Digestive Endoscopy 2025; ••: ••–•• doi: 10.1111/den.15010

Review

Endoscopic management of primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is a progressive autoimmune hepatobiliary disease characterized by fibrotic strictures in the bile ducts, leading to chronic cholestasis and cirrhosis. Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method for evaluating the condition of the bile ducts, and has high sensitivity and specificity, making it the first-line diagnostic tool for PSC. However, the importance of endoscopic retrograde cholangiopancreatography (ERCP) remains unchanged. ERCP is particularly useful in differentiating PSC from cholangiocarcinoma. It allows for tissue sampling from strictures and offers superior spatial resolution to detect subtle changes in the bile ducts. Endoscopic ultrasonography (EUS) is a minimally invasive endoscopic modality with growing importance in the management of pancreato-biliary diseases. Although the role of EUS in PSC patients has not been established, future research in this area is warranted. ERCP is particularly important for patients who are not eligible for liver transplantation, as it allows bile drainage from the dominant or high-grade strictures through balloon dilation and stenting, alleviating symptoms and extending survival. Balloon dilation is currently considered superior to biliary stenting, due to its lower risk of bacterial cholangitis. However, refractory complications, such as bacterial cholangitis and pancreatitis, can still occur in some cases. Therefore, careful patient selection and involvement of highly skilled specialists are essential. In the diagnosis and treatment of PSC, it is crucial to perform endoscopic procedures tailored to its unique pathophysiology. Further research is needed to optimize treatment protocols and improve outcomes. This review presents the latest insights on these topics.

Key words: biliary stricture, cholangiocarcinoma, endoscopic retrograde cholangiopancreatography, liver transplantation, primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is an autoimmune hepatobiliary disease characterized by fibrotic strictures of the bile ducts. Typically, these strictures occur diffusely and multifocally in both intrahepatic and extrahepatic bile ducts, leading to chronic cholestasis and eventually progressing to liver cirrhosis. The etiology of PSC remains indeterminate, and its diagnosis and management can be challenging even for gastroenterologists.

The diagnosis of PSC is primarily based on typical cholangiographic findings, as outlined in clinical guidelines from various countries.[1–3] Recently, magnetic resonance cholangiopancreatography (MRCP) has been recommended as the initial modality for evaluating the biliary tree. However, endoscopic retrograde cholangiopancreatography (ERCP) continues to play a crucial role in differentiating PSC from cholangiocarcinoma. Regarding treatment, while liver transplantation remains the only curative option, many patients are not eligible due to the limited availability of donor organs. This issue is particularly pronounced in Japan, where living donor liver transplantation predominates, making endoscopic interventions crucial for managing these patients.

This review discusses the role of endoscopy in the diagnosis and treatment of PSC and presents the latest insights into key considerations for performing endoscopic procedures. Figures 1 and 2 provide flowcharts outlining the diagnostic and therapeutic course for PSC, with a particular focus on the role of endoscopic techniques.

DIAGNOSIS OF PSC

PSC IS CLASSIFIED into two subtypes: small duct PSC and large duct PSC. PSC with small duct PSC exhibit chronic cholestasis but have normal cholangiographic findings. Its diagnosis can only be confirmed through liver biopsy. In contrast, large duct PSC can be diagnosed based on characteristic cholangiographic features

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Received 18 September 2024; accepted 3 February 2025.

