
49. Johnson GK, Saeian K, Geenen JE. Primary sclerosing cholangitis treated by endoscopic biliary dilation: review and long-term follow-up evaluation. Curr Gastroenterol Rep. 2006;8(2):147-55.
50. Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. Hepatology. 1995;21(3):661-7.
51. Wagner S, Gebel M, Meier P, Trautwein C, Bleck J, Nashan B, et al. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. Endoscopy. 1996;28(7):546-51.
52. Ahrendt SA, Pitt HA, Kalloo AN, Venbrux AC, Klein AS, Herlong HF, et al. Primary sclerosing cholangitis: resect, dilate, or transplant? Ann Surg. 1998;227(3):412-23.
53. Kaya M, Petersen BT, Angulo P, Baron TH, Andrews JC, Gostout CJ, et al. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. The American journal of gastroenterology. 2001;96(4):1059-66.

54. Beuers U, Spengler U, Sackmann M, Paumgartner G, Sauerbruch T. Deterioration of cholestasis after endoscopic retrograde cholangiography in advanced primary sclerosing cholangitis. Journal of hepatology. 1992;15(1-2):140-3.
55. Ponsioen CY, Lam K, van Milligen de Wit AW, Huibregtse K, Tytgat GN. Four years experience with short term stenting in primary sclerosing cholangitis. The American journal of gastroenterology. 1999;94(9):2403-7.
56. Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2001;53(3):308-12.
57. Dumonceau JM, Tringali A, Blero D, Devière J, Laugiers R, Heresbach D, et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. 2012. p. 277-98.
58. Ismail S, Kylänpää L, Mustonen H, Halttunen J, Lindström O, Jokelainen K, et al. Risk factors for complications of ERCP in primary sclerosing cholangitis. Endoscopy. 2012;44(12):1133-8.
59. Navaneethan U, Jegadeesan R, Nayak S, Lourdusamy V, Sanaka MR, Vargo JJ, et al. ERCP-related adverse events in patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2015;81(2):410-9.
60. Gotthardt DN, Rudolph G, Klöters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. Gastrointestinal endoscopy. 2010;71(3):527-34.
61. van Milligen de Wit AW, Rauws EA, van Bracht J, Mulder CJ, Jones EA, Tytgat GN, et al. Lack of complications following short-term stent therapy for extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointestinal endoscopy. 1997;46(4):344-7.
62. van Milligen de Wit AW, van Bracht J, Rauws EA, Jones EA, Tytgat GN, Huibregtse K. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointestinal endoscopy. 1996;44(3):293-9.
63. Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2001;53(3):308-12.
64. Stiehl A, Rudolph G, Kloters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. Journal of hepatology. 2002;36(2):151-6.
65. Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. Hepatology. 1995;21(3):661-7.
66. van den Hazel SJ, Wolfhagen EH, van Buuren HR, van de Meeberg PC, Van Leeuwen DJ. Prospective risk assessment of endoscopic retrograde cholangiography in patients with primary sclerosing cholangitis. Dutch PSC Study Group. Endoscopy. 2000;32(10):779-82.
67. Enns R, Eloubeidi MA, Mergener K, Jowell PS, Branch MS, Baillie J. Predictors of successful clinical and laboratory outcomes in patients with primary sclerosing cholangitis undergoing endoscopic retrograde cholangiopancreatography. Canadian journal of gastroenterology = Journal canadien de gastroenterologie. 2003;17(4):243-8.
68. Gluck M, Cantone NR, Brandabur JJ, Patterson DJ, Bredfeldt JE, Kozarek RA. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. Journal of clinical gastroenterology. 2008;42(9):1032-9.
69. Bangarulingam SY, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. The American journal of gastroenterology. 2009;104(4):855-60.
70. Alkhatib AA, Hilden K, Adler DG. Comorbidities, sphincterotomy, and balloon dilation predict post-ERCP adverse events in PSC patients: operator experience is protective. Dig Dis Sci. 2011;56(12):3685-8.

71. Ismail S, Kylanpaa L, Mustonen H, Halttunen J, Lindstrom O, Jokelainen K, et al. Risk factors for complications of ERCP in primary sclerosing cholangitis. Endoscopy. 2012;44(12):1133-8.
