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CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Surveillance for Hepatobiliary Cancers in Patients With Primary Sclerosing Cholangitis: Expert Review

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DESCRIPTION: The purpose of this clinical practice update is to define key principles in the surveillance of hepatobiliary cancers including cholangiocarcinoma, gallbladder adenocarcinoma, and hepatocellular carcinoma in patients with primary sclerosing cholangitis (PSC).

METHODS: The recommendations outlined in this expert review are based on available published evidence including observational studies and systematic reviews, and incorporates expert opinion where applicable.

BEST PRACTICE ADVICE 1: Surveillance for cholangiocarcinoma and gallbladder cancer should be considered in all adult patients with PSC regardless of disease stage, especially in the first year after diagnosis and in patients with ulcerative colitis and those diagnosed at an older age.

BEST PRACTICE ADVICE 2: Surveillance for cholangiocarcinoma and gallbladder cancer should include imaging by ultrasound, computed tomography, or magnetic resonance imaging, with or without serum carbohydrate antigen 19-9, every 6 to 12 months

BEST PRACTICE ADVICE 3: Endoscopic retrograde cholangiopancreatography with brush cytology should not be used routinely for surveillance of cholangiocarcinomas in PSC.

BEST PRACTICE ADVICE 4: Cholangiocarcinomas should be investigated by endoscopic retrograde cholangiopancreatography with brush cytology with or without fluorescence in situ hybridization analysis and/or cholangioscopy in PSC patients with worsening clinical symptoms, worsening cholestasis, or a dominant stricture.

BEST PRACTICE ADVICE 5: Fine-needle aspiration of perihilar biliary strictures should be used with caution in PSC patients considered to be liver transplant candidates because of concerns for tumor seeding if the lesion is a cholangiocarcinoma.

BEST PRACTICE ADVICE 6: Surveillance for cholangiocarcinoma should not be performed in PSC patients with small-duct PSCs or those younger than age 20.

BEST PRACTICE ADVICE 7: The decision to perform a cholecystectomy in PSC patients with a gallbladder polyp should be based on the size and growth of the polyp, as well as the clinical status of the patient, with the knowledge of the increased risk of gallbladder cancer in polyps greater than 8 mm.

BEST PRACTICE ADVICE 8: Surveillance for hepatocellular carcinoma in PSC patients with cirrhosis should include ultrasound, computed tomography, or magnetic resonance imaging, with or without α-fetoprotein every 6 months.

Abbreviations used in this paper: CA19-9, carbohydrate antigen 19-9; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; FISH, fluorescence in situ hybridization; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PSC, primary sclerosing cholangitis; US, ultrasound.

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Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease characterized by strictures within the intrahepatic and extrahepatic biliary tree, and has a global impact, affecting more than 4.15 to 13.6 per 100,000 population in the United States,[1,2] and as high as 16.2 per 100,000 population globally.[3] The highest prevalence of PSC has been observed in Scandinavia and northern Europe, and is less common in southern Europe and Asia. PSC appears to be equally prevalent among African Americans as white Americans.[4,5] The natural progression of PSC is toward biliary cirrhosis and liver failure, with the median time from diagnosis to death or liver transplantation estimated to be 9 to 18 years in transplant centers[6–8] compared with 21.3 years at nontransplant centers.[9] PSC is strongly associated with inflammatory bowel disease (IBD), which is present in approximately two thirds of PSC patients, and significantly increases the risk of colon cancer to greater than that of IBD alone.[10,11]

Patients with PSC are at risk of developing hepatobiliary cancers including cholangiocarcinoma, gallbladder cancer, and hepatocellular carcinoma (HCC). The annual risk for cholangiocarcinoma is approximately 0.5% to 1.0%, with 10- and 30-year cumulative incidence rates of 6% to 11% and 20%, respectively; 400-fold the risk of the general population.[12] Population-based studies have suggested that 27% to 37% of incident cholangiocarcinomas are detected within 1 year of the diagnosis of PSC. Despite increasing recognition that PSC-associated hepatobiliary cancers represent an important long-term risk, limited guidance is provided within current guidelines on surveillance for hepatobiliary cancers, and cholangiocarcinomas in particular. Risk profiling based on multiple clinical factors and comorbid medical conditions may be beneficial to individualize cholangiocarcinoma surveillance recommendations.