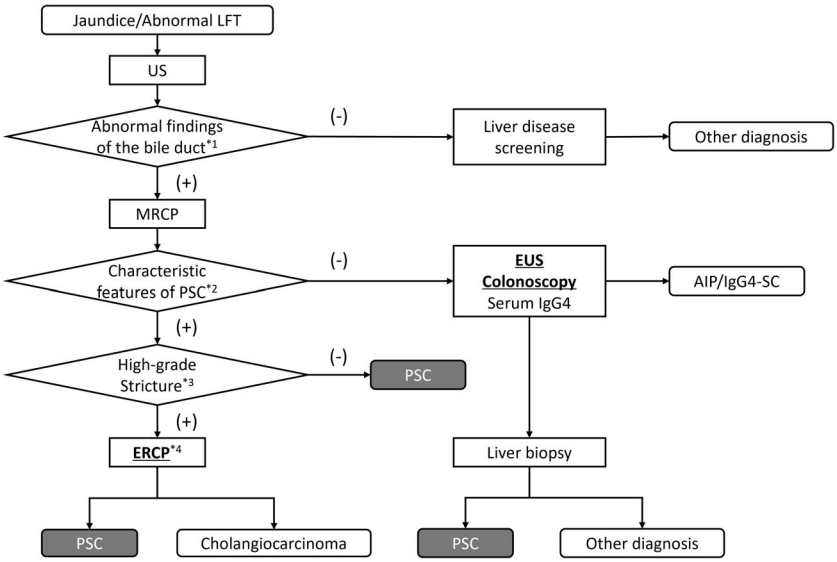

Figure 1 Flowchart of a diagnostic course of primary sclerosing cholangitis (PSC). *1 Abnormal findings of the bile duct include dilations, strictures, and wall thickening. *2 Characteristic features of PSC include band-like stricture, beaded appearance, pruned tree appearance, and diverticulum-like outpouching. *3 High-grade stricture is defined as a >75% reduction in the lumen of the common bile duct or hepatic ducts on magnetic resonance cholangiopancreatography (MRCP). *4 Differentiation between PSC and cholangiocarcinoma should be performed using brush cytology, bile duct biopsy, and other diagnostic techniques. AIP, autoimmune pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IgG4-SC, immunoglobulin G4-related sclerosing cholangitis; LFT, liver function test; US, ultrasonography.

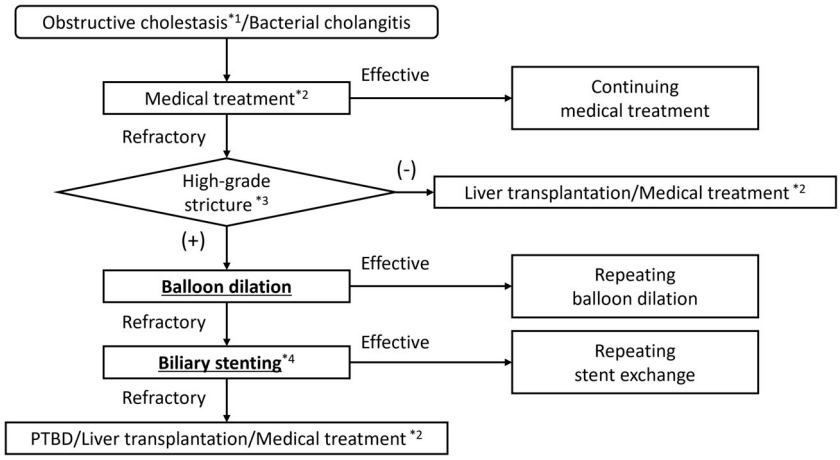

Figure 2 Flowchart of a therapeutic course of primary sclerosing cholangitis (PSC). *1 Obstructive cholestasis includes progressive jaundice and new or worsening pruritus, often accompanied by abnormalities in liver function test. *2 No effective medical treatments for PSC have been established to date. For patients with mild bacterial cholangitis who show improvement with antibiotic treatment, endoscopic intervention can be deferred. *3 High-grade stricture is defined as a >75% reduction in the lumen of the common bile duct or hepatic ducts on MRCP. *4 It should be noted that Western guidelines recommend a short stenting duration of 1–4 weeks due to the potential for early stent occlusion. PTBD, percutaneous transhepatic biliary drainage.

