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Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline

Authors

Lars Aabakken[1], Tom H. Karlsen[2], Jörg Albert[3], Marianna Arvanitakis[4], Olivier Chazouilleres[5], Jean-Marc Dumonceau[6], Martti Färkkilä[7], Peter Fickert[8], Gideon M. Hirschfield[9], Andrea Laghi[10], Marco Marzioni[11], Michael Fernandez[4], Stephen P. Pereira[12], Jürgen Pohl[13], Jan-Werner Poley[14], Cyriel Y. Ponsioen[15], Christoph Schramm[16], Fredrik Swahn[17], Andrea Tringali[18], Cesare Hassan[19]

Institutions

1 GI Endoscopy, Rikshospitalet University Hospital, Hospital, and Faculty of Medicine, University of Oslo, Oslo, Norway
2 Norwegian PSC Research Center and Section for Gastroenterology, Department of Transplantation Medicine, Division of Cancer Medicine, Surgery and Transplantation, Oslo University Hospital, Rikshospitalet, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
3 Abteilung für Gastroenterologie, Hepatologie und Endokrinologie, Robert-Bosch-Krankenhaus, Stuttgart, Germany
4 Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium
5 Service d'Hépatologie, Hôpital Saint-Antoine, Assistance Publique – Hôpitaux de Paris, Centre de référence des maladies inflammatoires du foie et des voies biliaires, Filière Maladies Rares du Foie de l'Adulte et de l'Enfant (FILFOIE), UPMC UNIV Paris 06, France
6 Gedyt Endoscopy Center, Buenos Aires, Argentina
7 Department of Gastroenterology, Helsinki University Central Hospital, Helsinki, Finland
8 Research Unit for Experimental and Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Austria
9 National Institute for Health Research (NIHR), Birmingham Liver Biomedical Research Unit (BRU), and Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom
10 Pathological Sciences, Sapienza-University, Rome, Italy
11 Clinic of Gastroenterology and Hepatology, Università Politecnica delle Marche – Ospedali Riuniti University Hospital, Ancona, Italy
12 Institute for Liver and Digestive Health, University College London, Royal Free Campus, London, UK
13 Department of Gastroenterology and Interventional Endoscopy, Klinikum Friedrichshain, Berlin, Germany
14 Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands
15 Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands
16 Department of Medicine I and Martin Zeitz Centre for Rare Diseases, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
17 Center for Digestive Diseases, Karolinska University Hospital and Division of Surgery, CLINTEC, Karolinska Institute, Stockholm, Sweden
18 Digestive Endoscopy Unit, Catholic University, Rome, Italy
19 Digestive Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy

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Corresponding author

Professor Lars Aabakken, Department of Medical Gastroenterology, Oslo University Hospital-Rikshospitalet, N-0027 Oslo, Norway
lars.aabakken@medisin.uio.no

Appendix e1
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MAIN RECOMMENDATIONS

1 ESGE/EASL recommend that, as the primary diagnostic modality for PSC, magnetic resonance cholangiography (MRC) should be preferred over endoscopic retrograde cholangiopancreatography (ERCP).
Moderate quality evidence, strong recommendation.

2 ESGE/EASL suggest that ERCP can be considered if MRC plus 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.

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

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

9 ESGE/EASL recommend weighing the anticipated benefits of biliary papillotomy/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.

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

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

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.

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE) and of the European Association for the Study of the Liver (EASL) on the role of endoscopy in primary sclerosing cholangitis. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

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 to be in the range 1 % – 5 % [1]. Magnetic resonance imaging (MRI) studies have shown that the prevalence of imaging changes compatible with PSC in ulcerative colitis is almost fourfold higher than that detected based on clinical assessments [2]. PSC is more common in men (comprising 60 % – 70 % of patients) and most patients present with pancolitis, often with a right-sided predominance [3 – 5]. A major challenge in the clinical management of 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 test findings, especially elevated alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) values, as well as in non-IBD patients with elevated cholestatic liver enzymes not otherwise explained. A proposed algorithm for PSC diagnosis has already been presented by earlier 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 cholangiopancreatography (ERCP) plays a significant role in the handling of PSC because of its high accuracy and prognostic value as well as its sampling and therapeutic possibilities. However, ERCP must be integrated within well-defined clinical algorithms together with less invasive or noninvasive imaging and biochemical tests. In particular, the widespread implementation of magnetic resonance cholangiography (MRC) has led to increasing restriction of 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 Guideline, 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 their benefit and minimize their 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 (see **Appendix 1**, online-

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ABBREVIATIONS

ALP	alkaline phosphatase
ASGE	American Society for Gastrointestinal Endoscopy
CCA	cholangiocarcinoma
CI	confidence interval
CRC	colorectal cancer
CT	computed tomography
EASL	European Association for the Study of the Liver
ECCO	European Crohn's and Colitis Organisation
ERC	endoscopic retrograde cholangiography
ERCP	endoscopic retrograde cholangiopancreatography
ESGE	European Society of Gastrointestinal Endoscopy
FISH	fluorescence in situ hybridization
GGT	gamma glutamyl transferase
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HGD	high grade dysplasia
IBD	inflammatory bowel disease
IDUS	intraductal ultrasound
LGD	low grade dysplasia
MRC	magnetic resonance cholangiography
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NLR	negative likelihood ratio
NPV	negative predictive value
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PBC	primary biliary cholangitis
pCLE	probe-based confocal laser endomicroscopy
PLR	positive likelihood ratio
POCS	peroral cholangioscopy
PPV	positive predictive value
PSC	primary sclerosing cholangitis
PTBD	percutaneous transhepatic biliary drainage
RCT	randomized controlled trial
RR	relative risk

only) were prepared by the coordinating team. A systematic literature search in PubMed/MEDLINE and the Cochrane Library was conducted, using at a minimum the search terms "Primary Sclerosing Cholangitis" and "Endoscopy," and "Colonoscopy" for the part related to the diagnosis and surveillance of IBD in PSC. Articles were first selected by title, their relevance was then assessed by review of 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 of the 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 subsequently forwarded to *Endoscopy* and the *Journal of Hepatology* for publication.