72. Navaneethan U, Jegadeesan R, Nayak S, Lourdusamy V, Sanaka MR, Vargo JJ, et al. ERCP-related adverse events in patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2015;81(2):410-9.
73. von Seth E, Arnelo U, Enochsson L, Bergquist A. Primary sclerosing cholangitis increases the risk for pancreatitis after endoscopic retrograde cholangiopancreatography. Liver international : official journal of the International Association for the Study of the Liver. 2015;35(1):254-62.
74. Etzel JP, Eng SC, Ko CW, Lee SD, Saunders MD, Tung BY, et al. Complications after ERCP in patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2008;67(4):643-8.
75. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, et al. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. The American journal of gastroenterology. 2007;102(8):1781-8.
76. Cotton PB, Garrow DA, Gallagher J, Romagnuolo J. Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years. Gastrointestinal endoscopy. 2009;70(1):80-8.
77. Lombard M, Farrant M, Karani J, Westaby D, Williams R. Improving biliary-enteric drainage in primary sclerosing cholangitis: experience with endoscopic methods. Gut. 1991;32(11):1364-8.
78. Wagner S, Gebel M, Meier P, Trautwein C, Bleck J, Nashan B, et al. Endoscopic management of biliary tract strictures in primary sclerosing cholangitis. Endoscopy. 1996;28(7):546-51.
79. Stiehl A, Rudolph G, Sauer P, Benz C, Stremmel W, Walker S, et al. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. Journal of hepatology. 1997;26(3):560-6.
80. Linder S, Soderlund C. Endoscopic therapy in primary sclerosing cholangitis: outcome of treatment and risk of cancer. Hepato-gastroenterology. 2001;48(38):387-92.
81. Moreno Luna LE, Gores GJ. Advances in the diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis. Liver Transpl. 2006;12(11 Suppl 2):S15-9.
82. Tse F, Yuan Y, Moayyedi P, Leontiadis GI. Guidewire-assisted cannulation of the common bile duct for the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. The Cochrane database of systematic reviews. 2012;12:CD009662.
83. Dumonceau JM, Andriulli A, Elmunzer BJ, Mariani A, Meister T, Deviere J, et al. Prophylaxis of post-ERCP pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - updated June 2014. Endoscopy. 2014;46(9):799-815.
84. Shi N, Deng L, Altaf K, Huang W, Xue P, Xia Q. Rectal indomethacin for the prevention of post-ERCP pancreatitis: A meta-analysis of randomized controlled trials. The Turkish journal of gastroenterology : the official journal of Turkish Society of Gastroenterology. 2015;26(3):236-40.
85. Andrade-Davila VF, Chavez-Tostado M, Davalos-Cobian C, Garcia-Correa J, Montano-Loza A, Fuentes-Orozco C, et al. Rectal indomethacin versus placebo to reduce the incidence of pancreatitis after endoscopic retrograde cholangiopancreatography: results of a controlled clinical trial. BMC gastroenterology. 2015;15:85.
86. Nicolas-Perez D, Castilla-Rodriguez I, Gimeno-Garcia AZ, Romero-Garcia R, Nunez-Diaz V, Quintero E. Prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a cost-effectiveness analysis. Pancreas. 2015;44(2):204-10.
87. Brand M, Bizos D, O'Farrell P, Jr. Antibiotic prophylaxis for patients undergoing elective endoscopic retrograde cholangiopancreatography. The Cochrane database of systematic reviews. 2010(10):CD007345.
88. Khashab MA, Chithadi KV, Acosta RD, Bruining DH, Chandrasekhara V, Eloubeidi MA, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointestinal endoscopy. 2015;81(1):81-9.
89. Negm AA, Schott A, Vonberg RP, Weismueller TJ, Schneider AS, Kubicka S, et al. Routine bile collection for microbiological analysis during cholangiography and its impact on the management of cholangitis. Gastrointestinal endoscopy. 2010;72(2):284-91.

90. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology. 2011;54(5):1842-52.
91. Claessen MM, Vleggaar FP, Tytgat KM, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. Journal of hepatology. 2009;50(1):158-64.
92. 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):2045-55.