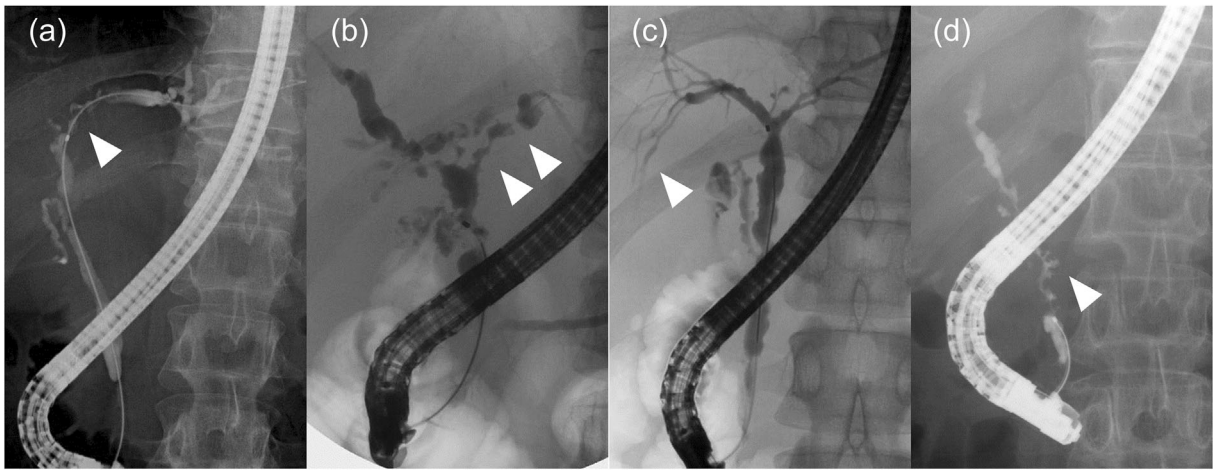

Figure 3 Characteristic cholangiographic features of primary sclerosing cholangitis. (a) Band-like stricture: A short, annular stricture is seen in the intrahepatic bile duct (arrowhead). (b) Beaded appearance: Alternating strictures and slightly dilated segments are seen in the intrahepatic bile duct (arrowheads). (c) Pruned tree appearance: Intrahepatic branch ducts appear absent, resembling a pruned tree (arrowhead). (d) Diverticulum-like outpouching: The cholangiogram shows a protrusion resembling a diverticulum between adjacent strictures in the common bile duct (arrowhead).

Table 1 Japanese diagnostic criteria for primary sclerosing cholangitis (PSC)

Diagnostic items	
I. Major	
A. Biliary tract imaging	1. Cholangiographic findings characteristic of PSC
	2. Cholangiographic findings not specific to PSC
B. An increased ALP level	
II. Minor items	
a. Association with IBD	
b. Liver histology	Fibrous cholangitis/onion skin lesion
Diagnosis	
Definite	A1 + (B/a/b)
	A2 + B + a + b
Probable	A1
	A2 + B + (a/b)
	A2 + a + b
Possible	A2 + (a/b)

ALP, alkaline phosphatase; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

such as band-like stricture, beaded appearance, pruned tree appearance, and diverticulum-like outpouching (Fig. 3).[1] The Japanese diagnostic criteria for PSC (Table 1)[4] primarily focus on this large duct type (Table 1). In the diagnosis of large duct PSC, the role of liver biopsy is limited. Although fibrous obliterative cholangitis, commonly referred to as onion-skin fibrosis, can be observed, it is not a specific pathological finding for PSC. Fibrous obliterative cholangitis can be found also in pediatric vanishing bile duct syndrome[5] and drug-induced liver injury.[6] Moreover, the detection rate in liver biopsy specimens is low.[5,7]

ERCP was once considered the gold standard for evaluating the biliary tree. However, ERCP involves radiation exposure and carries risks of postprocedural complications such as cholangitis and pancreatitis. On the other hand, MRCP is noninvasive and has shown good accuracy in diagnosing PSC (Fig. 4), with a sensitivity of 86% and a specificity of 94%.[8] Therefore, current clinical guidelines recommend MRCP as the first-choice imaging modality.[1–3] Additionally, magnetic resonance imaging (MRI) can measure liver stiffness, providing information on the extent of liver fibrosis and patient prognosis.[9]

The most significant advantage of ERCP in the diagnosis of PSC is its ability to obtain tissue samples to differentiate PSC from cholangiocarcinoma. It is well known that patients with PSC are at risk of developing cholangiocarcinoma. A large population-based study has reported cumulative risks of developing cholangiocarcinoma of 6%, 14%, and 20% after 10, 20, and 30 years of PSC, respectively.[10] Additionally, the cholangiographic appearance of PSC can sometimes closely resemble that of