Endoscopic diagnosis and surveillance of PSC

Diagnosis of PSC

RECOMMENDATION

1. ESGE/EASL recommend that, as the primary diagnostic modality for PSC, magnetic resonance cholangiography (MRC) should be preferred over endoscopic retrograde cholangiopancreatography (ERCP).
Moderate quality evidence, strong recommendation.

Although ERCP has been regarded as the standard of reference in diagnosing PSC, MRC is now recommended as a first-line noninvasive imaging method for patients with suspected PSC that offers comparable accuracy (except in early-stage PSC restricted to intrahepatic bile ducts, and in the rare cases of contraindications to MRC) [8 – 12]. A meta-analysis based on 6 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].

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 on the basis of 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].

RECOMMENDATION

2. ESGE/EASL suggest that ERCP can be considered if MRC plus 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.

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▶ **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
Mechanical/toxic	Cholelithiasis/choledocholithiasis
	Surgical bile duct trauma
	Intra-arterial chemotherapy
	Drug-induced sclerosing cholangitis
Ischemic	Vascular trauma
	Hepatic allograft arterial insufficiency
	Paroxysmal nocturnal hemoglobinuria
Other pancreatico-biliary 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

HIV, human immunodeficiency virus; IgG4, immunoglobulin G4.

Whether or not to perform ERCP in patients with high quality normal findings at MRC depends on the level of clinical suspicion for PSC and on the impact of the diagnosis on patient management and prognosis. ERCP is regarded as unnecessary in patients with a low level of clinical suspicion, but it could be considered in patients with an 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 three-dimensional image acquisition, is likely to further decrease the probability of abnormal ERCP findings in patients with normal MRC results. In addition, as detailed reports including the clinical, biochemical, and histological characteristics and outcomes of these patients with negative MRC but positive ERCP findings 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 the 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 & Goldberg [20]. Typical changes seen in PSC consist of minor irregularities of duct contour and local narrowing with pre-stenotic 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 demographic data and the clinical features. Review by teams with expertise in complex biliary disease is often useful, as multiple secondary causes of sclerosing cholangitis must be considered [25] (▶ **Table 3**).

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 deficiency which may be characterized by large unifocal or multifocal spindle-shaped intrahepatic bile duct dilatations with or without apparent bile duct stenosis [12, 26]. This diagnosis should be suspected on familial clustering of excessive gallstone disease and often a history of prior cholecystectomy at age < 40 years

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and associated intrahepatic cholestasis of pregnancy, and is confirmed by *ABCB4* genotyping.

RECOMMENDATION

3. For the diagnosis of PSC, ESGE/EASL do not suggest routine use of endoscopic techniques other than ERCP (i. e., endoscopic ultrasound including intraductal ultrasound [IDUS], cholangioscopy, confocal endomicroscopy).
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 endomicroscopy. In selected cases with suspected extrahepatic disease and inconclusive MRC findings, endoscopic ultrasound (including IDUS) and elastography may add information on common bile duct strictures, wall thickening, and liver fibrosis stage [27 – 30].

ERCP in established PSC

RECOMMENDATION

4. ESGE/EASL suggest that a dominant stricture at ERCP should be defined as a stenosis with a diameter of ≤ 1.5 mm in the common bile duct and/or ≤ 1.0 mm in an 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 “dominant stricture” 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 dominant stricture was introduced by Stiehl et al. in 2002 for use in endoscopic studies as a severity measure [33, 34], although it employs a somewhat arbitrary value, depending, for example, on filling pressure. A number of endoscopic studies, both before and after 2002, do not apply the diameter criterion strictly when determining a dominant stricture [35, 36], and focus on suspected clinical relevance. Determination of 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 as a compound clinical decision.

Multiple dominant strictures can be found in the same patient (12 % in the study by Bjornsson et al.) [34].

Of note, the ERCP definition of a dominant stricture is usually considered to be not applicable to MRC, in particular in the extrahepatic ducts, given the insufficient spatial resolution of MRC [10, 17] and the lack of the hydrostatic pressure that is present during 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 dominant stricture suspected at MRC is indeed not a stricture [37].

RECOMMENDATION

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 enzyme levels; or (iii) new dominant stricture or progression of existing dominant strictures identified at MRC 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 identify biliary strictures amenable to intervention.

(i) 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 treat-

▶ **Table 2** Amsterdam classification of cholangiographic changes in primary sclerosing cholangitis (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 pruning	Strictures of almost entire length of duct
IV	–	Extremely irregular margins; diverticulum-like outpouchings

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

Diagnosis	Main cholangiographic features
PSC	Multifocal intrahepatic and extrahepatic 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
Ischemic 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

ment of dominant strictures and to perform ductal brush sampling to exclude malignancy [8, 38]. Worsening pain in the right upper abdominal quadrant, fatigue, and weight loss also need careful evaluation.