93. de Valle MB, Bjornsson E, Lindkvist B. Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort. Liver international : official journal of the International Association for the Study of the Liver. 2012;32(3):441-8.
94. Boberg KM, Bergquist A, Mitchell S, Pares A, Rosina F, Broome U, et al. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. Scandinavian journal of gastroenterology. 2002;37(10):1205-11.
95. 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):2045-55.
96. 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):1734-40.
97. Sinakos E, Saenger AK, Keach J, Kim WR, Lindor KD. Many patients with primary sclerosing cholangitis and increased serum levels of carbohydrate antigen 19-9 do not have cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9(5):434-9 e1.
98. Venkatesh PG, Navaneethan U, Shen B, McCullough AJ. Increased serum levels of carbohydrate antigen 19-9 and outcomes in primary sclerosing cholangitis patients without cholangiocarcinoma. Dig Dis Sci. 2013;58(3):850-7.
99. Wannhoff A, Hov JR, Folseraas T, Rupp C, Friedrich K, Anmarkrud JA, et al. FUT2 and FUT3 genotype determines CA19-9 cut-off values for detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. Journal of hepatology. 2013;59(6):1278-84.
100. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg. 2007;245(5):755-62.
101. Trikudanathan G, Navaneethan U, Njei B, Vargo JJ, Parsi MA. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointestinal endoscopy. 2014;79(5):783-9.
102. Moreno Luna LE, Kipp B, Halling KC, Sebo TJ, Kremers WK, Roberts LR, et al. Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures. Gastroenterology. 2006;131(4):1064-72.
103. Halme L, Arola J, Numminen K, Krogerus L, Makisalo H, Farkkila M. Biliary dysplasia in patients with primary sclerosing cholangitis: additional value of DNA ploidity. Liver international : official journal of the International Association for the Study of the Liver. 2012;32(5):783-9.
104. Navaneethan U, Njei B, Venkatesh PG, Vargo JJ, Parsi MA. Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointestinal endoscopy. 2014;79(6):943-50 e3.
105. Karlsen TH, Vesterhus M, Boberg KM. Review article: controversies in the management of primary biliary cirrhosis and primary sclerosing cholangitis. Alimentary pharmacology & therapeutics. 2014;39(3):282-301.
106. Nanda A, Brown JM, Berger SH, Lewis MM, Barr Fritcher EG, Gores GJ, et al. Triple modality testing by endoscopic retrograde cholangiopancreatography for the diagnosis of cholangiocarcinoma. Therapeutic advances in gastroenterology. 2015;8(2):56-65.
107. Fukuda Y, Tsuyuguchi T, Sakai Y, Tsuchiya S, Saisyo H. Diagnostic utility of peroral cholangioscopy for various bile-duct lesions. Gastrointestinal endoscopy. 2005;62(3):374-82.

108. Kawakami H, Kuwatani M, Etoh K, Haba S, Yamato H, Shinada K, et al. Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer. Endoscopy. 2009;41(11):959-64.
109. Nishikawa T, Tsuyuguchi T, Sakai Y, Sugiyama H, Miyazaki M, Yokosuka O. Comparison of the diagnostic accuracy of peroral video-cholangioscopic visual findings and cholangioscopy-guided forceps biopsy findings for indeterminate biliary lesions: a prospective study. Gastrointestinal endoscopy. 2013;77(2):219-26.
110. Arnelo U, von Seth E, Bergquist A. Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis. Endoscopy. 2015;47(8):696-702.
111. Ponsioen CY, Vrouenraets SM, van Milligen de Wit AW, Sturm P, Tascilar M, Offerhaus GJ, et al. Value of brush cytology for dominant strictures in primary sclerosing cholangitis. Endoscopy. 1999;31(4):305-9.
112. Lindberg B, Arnelo U, Bergquist A, Thorne A, Hjerpe A, Granqvist S, et al. Diagnosis of biliary strictures in conjunction with endoscopic retrograde cholangiopancreaticography, with special reference to patients with primary sclerosing cholangitis. Endoscopy. 2002;34(11):909-16.
113. Siqueira E, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, et al. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointestinal endoscopy. 2002;56(1):40-7.