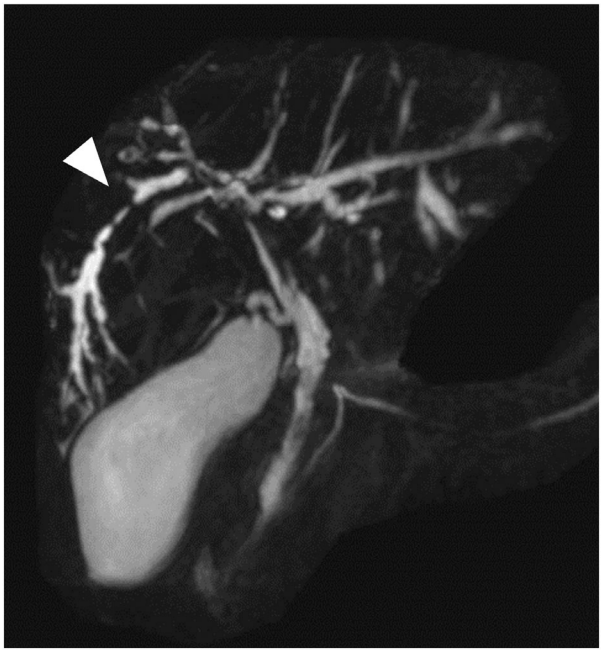

Figure 4 Magnetic resonance cholangiopancreatography (MRCP) in primary sclerosing cholangitis. The MRCP demonstrates band-like strictures in the intrahepatic bile ducts (arrowhead).

Table 2 Comparison between endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography/imaging (MRCP/MRI) for the diagnosis of primary sclerosing cholangitis (PSC)

	Advantages	Disadvantages
ERCP	Tissue sample acquisition to differentiate PSC from CC Higher spatial resolution	Radiation exposure Postprocedural complications (cholangitis and pancreatitis, etc.)
MRCP/MRI	Noninvasiveness Liver stiffness measurement	Poorer spatial resolution

CC, cholangiocarcinoma.

cholangiocarcinoma. Therefore, the ability to obtain tissue samples from biliary strictures is a significant benefit of performing ERCP. A comparison between ERCP and MRCP/MRI for the diagnosis of PSC is summarized in Table 2.

In patients with PSC, if there is particularly severe stricture in part of the bile duct or if a rapidly progressing stricture is observed, there is a high likelihood of cholangiocarcinoma,[11,12] and evaluation by ERCP is necessary. A dominant stricture is defined by ERCP as a stricture with a diameter of ≤1.5 mm in the common bile duct or ≤1.0 mm in the hepatic duct within 2 cm of the bifurcation.[13,14] On the other hand, due to the specific spatial resolution of MRCP, the term "dominant stricture" should not be used. Instead, the term "high-grade stricture" is proposed, defined as a >75% reduction in the lumen of the common bile duct or hepatic ducts.[15,16] Additionally, strictures in the common bile duct or hepatic ducts associated with persistent obstructive cholestasis or bacterial cholangitis are referred to as relevant strictures.[2,3]

Table 3 Diagnostic yields of endoscopic procedures for diagnosing cholangiocarcinoma in patients with primary sclerosing cholangitis

Procedures	Sensitivity*	Specificity*
Brush cytology[17]	43% (35–52%)	97% (95–98%)
FISH analysis[18]	68% (61–74%)	70% (66–73%)
POCS[19]	65% (35–87%)	97% (87–99%)
pCLE[21]	88% (84–91%)	79% (74–83%)

*Values are expressed with 95% confidence intervals.
FISH, fluorescence in situ hybridization; pCLE, probe-based confocal laser endomicroscopy; POCS, peroral cholangioscopy.

In patients with PSC, if dominant or relevant strictures are observed during ERCP, tissue samples from the stricture sites should be obtained for pathological examination. Diagnostic yields of endoscopic procedures for diagnosing cholangiocarcinoma in patients with PSC are summarized in Table 3. Brush cytology is the most common method for tissue sampling; however, its sensitivity is low. According to a systematic review, the diagnostic performance of brush cytology for cholangiocarcinoma in PSC patients is reported to have a sensitivity of 43% (95% confidence interval [CI] 35–52%) and a specificity of 97% (95% CI 95–98%).[17] Therefore, to improve diagnostic accuracy, repeated brush cytology is necessary.