(ii) Laboratory results

Serum laboratory tests are neither sensitive nor specific enough to evaluate PSC progression [38], but in the case of rapid increase of serum bilirubin levels and/or cholestatic liver enzymes (serum ALP, serum GGT) 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 (PPV) (67 %) for the diagnosis of CCA [36, 38, 39], and is not helpful in selecting patients for ERCP.

(iii) Progression/new-onset clinically significant strictures on MRC

Progressive intrahepatic or extrahepatic 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, because of the increased risk of CCA in this situation.

In detail, a stricture that is disproportionately severe relative to others, concomitant biliary filling defects, marked biliary dilatation (≥ 2 cm for the common bile duct, ≥ 1 cm for the right or left intrahepatic ducts, ≥ 5 mm for other intrahepatic ducts) suggests CCA [40]. Conversely, this risk was low in patients without dominant strictures according to a 25-year experience [41]. 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 to be warranted.

The utility of ERCP in handling dominant strictures was shown in a prospective study [42] 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.

RECOMMENDATION

6. ESGE/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, to exclude focal parenchymal changes, and to give the clinicians performing the ERCP imaging-based guidance to minimize the risk of complications. Regarding MRC in established PSC, a retrospective single-center study reported a 76 % accuracy of MRC in the diagnosis of CCA complicating PSC [40]. For these reasons, patients with an established diagnosis of PSC should have an MRC examination in their clinical records [13, 43].

RECOMMENDATION

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

Selected series reporting on endoscopic treatment in PSC patients are summarized in ▶ **Table 4**; none of these compared performance versus no performance of endoscopic treatment for dominant stricture. The benefits reported following dilation of dominant stricture included short-term improvement of symptoms and of liver biochemical test results, as well as a longer liver transplantation-free survival compared to that predicted using the Mayo clinical risk model. Similar findings have also been reported in several smaller case series [32, 47 – 50].

The main criticisms of these studies are as follows:

a) The Mayo clinical risk model was not designed to evaluate patients with dominant stricture; 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 test results for cholestasis may spontaneously fluctuate in patients with PSC complicated or not with a dominant stricture. In 125 PSC patients, Bjornsson et al. reported changes in serum ALP and serum bilirubin from baseline up to 12 months following ERCP. As patients with dominant

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stricture 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 versus before ERCP were not significant, in contrast with various studies listed in ▶ **Table 4** that used dominant stricture 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 retrospective design, selection bias, and reporting of results for a mixture of treatments, namely dilation with and without stenting of dominant strictures as well as, in a minority of patients, treatment with ursodeoxycholic acid started during follow-up.

A critical issue is that potential benefits must be weighed against the certain risks of therapeutic ERCP in patients with no other therapeutic option except liver transplantation. Symptoms likely to improve following dominant stricture 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 1 year following endoscopic and/or percutaneous stricture dilation in 10 patients with cirrhosis and a baseline serum bilirubin ≥ 5 mg/dL [51]. Death following endoscopic balloon dilation of dominant stricture has been reported in a patient with PSC and end-stage liver disease [46]. Diagnostic ERCP was followed by deterioration of cholestasis in 7 of 8 patients with more advanced PSC at biopsy (Ludwig stage III or IV) versus 1 of 7 with less advanced disease (Ludwig stage I or II) [52].

Balloon dilation versus stent therapy

RECOMMENDATION

8. ESGE/EASL suggest that the choice between stenting and balloon dilation should be left to 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 dominant stricture, stents were inserted in a minority of patients; (ii) a significant improvement in liver transplantation-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 versus balloon dilation combined with stenting for dominant stricture in PSC patients (n = 34 and n = 37, respectively) [46]. The "balloon dilation alone" group was treated by endoscopic means only, while 23 patients (62 %) in the "stenting" group underwent percutaneous treatment because of failed endoscopic access and/or dominant stricture dilation. Serum bilirubin decreased similarly in both groups of patients, but more procedures and more complications were recorded in the stent versus 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 patients (10 %), 5 of whom were in the stent group. However, it is difficult to draw conclusions because of the different access routes used (percutaneous in 62 % in the stent group vs. 0 in the balloon dilation group), a selection bias due to more severe stricture in the stent group, and 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 (Dr. C.Y. Ponsioen, personal communication).

Role of sphincterotomy

RECOMMENDATION

9. ESGE/EASL recommend weighing the anticipated benefits of biliary papillotomy/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 dominant stricture in some studies [46] 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 dominant stricture, sphincterotomy was performed in 12 patients (38 %) [36] while in another study of dominant stricture dilation with/without stenting, sphincterotomy was performed in 63 % of 63 patients [44].

Generally, biliary sphincterotomy is not recommended as a routine procedure prior to biliary stenting because of the associated risks as demonstrated in randomized controlled trials (RCTs) [53]. However, if cannulation is difficult, biliary sphincterotomy is advised, bearing in mind that these patients are likely to require multiple procedures. Many endoscopists prefer a small sphincterotomy in PSC in order to avoid ascending cholangitis.

Specifically in PSC, biliary sphincterotomy was independently associated with an increased risk of short-term adverse

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▶ **Table 4** Selected series reporting on endoscopic treatment of dominant strictures in primary sclerosing cholangitis.