114. Lal A, Okonkwo A, Schindler S, De Frias D, Nayar R. Role of biliary brush cytology in primary sclerosing cholangitis. Acta cytologica. 2004;48(1):9-12.
115. Furmanczyk PS, Grieco VS, Agoff SN. Biliary brush cytology and the detection of cholangiocarcinoma in primary sclerosing cholangitis: evaluation of specific cytomorphologic features and CA19-9 levels. American journal of clinical pathology. 2005;124(3):355-60.
116. Boberg KM, Jebsen P, Clausen OP, Foss A, Aabakken L, Schrumpf E. Diagnostic benefit of biliary brush cytology in cholangiocarcinoma in primary sclerosing cholangitis. Journal of hepatology. 2006;45(4):568-74.
117. Moff SL, Clark DP, Maitra A, Pandey A, Thuluvath PJ. Utility of bile duct brushings for the early detection of cholangiocarcinoma in patients with primary sclerosing cholangitis. J Clin Gastroenterol. 2006;40(4):336-41.
118. Navaneethan U, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi MA. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. Gastrointestinal endoscopy. 2015;81(1):168-76.
119. Walker SL, McCormick PA. Diagnosing cholangiocarcinoma in primary sclerosing cholangitis: an "evidence based radiology" review. Abdominal imaging. 2008;33(1):14-7.
120. Smith MP, Loe RH. Sclerosing Cholangitis; Review of Recent Case Reports and Associated Diseases and Four New Cases. Am J Surg. 1965;110:239-46.
121. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis--a risk factor for the development of dysplasia and DNA aneuploidy? Gastroenterology. 1992;102(6):1877-80.
122. Broome U, Lofberg R, Lundqvist K, Veress B. Subclinical time span of inflammatory bowel disease in patients with primary sclerosing cholangitis. Dis Colon Rectum. 1995;38(12):1301-5.
123. Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. Hepatology. 1995;22(5):1404-8.
124. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. Gastrointestinal endoscopy. 2002;56(1):48-54.
125. Broome U, Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. Semin Liver Dis. 2006;26(1):31-41.
126. Lindor KD, Kowdley KV, Harrison ME, American College of G. ACG Clinical Guideline: Primary Sclerosing Cholangitis. The American journal of gastroenterology. 2015;110(5):646-59; quiz 60.

127. Annese V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982-1018.
128. Tsaitas C, Semertzidou A, Sinakos E. Update on inflammatory bowel disease in patients with primary sclerosing cholangitis. World journal of hepatology. 2014;6(4):178-87.
129. Claessen MM, Lutgens MW, van Buuren HR, Oldenburg B, Stokkers PC, van der Woude CJ, et al. More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. Inflammatory bowel diseases. 2009;15(9):1331-6.
130. Vera A, Gunson BK, Ussatoff V, Nightingale P, Candinas D, Radley S, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. Transplantation. 2003;75(12):1983-8.
131. Jorgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, Schrumpf E, et al. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflammatory bowel diseases. 2012;18(3):536-45.
132. Fausa O, Schrumpf E, Elgjo K. Relationship of inflammatory bowel disease and primary sclerosing cholangitis. Semin Liver Dis. 1991;11(1):31-9.
133. Kaminski MF, Hassan C, Bisschops R, Pohl J, Pellise M, Dekker E, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2014;46(5):435-49.
134. Subramanian V, Mannath J, Ragunath K, Hawkey CJ. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2011;33(3):304-12.
135. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. Gastrointestinal endoscopy. 2004;60(3):334-9.
136. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? Gastrointestinal endoscopy. 2007;65(7):998-1004.
137. Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Human pathology. 1983;14(11):931-68.
138. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. Gastroenterology. 1994;107(4):934-44.
139. Ullman TA, Loftus EV, Jr., Kakar S, Burgart LJ, Sandborn WJ, Tremaine WJ. The fate of low grade dysplasia in ulcerative colitis. The American journal of gastroenterology. 2002;97(4):922-7.
140. Befrits R, Ljung T, Jaramillo E, Rubio C. Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: a follow-up study. Dis Colon Rectum. 2002;45(5):615-20.
141. Lim CH, Dixon MF, Vail A, Forman D, Lynch DA, Axon AT. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. Gut. 2003;52(8):1127-32.

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