To enhance the sensitivity of brush cytology, fluorescence in situ hybridization (FISH) analysis is utilized in Western countries. FISH analysis employs fluorescently labeled DNA probes to detect chromosomal abnormalities characteristic of cancer. According to a systematic meta-analysis, FISH analysis has a sensitivity of 68% (95% CI 61–74%) and a specificity of 70% (95% CI 66–73%) for diagnosing cholangiocarcinoma in PSC patients.[18] Thus, while FISH analysis provides valuable diagnostic information, its sensitivity and specificity are not perfect, and it should be used selectively for suitable patients.

Targeted biopsy under peroral cholangioscopy (POCS) is also useful for enhancing diagnostic accuracy for cholangiocarcinoma. A meta-analysis reported that for diagnosing

cholangiocarcinoma in PSC patients, POCS had a sensitivity of 65% (95% CI 35–87%) and a specificity of 97% (95% CI 87–99%).[19] Macroscopic findings under POCS that suggest malignancy include papillary projections, ulcerations, and dilated or tortuous vessels. However, distinguishing between benign and malignant strictures based solely on these findings remains challenging. In addition to differentiating PSC from cholangiocarcinoma, POCS is also useful for assessing the degree of biliary inflammation.[20] In cases of active inflammation, findings may include mucosal erythema, ulceration, fibrinous white exudate, and irregular surfaces, whereas chronic inflammation may present as scarring, pseudodiverticula, and bile duct stenosis. These features may be helpful in staging the disease and evaluating the response to medical treatment.

Probe-based confocal laser endomicroscopy (pCLE) is an emerging technique that allows real-time, 1000× magnified imaging for evaluating indeterminate biliary strictures. A meta-analysis reported that pCLE had a sensitivity of 88% (95% CI 84–91%) and a specificity of 79% (95% CI 74–83%) for diagnosing indeterminate biliary strictures.[21] While pCLE shows promise, its use in PSC patients is still limited, and further studies are needed to confirm its utility.[22,23]

Intraductal ultrasonography (IDUS) is an optional modality used in ERCP-related procedures. By employing high-frequency ultrasound, IDUS provides high-resolution images that enable a more detailed evaluation of the bile duct wall. Naitoh *et al*.[24] reported that circular-asymmetric wall thickness, irregular inner margin, unclear outer margin, diverticulum-like outpouching, heterogeneous internal echo, and the disappearance of three layers are characteristic findings of PSC. They concluded that these features are useful in distinguishing PSC from immunoglobulin G4-related sclerosing cholangitis (IgG4-SC).

Endoscopic ultrasonography (EUS) is an important diagnostic tool for biliary and pancreatic diseases, but its significance in diagnosing PSC is not yet fully established. However, due to its high sensitivity in detecting biliary abnormalities and its less invasive nature, EUS may be useful, especially in patients with early-stages PSC. Lutz *et al*.[25] conducted a prospective pilot study to investigate the role of EUS in the diagnosis of PSC. They reported that EUS frequently detected wall thickening, irregular wall structure, significant changes of caliber of the common bile duct, and perihilar lymphadenopathy in PSC patients. However, EUS was not diagnostic in patients with strictly intrahepatic disease.

Endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA) is a well-established method for tissue acquisition in the diagnosis of pancreatic diseases. Recently, its efficacy in diagnosing malignant biliary strictures has been reported.[26–28] Although the evidence remains limited, several reports have highlighted the utility of EUS-FNA in differentiating PSC from cholangiocarcinoma or IgG4-SC.[29,30]

TREATMENT OF PSC

PSC IS A progressive disease that ultimately leads to biliary cirrhosis. Currently, no effective medical treatments are established, and liver transplantation remains the only curative option. However, liver transplantation has its own issues. Particularly after liver transplantation, especially living-donor liver transplantation, there is a high rate of PSC recurrence.[31,32] In countries like Japan, where brain-dead donor organs are scarce and living-donor liver transplantation is more common, this issue is particularly significant. Therefore, endoscopic treatment plays a crucial role in either avoiding liver transplantation or delaying its necessity.