First author, Year [ref.]	Study design	Patients, n	Intervention	Outcomes	Results
1. Dilation ± stenting					
Gotthardt, 2010 [42] (Extension of Stiehl 2002 study [33])	Prospective	96 (ALP > 2 × ULN)	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 Liver transplantation-free survival Complications	▪ At 2 weeks, mean bilirubin level significantly decreased (by 56 %) ▪ Improvement in symptoms and liver transplantation-free survival ▪ Comparison with Mayo model not reported (5-year and 10-year liver transplantation-free survival, 81 % and 52 %) ▪ Overall complication rate, 3.8 %
Gluck, 2008 [35]	Retrospective	84 Symptomatic patients	Balloon dilation and stenting (70 % and 51 % of patients, respectively)	Liver transplantation-free survival	▪ Higher proportion of patients alive with no liver transplantation at 3 and 4 years than predicted using Mayo model (P < 0.05); at 1 and 2 years survival similar to Mayo prediction ▪ Adverse events in 21 therapeutic ERCPs (7.2 % of 291 procedures, 25 % of patients)
Stiehl, 2002 [33]	Prospective	52 (ALP > 2 × ULN)	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 Liver transplantation-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 liver transplantation-free survival than predicted using 1992 Mayo model (P < 0.0001)
Baluyut, 2001 [44]	Retrospective	56 with symptoms 7 without symptoms	Balloon dilation (4 – 12 mm, n = 61) Once per year, with stent if no significant radiological improvement following dilation (n = 33)	Liver transplantation-free survival Complication rate	▪ Longer liver transplantation-free survival than predicted using 1999 Mayo model (P = 0.027) ▪ 12 % complications
2. Stenting					
Ponsioen, 1999 [36]	Retrospective	32 Symptomatic patients with successful stenting for dominant stricture	1-week stenting (10-Fr stent) with no balloon dilation	2-month symptomatic and biochemical improvement, Actuarial curve of re-intervention-free patients	▪ Improvement of symptoms in 83 % ▪ Significant decrease in bilirubin (44 % had increased conjugated bilirubin at baseline) and cholestasis enzymes ▪ Re-intervention-free patients (actuarial): 60 % at 3 years
van Milligen de Wit, 1996 [45]	Retrospective	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 events	▪ 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

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▲ Table 4 (Continuation)

First author, Year [ref.]	Study design	Patients, n	Intervention	Outcomes	Results
3. Dilation vs. dilation + stenting					
Kaya, 2001 [46]	Retrospective	71 with symptoms	Balloon dilation (4 – 8 mm, n = 34) vs. Balloon dilation with 3 – 4-month stenting (n = 37) Intervention via PTBD in 0/34 of balloon group vs. 23 /37 of stent group	Biochemical course up to 24 months	▪ Both strategies improved liver biochemistry; fever resolved only in the dilation without stent group. No additional benefit of stenting after balloon dilation ▪ More complications in stent vs. dilation alone group ($P = 0.001$) ▪ More complications in PTBD vs. ERCP group ($P < 0.001$) ▪ (No multivariate analysis)

ALP, alkaline phosphatases; ULN, upper limit of normal values; CBD, common bile duct; IHBD, intrahepatic bile duct; ERCP, endoscopic retrograde cholangiopancreatography; PTBD, percutaneous transhepatic biliary drainage.

events in two retrospective studies (odds ratios [OR] 4.7 and 5.0) [54, 55] while previous biliary papillotomy/sphincterotomy was protective for subsequent ERCPs [54]. Therefore experienced endoscopists perform biliary sphincterotomy in patients with difficult cannulation in whom ERCP is likely to be repeated during follow-up.

Balloon dilation

RECOMMENDATION

10. ESGE/EASL suggest selecting a balloon caliber of up to the maximum caliber of the ducts delimiting the stricture.

Weak recommendation, low quality evidence.

RECOMMENDATION

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

Weak recommendation, very low quality evidence.

There are no comparative data on the optimal dilation scheme or balloon diameter for treating dominant strictures. In the largest prospective study (500 endoscopic balloon dilations in 96 patients), the authors performed stepwise dominant stricture dilation up to diameters of 8 mm and 6 – 8 mm in the common bile duct and the hepatic ducts, respectively [42]. Bile duct diameter upstream and downstream of the dominant stricture 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 1 to 4 weeks up to technical success, for an average of 2 – 3 balloon dilations [33, 42, 50]. Technical success has been defined as complete balloon inflation within the dominant stricture with no waist observed fluoroscopically, followed by the unobstructed passage of contrast medium through the dilated biliary segment to the duodenum [42, 50]. Using this technique, bile duct perforation was reported in 0.2 % of dominant stricture dilations (1 % of patients) [42]. In contrast, another study that used balloons of diameter 4 – 12 mm for dilation reported dilation-related biliary perforations in 3.5 % of procedures [44].

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, have been reported [33, 50].

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Stent therapy

RECOMMENDATION

12. ESGE/EASL suggest selecting a single 10-Fr stent for dominant stricture in the extrahepatic ducts or two 7-Fr stents for 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 dominant stricture, plastic stents measuring 7 to 10 Fr in diameter have been used, with no reported comparison of the results obtained with various stent diameters. 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 [36, 56]. The Mayo group used 7 – 10-Fr stents at the endoscopist's discretion [46]. The Indianapolis group did not mention the diameter of stents used [44]. Two 7-Fr stents have typically been used in patients with multiple bilateral dominant strictures, 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 (1-month) patency than Teflon models and that, in the long term, 10-Fr models provide longer biliary patency compared with thinner ones (11.5-Fr models do not provide longer patency) [53].