Therapeutic endoscopic interventions are recommended for patients with dominant or high-grade strictures, who present symptoms of obstructive cholestasis or bacterial cholangitis. Key physical signs of obstructive cholestasis include progressive jaundice and new or worsening pruritus, often accompanied by abnormalities in liver function tests.[1–3] However, endoscopic treatment can sometimes lead to bacterial cholangitis, which may exacerbate these clinical findings. Post-ERCP bacterial cholangitis occurs in 2–8% of cases[33,34] and can be challenging to be managed. Therefore, careful consideration of patient selection is essential when deciding on endoscopic interventions, and interventions should be performed by skilled endoscopists. Proper patient selection is crucial for the success of endoscopic interventions in PSC patients. PSC patients with intrahepatic stones are considered to have a higher risk of refractory postprocedural bacterial cholangitis based on the authors' experience. Therefore, endoscopists should exercise the utmost caution when deciding to perform endoscopic interventions in such cases.

Acute bacterial cholangitis is a common complication in PSC patients and requires prompt initiation of antibiotic therapy. However, severe cases with high-grade strictures necessitate urgent biliary decompression. In contrast, for patients with mild bacterial cholangitis who show improvement with antibiotic treatment, endoscopic intervention can be deferred. For bacterial cholangitis that is refractory to both antibiotics and endoscopic treatment, percutaneous drainage should also be considered. Patients with recurrent cholangitis may be candidates for liver transplantation, and close collaboration with a transplant surgeon is essential.

Endoscopic balloon dilation of relevant strictures has been associated with symptom improvement, such as relief

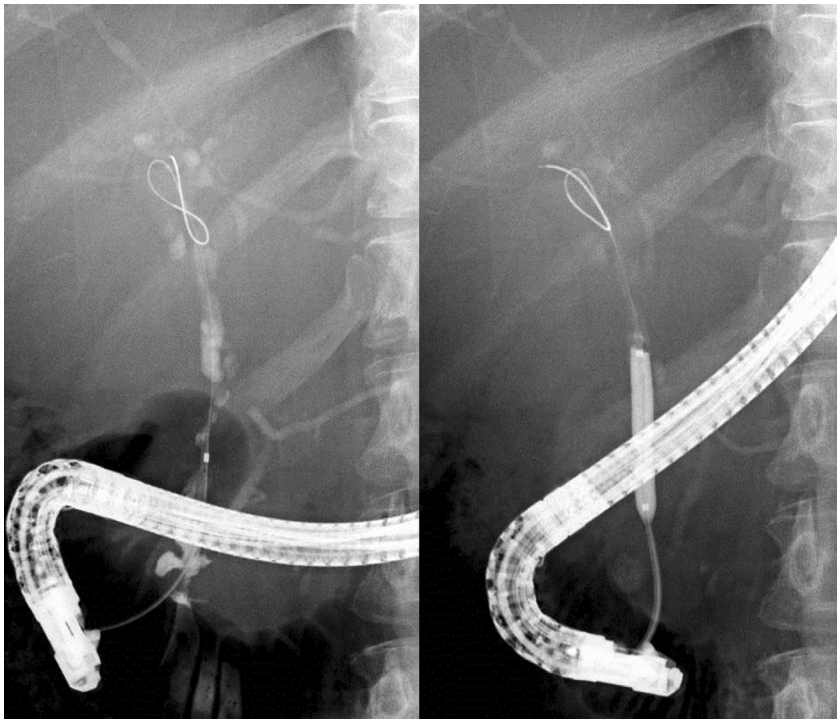

Figure 5 Endoscopic balloon dilation of a dominant stricture in primary sclerosing cholangitis. A 4 mm balloon is inflated in the distal common bile duct.

of jaundice and pruritus (Fig. 5), and has been reported to extend transplantation-free survival beyond what is predicted by the Mayo model.[13,35–37] However, there is no consensus on a dilation protocol or optimal balloon size. In the largest prospective study involving 96 participants, stepwise dilation of the bile ducts was performed, achieving a maximum diameter of 8 mm in the common bile duct and 6 mm in the hepatic ducts.[35] It is important to select a balloon size that matches the maximum diameter of the ducts, considering the sizes of the ducts upstream and downstream of the stricture, to avoid perforation.

In patients who show a favorable response to initial balloon dilation, repeating the procedure may be considered. A recent retrospective study reported that scheduled balloon dilation in patients with dominant strictures, regardless of symptoms, was associated with higher transplantation-free survival compared to those who received dilation on-demand after symptom onset.[38] However, further research is needed regarding repeated balloon dilation, and endoscopic interventions are not currently recommended for asymptomatic patients.

Biliary stenting is another treatment option for PSC patients undergoing endoscopic intervention (Fig. 6). For complex or refractory strictures, indwelling plastic stents may be effective. A single 10F stent is recommended for extrahepatic strictures, while two 7F stents are suggested for hilar strictures.[39] A retrospective study of short-term stenting (1 week) reported symptom improvement and significant reductions in serum total bilirubin and biliary enzyme levels, with no stent dysfunction observed.[40] In contrast, a retrospective study of long-term stenting (3 months) demonstrated similar efficacy but reported a total of 32 instances of stent occlusion occurring within 2–3 months among 25 patients, necessitating unscheduled stent exchanges.[41] Therefore, considering the potential for early stent occlusion, a short stenting duration of 1–4 weeks is recommended.[2,3,39]

Generally, Western guidelines leave the choice between balloon dilation and biliary stenting to the discretion of the endoscopist.[2,3] In contrast, the Japanese guidelines recommend balloon dilation as the preferred method for patients with PSC.[1] A comparison between balloon dilation and stenting in treatment outcomes for PSC patients is summarized in Table 4. A retrospective study comparing balloon dilation alone with a combination of balloon dilation and stenting in PSC patients with dominant

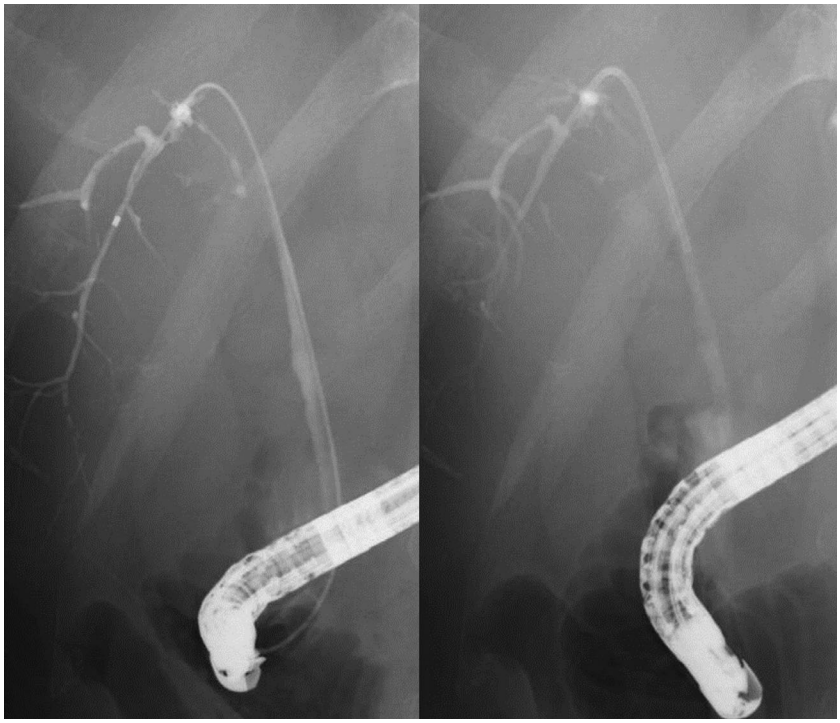

Figure 6 Biliary stenting in primary sclerosing cholangitis. A 7F plastic stent is positioned at the hilar stricture, with its distal end placed above the papilla.

Table 4 Comparison between balloon dilation and stenting in treatment outcomes for patients with primary sclerosing cholangitis