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

Duration of stenting

RECOMMENDATION

13. ESGE/EASL suggest that stents used for treating dominant stricture 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 dominant stricture. 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) versus standard (8 – 12 weeks) stenting duration. Specifically, a retrospective study of short-term stenting (mean duration 11 days) in 32 symptomatic PSC patients with dominant stricture showed, at 2 months, a symptomatic improvement in 83 % of the patients as well as a significant improvement of cholestasis test results; at 1 and 3 years, actuarial analysis showed that 80 % and 60 % of patients, respectively, would not require re-intervention [36]. 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 dominant stricture but, in that study, unscheduled stent exchange had to be performed on 32 occasions because of suspected stent clogging (cholangitis n = 23, jaundice n = 9) [45].

All studies mentioned focused on clinical and serum liver tests, not radiological data, to assess the short-term effect of therapeutic ERCP [36, 45, 46, 56]. 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 patient ranged between 3 and 5 during follow-up periods of 29 and 22 months in two studies [45, 46], while following a short stenting period (mean 11 days) repeat ERCP rates at 1 and 3 years after treatment were estimated at 20 % and 40 %, respectively [36]. Other details about repeated treatments were not reported.

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

Complications of endoscopic therapy

RECOMMENDATION

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 [33, 35, 44, 49, 54, 55, 57 – 62] (▶ **Table 5**). ERCP carries an increased risk for complications in the context of PSC, especially pancreatitis, cholangitis, and extravasation of contrast, although not all studies have documented such an increased risk in PSC [59, 62]. In a systematic survey [63] of post-ERCP complications associated with various indications for ERCP, including 21 prospective studies and 16 855 patients, the total complication rate was 6.85 % (95 %CI 6.46 % – 7.24 %). Pancreatitis occurred in 585 patients (3.47 %, 95 %CI 3.19 % – 3.75 %). In another large retrospective single-center study [47], 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 % [33, 35, 44, 49, 55, 57 – 62], which is higher than reported for other indications [47, 63].

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 % [33, 36, 41, 49, 50, 57, 62, 64 –

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▶ **Table 5** Complications of endoscopic retrograde cholangiopancreatography (ERCP) in primary sclerosing cholangitis (PSC) patients.

First author, Year [ref] Country	Study design	Patients/ERCPs	Complications, % of procedures		
			Total	Pancreatitis	Cholangitis
Lee, 1995 [49] USA	Retrospective	53/175	13.7	7	8
van den Hazel, 2000 [57] The Netherlands	Retrospective	83/106	9	3	2
Baluyut, 2001 [44] USA	Retrospective	63/63	1.8	1.26	0.6
Stiehl, 2002 [33] Germany	Retrospective	106/ERCP yearly, median 5 years	9	5.2	3.3
Enns, 2003 [58] Canada	Retrospective	104 patients	17	5	7.5
Gluck, 2008 [35] USA	Retrospective	106/317	7.3	3.8	0.95
Etzel, 2008 [62] USA	Retrospective	PSC: 30/85 Non-PSC: 45/70	12.9 8.6	2.4 2.9	5.9 1.4
Bangarulingam 2009 [59] USA	Retrospective	PSC: 168 Non-PSC: 981	11 8	5 4	3.6 0.2
Alkhatib, 2011 [60] USA	Retrospective	75/185	8	5	1
Ismail, 2012 [54] Finland	Retrospective	441/441	9	7	–
Navaneethan 2015 [55] USA	Retrospective	294/697	4.3	1.2	2.4
von Seth 2015 [61] Sweden	Retrospective, national registry study	PSC: 141/141 Non-PSC: 8791	18.4 7.3	7.8 3.2	7.1 2.1

66]. 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. [54]. In this retrospective review of 441 ERCP procedures over a 3-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%. The 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

RECOMMENDATION

15. ESGE/EASL recommends routine rectal administration of 100 mg 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.

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Post-ERCP pancreatitis (PEP) is the most common and feared complication associated with ERCP. The risk for PEP in PSC varies from 1 % to 7 %, although the diagnostic criteria vary between studies [67]. Although the quality of the evidence is low, the factors increasing the risk for PEP are probably not different in PSC patients from those in the general population: female sex (OR 2.6, $P = 0.015$) and a guidewire in the pancreatic duct (OR 8.2, $P < 0.01$). Presence of a native papilla increases the risk whereas previous sphincterotomy decreases it [54], suggesting that pre-emptive endoscopic papillotomy 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 dilation, are associated with increased risk of PEP. Precut biliary and pancreatic sphincterotomy is markedly associated with PEP [54], possibly reflecting the difficult cannulation and prolonged procedure time. A recent Cochrane analysis comparing the contrast-assisted with the guidewire-assisted cannulation technique showed that the 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 [68].

Rectal nonsteroidal anti-inflammatory drugs (NSAIDs). In its 2014 update to a Guideline on the prophylaxis of PEP, ESGE recommends routine rectal administration of 100 mg of diclofenac or indomethacin immediately before or after ERCP in all patients undergoing ERCP who were without contraindication to NSAIDs [69]. The recommendation was supported by the results of six meta-analyses published between 2009 and 2014 that compared NSAIDs versus 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 [70, 71] and the cost-efficiency of this approach has been demonstrated [72]. This recommendation applies to PSC patients.

Pancreatic stenting: The ESGE 2014 recommendation on 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, duration of cannulation attempts > 10 min, > 1 pancreatic guidewire passage, pancreatic injection, failure to clear bile duct stones, intraductal ultrasound.

RECOMMENDATION

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 a not infrequent finding among patients with PSC. In studies evaluating the complications of ERCP in PSC the risk for cholangitis has varied from 0.25 % to 8 % [33, 35, 44, 49, 54, 55, 57 – 62] depending on, among other items, the criteria used to define cholangitis. The use of prophylactic antibiotics varies markedly between studies, in terms of prevalence, type of antibiotic, and duration of administration (from 1 oral dose before the procedure to 1-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 – 0.91), septicemia (RR 0.35, 95 %CI 0.11 – 1.11), bacteremia (RR 0.50, 95 %CI 0.33 – 0.78), and pancreatitis (RR 0.54, 95 %CI 0.29 – 1.00). It was concluded that prophylactic antibiotics reduce bacteremia and seem to prevent cholangitis and septicemia in patients undergoing elective ERCP [73]. Our recommendation is in line with the American Society for Gastrointestinal Endoscopy (ASGE) recommendation to prescribe antibiotic prophylaxis in procedures where drainage achieved at ERCP is incomplete or achieved with difficulty, such as in PSC [74]. Bile fluid sampling could be considered during ERCP, to guide antibiotic treatment in case cholangitis occurs despite the prophylaxis [75].

PSC and cholangiocarcinoma

RECOMMENDATION

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

RECOMMENDATION

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 % [76, 77], or up to 400-fold compared with the general population [78]. CCA represents a common cause of death among PSC patients [79], whereby 27 % – 50 % of all CCAs are detected within 1 year of a PSC diagnosis [41, 78, 80] depending on the indications for ERCP.

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CCA should be suspected in PSC patients experiencing rapid deterioration of liver function test findings, 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 US on 230 patients affected by PSC, 23 of whom had CCA, showed no major differences in clinical features between patients without CCA and those with CCA at an earlier stage [40].

Increased serum CA19-9 levels have been reported to indicate the development of CCA in PSC patients. Cutoff levels of 129 or 100 U/mL detected CCA with high sensitivity (nearly 80 %) and specificity (nearly 100 %) [81], but only in advanced cases of CCA. These data are in contrast with other observations that showed that one third of PSC patients with high CA19-9 levels did not have CCA [82, 83]. In a recent study performed on 433 PSC patients, 41 of whom had biliary malignancy, the use of FUT2/3 genotype-dependent cutoff values for CA19-9 improved sensitivity and reduced the number of false-positive results [84]. In a study screening for biliary dysplasia using ERCP and brush cytology, serum CA19-9 had no prognostic value for biliary dysplasia or CCA [37].

Currently, there are no definite radiologic features that indicate CCA in a PSC patient, although the detection of a dominant stricture by MRC may be suggestive for CCA. However, 50 % of PSC patients experience a dominant stricture and its absence does not rule out CCA. In a cohort of 230 patients, ultrasound, computed tomography (CT), and MRCP were found to have high specificity but low sensitivity (10 % – 32 %) [40].

ERCP findings indicative of CCA

Dominant strictures are frequent in PSC [42] and do not per se indicate development of a malignancy. In a large single-center study, CCA was seen in 6/95 dominant strictures (6 %). In general it could be inferred that the chance of any dominant stricture of harboring a CCA is around 5 %. Most CCAs develop in the perihilar region or in extrahepatic bile ducts, and are reachable with a cytological brush. In a large series of patients with CCA [85], 50 % had perihilar cancers, 42 % had distal cancers, and only 8 % were intrahepatic CCAs. 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 always requires additional techniques such as imaging or biliary cytology or histology.

RECOMMENDATION

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.

RECOMMENDATION

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.

RECOMMENDATION

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 (▶ **Table 6**, ▶ **Table 7**). In a recent meta-analysis (11 studies, 747 patients) [95], the pooled diagnostic values of bile duct brushing for diagnosis of CCA in patients with PSC were: sensitivity 43 % (95 %CI 35 % – 52 %), specificity 97 % (95 % – 98 %), PPV 78.2 % (63.6 % – 86.7 %), and negative predictive value (NPV) 87.2 % (85.4 % – 89.1 %). 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 asymptomatic (81 %) patients with PSC, who had been referred for their first ERC to confirm the diagnosis and to 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 % [37].

Addition of FISH analysis of cytology specimens enhanced the sensitivity for detecting CCA in patients with PSC in several patient series [39, 40, 93, 94]. The ideal modality (e. g. FISH vs. digital image analysis vs. flow cytometry) and the appropriate threshold values for markers assessed by each of these modalities have not been robustly established, and this makes meta-analysis of available data challenging [96]. For this reason, chromosomal assessments can so far only be recommended in equivocal cases [96]. As DNA technologies evolve, new markers are likely to emerge.

Ductal biopsy

Ductal biopsy has been shown to improve sensitivity, specificity, and accuracy in diagnosing CCA compared to brush cytology alone [99]. Since the sampling area for ductal biopsies is limited, complementary biliary brushings should be considered in all patients. In published studies the sensitivity for the detection of CCA by ductal biopsy varies from 30 % to 88 % and the specificity from 97 % to 100 % [100]. Combined brush cytology

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▶ **Table 6** Detection of biliary malignancy in primary sclerosing cholangitis (PSC) using brush cytology.