Publication type	Interventions	Outcomes	Overall complications	Postprocedural cholangitis
Case–control study[43]		Improvement in jaundice		
	Balloon dilation	32%	15%	3%
	Balloon dilation plus stenting	24%	54%	32%
Randomized controlled trial[44]		Median recurrence-free patency		
	Balloon dilation	26 weeks	7%	3%
	Stenting	34 weeks	45%	12%
Meta-analysis[45]		Improvement in symptoms		
	Balloon dilation	87%	11%	5%
	Balloon dilation plus stenting	71%	27%	11%
Meta-analysis[46]		Clinical efficacy		
	Balloon dilation	66%	9%	2%
	Stenting	86%	36%	20%

strictures found similar efficacy in reducing serum bilirubin levels; however, the combination therapy required more procedures (5.0 vs. 2.1 per patient) and had a higher complication rate (54% vs. 15%, $P = 0.003$).[42] A European multicenter randomized trial comparing single balloon dilation with short-term stenting was prematurely terminated due to the increased risk of serious adverse events such as bacterial cholangitis and pancreatitis in the stenting

group (45% vs. 6.7%, $P = 0.001$).[43] A recent meta-analysis has reported that patients undergoing balloon dilation alone have higher technical success rates (97% vs. 92%, $P < 0.001$), clinical success rates (87% vs. 71%, $P < 0.001$), and lower complication rates (11% vs. 27%, $P < 0.001$) compared to those receiving combined balloon dilation and stenting.[44] Additionally, another meta-analysis has shown that stenting is associated with a higher incidence of complications.[45] Therefore, balloon dilation is currently considered superior to biliary stenting for the treatment of strictures in PSC patients.

In benign biliary strictures unrelated to PSC, the effectiveness of multiple plastic stents and fully covered self-expandable metallic stents (SEMS) has been demonstrated. A small retrospective study evaluating the efficacy of SEMS in patients with refractory dominant strictures reported improvements in pruritus and liver function tests after 3 months of SEMS placement.[46] These approaches may potentially be introduced into the treatment of PSC in the future. EUS-guided biliary drainage (EUS-BD) has emerged as a salvage procedure for cases where transpapillary drainage is challenging. While its efficacy in patients with PSC is presumed to be limited due to the disease's characteristic multiple and diffuse biliary strictures, EUS-BD may still be beneficial depending on the individual patient's condition.

COMPLICATIONS OF ENDOSCOPIC INTERVENTIONS

ENDOSCOPIC INTERVENTIONS PLAY a crucial role in the diagnosis and treatment of PSC. However, ERCP carries the risk of complications such as pancreatitis and bacterial cholangitis. A retrospective analysis using a nationwide registry in Sweden reported a significantly higher overall complication rate in PSC patients compared to those with other biliary diseases (18.4% vs. 7.3%, $P < 0.01$), with higher rates of pancreatitis (7.8% vs. 3.2%, $P = 0.002$) and bacterial cholangitis (7.1% vs. 2.1%, $P < 0.001$).[47] On the other hand, a retrospective analysis of consecutive patients who underwent ERCP found no significant difference in overall complication rates between PSC patients and those with other biliary diseases (12.9% vs. 8.6%, $P = 0.45$), nor in the rates of pancreatitis (2.4% vs. 2.9%, $P = 0.76$) or bacterial cholangitis (5.9% vs. 1.4%, $P = 0.11$).[48]

The incidence of post-ERCP bacterial cholangitis in PSC patients has been reported to range from 2% to 8%,[33,34] thus prophylactic administration of antibiotics before and after the procedure is recommended.[2,3] However, there is no consensus on the optimal choice of antibiotics or the appropriate duration of treatment. Additionally, in PSC patients who have progressed to liver cirrhosis, attention must be paid to coagulopathy, thrombocytopenia, and the risk of esophageal or gastric varices due to portal hypertension, as these factors increase the risk of bleeding. The decision on whether to perform biliary sphincterotomy in PSC patients also lacks consensus. Biliary sphincterotomy is generally performed when biliary cannulation is difficult or when repeated interventions are anticipated, but in PSC patients with advanced liver cirrhosis, its indication must be carefully considered.

CONCLUSION

IN THE DIAGNOSIS of biliary diseases, MRCP is increasingly replacing ERCP, but ERCP remains crucial for differentiating PSC from cholangiocarcinoma in patients with high-grade strictures. Therapeutically, endoscopic balloon dilation is recommended for treating relevant strictures in cases complicated by obstructive cholestasis or bacterial cholangitis. To ensure safety and achieve optimal therapeutic outcomes, careful patient selection is essential. Endoscopic procedures should be performed by experienced endoscopists who are familiar with the unique challenges of PSC and who can make informed decisions about the appropriate treatment.

FUNDING INFORMATION

NONE.

CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interests for this article.

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