First author, Year [ref]	Study design	Intervention	Participants, n	Outcomes	Results			
					Sensitivity	Specificity	PPV	NPV
Ponsioen, 1999 [86]	Prospective	ERCP with brush cytology from dominant strictures	43	Detection of malignancy/CCA	60 %	89 %	59 %	89 %
Lindberg, 2002 [87]	Prospective	Brush cytology + DNA flow cytometry from biliary strictures	57	Detection of malignancy/CCA	71 %	100 %	NA	NA
Siqueira, 2002 [88]	Retrospective	Brush cytology from bile ducts	151	Detection of malignancy/CCA	46.4 %	100 %	NA	NA
Lal, 2004 [89]	Retrospective	Brush cytology from bile ducts	21	Detection of malignancy/CCA	67 %	94 %,	NA	NA
Furmanczyk, 2005 [90]	Retrospective	Brush cytology from bile ducts	51	Detection of malignancy/CCA	62.5 %	100 %	NA	NA
Boberg, 2006 [91]	Prospective	Brush cytology from biliary strictures	61	Detection of malignancy/CCA	100 %	84 %	68 %	100 %
Moff, 2006 [92]	Retrospective	Brush cytology from bile ducts	47	Detection of malignancy/CCA	50 %	91 %	NA	NA
Moreno Luna, 2006 [93]	Prospective	Brush cytology from biliary strictures	86 PSC	Detection of malignancy/CCA	18 %	100 %	100 %	83 %
Charatcharoenwitthaya, 2008, [40]	Prospective	Brush cytology from biliary strictures	230	Detection of malignancy/CCA	8 %	100 %	100 %	89 %
Levy, 2008 [39]	Prospective	Brush cytology from biliary strictures	32 PSC	Detection of malignancy/CCA	7 %	100 %	NA	NA
Halme, 2012 [94]	Retrospective	Brush cytology from bile ducts	102	Detection of dysplasia/CCA	46 %	88 %	86 %	52 %

CCA, cholangiocarcinoma; PPV, positive predictive value; NPV, negative predictive value; ERCP, endoscopic retrograde cholangiopancreatography; NA, not available.

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▶ **Table 7** Detection of biliary malignancy in primary sclerosing cholangitis (PSC) using brush cytology: meta-analyses and reviews.

First author, Year [ref]	Study design	Intervention	Patients,n	Outcomes	Results				Comments
					Sensitivity, %	Specificity, %	Positive likelihood ratio (PLR)	Negative likelihood ratio (NLR)	
Trikudanathan, 2014 [95]	Meta-analysis including 11 studies (prospective and retrospective)	Bile duct brushing	747	Diagnostic yield of bile duct brushing in diagnosing CCA in PSC strictures	43%	97%	8.87	0.56	The moderate sensitivity in detecting CCA, precludes its utility as a surveillance tool for early diagnosis of CCA.
Navaneethan, 2014 [96]	Meta-analysis including 4 studies (prospective and retrospective)	FISH	629	Diagnostic yield of FISH in diagnosing CCA 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 polysomy	690	Diagnostic yield of FISH polysomy in diagnosing CCA in PSC strictures	51%	93%	6.81	0.56	FISH polysomy is highly specific; however, it has limited sensitivity.
Navaneethan, 2014 [97]	Meta-analysis including 9 studies (prospective and retrospective)	Intraductal 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)	Intraductal biopsy AND Brush cytology	628	Diagnostic yield of both brush cytology and intraductal biopsies performed during ERCP	59%	100%	53.8	0.42	Brushings and biopsy are comparable and have limited sensitivity.
Walker, 2007 [98]	Systematic review	MRI	NA	Diagnosing cholangiocarcinoma in PSC	NA				Lack of evidence
	Systematic review	CT	45	Diagnosing cholangiocarcinoma in PSC	82%	80%	4.10	0.25	CT provides good sensitivity and specificity in detecting biliary tract carcinoma complicating PSC.

FISH, fluorescence in situ hybridization: CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging; CT, computed tomography; NA, not available.

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and biopsy has a sensitivity varying from 47 % to 86 % and specificity from 97 % to 100 %. A retrospective study [100] assessed the accuracy of triple modality testing, namely brush cytology, biopsy, and FISH, and their combinations, in one patient group, and the accuracy of brush cytology alone in a separate patient group. It demonstrated that brush cytology alone had a sensitivity of 42 %, specificity 100 %, PPV 100 %, and NPV 88 %. The triple sample assessment modality markedly improved the overall sensitivity (82 %), with similar specificity (100 %), PPV (100 %), and NPV (87 %).

Cholangioscopy

Peroral cholangioscopy (POCS) allows direct visualization of extrahepatic bile duct strictures. The recent development of video-based systems provides better image resolution and offers clearer views than fiberoptic cholangioscopy. Compared to ERC and tissue sampling, POCS was shown to improve diagnostic accuracy [101 – 103]. 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. Its utility in PSC was studied in a recent case series [104], 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 liver transplantation in some centers; thus any such sampling should be discussed with local multidisciplinary teams.

Endoscopic surveillance of PSC-associated inflammatory bowel disease (IBD)

The relationship between PSC and IBD is well established [105]. The prevalence of IBD in patients with established PSC varies widely, but is reported as 80 % in Scandinavian countries [106]. 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 [107] 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 [108, 109] hence makes it crucial to perform a full ileocolonoscopy at the time of PSC diagnosis in all 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 [8].

Timing of screening

RECOMMENDATION

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

RECOMMENDATION

23. ESGE/EASL suggest that if no IBD is documented, the 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, 110] since it has been shown that PSC-IBD patients whose colorectal cancer (CRC) is detected in a surveillance program have a significantly lower risk of CRC-related mortality as compared to non-surveilled patients [78]. If not, repeat colonoscopy should be done with the occurrence of symptoms suggestive of IBD, or of elevated F-calprotectin, or otherwise at 3 – 5 years [111], although this recommendation lacks any scientific evidence beyond extrapolation from general IBD recommendations [112].

Endoscopic modality

RECOMMENDATION

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

RECOMMENDATION

25. For dysplasia surveillance of PSC-associated IBD, EASL/ESGE recommend ileocolonoscopy with dye-based chromoendoscopy with targeted biopsies.
Strong recommendation, low quality evidence.

PSC-associated colitis seems to be distinctive from other IBD: colitis is predominant in the right colon [113] and colon cancer is typically right-sided [114]. Lack of inflammation in the rectum (“rectal sparing”) is reported in some studies but less frequently observed in others [3]. Endoscopic surveillance

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of PSC-associated colitis is presumed to increase the chance of early detection of dysplasia or malignancy [115].

Screening for IBD at diagnosis of PSC is best performed by high definition ileocolonoscopy 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 [111, 116, 117].

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 [118]. This approach is also endorsed by the European Crohn's and Colitis Organisation (ECCO) [112]. 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 videocolonoscopy. For the detection of patients with neoplasia, the pooled incremental yield of conventional chromoendoscopy with random biopsies over standard white-light endoscopy with random biopsies was 7 % (95 %CI 3.2 % – 11.3 %) [119]. The benefit of conventional chromoendoscopy over white-light endoscopy with latest-generation high definition colonoscopes is unknown to date.

Handling of polyps and colorectal dysplasia

RECOMMENDATION

26. ESGE/EASL recommend endoscopic resection of any visible lesions and assessment of the surrounding mucosa. We recommend proctocolectomy in the 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.

RECOMMENDATION

27. In the case of invisible lesions with high grade dysplasia (HGD) confirmed by two expert pathologists, proctocolectomy should be advised
Strong recommendation, low quality evidence.

RECOMMENDATION

28. In the case of invisible lesions with low grade dysplasia (LGD) confirmed by two expert pathologists, repeat colonoscopy after 3 months with chromoendoscopy is recommended.
Strong recommendation, low quality evidence.

Colorectal cancer (CRC) risk is significantly increased in patients with coexisting IBD and PSC. A meta-analysis of 11 studies concluded that patients with ulcerative colitis and PSC were at increased risk of developing CRC compared to patients with ulcerative colitis alone (OR 4.09; 95 %CI 2.89 – 5.76) [109]. A recent large population-based study in the Netherlands found a 9-fold increased risk of developing CRC in PSC-ulcerative colitis patients, compared to the age- and gender-matched population (standardized incidence ratio [SIR] 8.6, 95 %CI 3.5 – 17.7), and a 10-fold increased risk, compared to ulcerative colitis controls (ratio of SIRs 9.8, 95 %CI 1.9 – 96.6) [78].

Most dysplasia is visible at colonoscopy [120, 121]. On the other hand, invisible dysplastic lesions can also be diagnosed by random biopsies during surveillance. According to the IBD Dysplasia Morphology Study Group [122], dysplasia is subdivided into LGD and HGD.

Recent ECCO guidelines state that a visible lesion with dysplasia should be completely resected endoscopically irrespective of the grade of dysplasia or the location relative to the inflamed mucosal areas [112]. Subsequently, the surrounding mucosa (around the visible lesion) should be examined (with chromoendoscopy-guided targeted biopsies or random biopsies if chromoendoscopy is not available). If endoscopic resection is incomplete or impossible, or if dysplasia is detected in the surrounding mucosa, total proctocolectomy 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 [123, 124], whereas others showed low progression rates [125, 126]. Finally, in the case of invisible lesions with HGD or adenocarcinoma, total proctocolectomy is indicated.

This Guideline from ESGE and EASL represents a consensus of best practice based on the available evidence at the time of preparation. The recommendations might not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of the Guideline, and revision may be necessary as new data appear. Clinical considerations may justify a course of action at variance to these recommendations. This ESGE/EASL Guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. It is not a set of rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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Competing interests

J. Albert has received (from 2015 to 2016) speaker's honoraria from Fujifilm, the Falk Foundation, Covidien/Medtronic, and Olympus Europe, an honorarium from Covidien/Medtronic for advisory services, and research support from Olympus Europe. P. Fickert has served on advisory boards for Dr. Falk Pharma and Intercept; his department has received unrestricted research grants from the Falk Foundation (since 2010) and Gilead (since 2012); he is listed as co-inventor in two patents filed by the Medical University of Graz for the use of norUDCA in the treatment of liver diseases and arteriosclerosis (publication numbers WO2006119803 and WO20099013334). A. Laghi has received a speaker fee from GE Healthcare (October 2016). J.-W. Poley receives consultancy, travel, and speaker fees from Cook Endoscopy; his department receives financial support for consultancy, travel, and speaking from Boston Scientific; he receives travel and consultancy fees from Pentax. C. Ponsioen's department is receiving research support from Olympus and Fujifilm. C. Schramm has served on an advisory board for Intercept Pharmaceuticals (2016), and has given lectures sponsored by Intercept and the Falk Foundation. F. Swahn has served on a scientific advisory board for Rhenman & Partners, and has given lectures sponsored by Cook Medical Sweden and Boston Scientific Nordic. L. Aabakken, M. Arvanitakis, O. Chazouilleres, J.-M. Dumonceau, M. Färrkkilä, C. Hassan, G. Hirschfield, T. Karlsen, M. Marzioni, M. Fernandez, S. Pereira, J. Pohl, and A. Tringali have no competing interests.

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