Although significant data are available to support the epidemiologic observation of the increasing incidence of cirrhosis, hepatic decompensation, HCC, and liver transplant listing among patients with PSC in the United States and industrialized nations, there is a deficiency of level 1 evidence specific to cholangiocarcinoma surveillance in patients with PSC. The absence of reliable risk-stratification tools to guide physician recommendations on cholangiocarcinoma surveillance leaves clinicians seeking guidance on the following:

- Which screening modality and how frequently should surveillance for cholangiocarcinoma be performed in patients with PSC?
- What, if any, role do serum markers such as carbohydrate antigen 19-9 (CA19-9) play in cholangiocarcinoma surveillance in PSC?
- Should co-existing patient- or disease-related risk factors influence surveillance recommendations?
- Should patients with PSC undergo HCC surveillance?

The purpose of this update is to provide guidance to clinicians on the surveillance of hepatobiliary cancer in patients with PSC based on the most contemporary data available.

Prevalence, Incidence, and Risk Factors for Cholangiocarcinoma in Primary Sclerosing Cholangitis

Patients with PSC are at increased risk of developing several hepatobiliary cancers, primarily cholangiocarcinoma, and, to a lesser degree, gallbladder cancer and hepatocellular carcinoma. Estimating the incidence and prevalence of cholangiocarcinoma is limited by several factors. First, cholangiocarcinoma may be the precipitating event leading to the concurrent diagnosis of PSC and cholangiocarcinoma. Second, the diagnosis of PSC in the presence of cholangiocarcinoma may be difficult because they can have similar or overlapping imaging features. Third, both PSC and cholangiocarcinoma are rare conditions, so cholangiocarcinoma rates in PSC may be limited by potential referral bias. The reported frequency of cholangiocarcinoma in patients with PSC ranges between 4% and 36%. Variability in the length of follow-up evaluation, patient population, and clinical setting likely explain many of these differences. Among adult cohorts not limited to liver transplant recipients, 531 of 6591 (8%; 95% CI, 7%–9%) patients developed cholangiocarcinoma with a median follow-up period ranging from 2.5 to 13 years. The International PSC Study Group reported that among 7120 patients, 821 (8%; 95% CI, 7%–9%) developed cholangiocarcinoma, with an incidence of 1.25 (95% CI, 0.90–1.60) per 100 patient-years among those with large-duct PSC.[13] From this same cohort, the prevalence of hepatobiliary malignancies (primarily cholangiocarcinoma) was 7%, 11%, 16%, and 22% at 5, 10, 15, and 20 years of follow-up evaluation, respectively. Notably, several studies have reported that the highest incidence of cholangiocarcinoma is observed in the first year after a PSC diagnosis, but this accounts for fewer than half of all cases of cholangiocarcinoma.[9,13–15]

Factors associated with the risk of cholangiocarcinoma in PSC include age, sex, and IBD status.[13] Increasing age is associated with an increased risk of cholangiocarcinoma, with incidence rates for patients younger than 20 years of 1.2 per 100 patient-years compared with 21.0 per 100 patient-years for patients older than age 60. Compared with patients with ulcerative colitis, PSC patients without IBD or with Crohn's disease have a significantly lower risk of cholangiocarcinoma (1.22 vs 1.02 and 1.11, respectively). A similar reduction in incidence of cholangiocarcinoma is seen in women compared with men (0.90 and 1.28 per 100 patient-years, respectively).

Effectiveness of Surveillance on Cholangiocarcinoma

Best Practice Advice 1

Although the lifetime risk of cholangiocarcinoma in PSC patients is high, the annual risk is low. Prospective studies of surveillance of cancer in PSC patients are lacking. However, in a large population of PSC patients, regular surveillance was associated with a higher 5-year survival rate compared with patients who did not receive regular surveillance (68% vs 20%; $P < .0061$).[16] Early detection of cholangiocarcinoma can lead to curative liver transplantation, and current European Association for the Study of the Liver[17] clinical guidelines recommend that biliary dysplasia detected with brush cytology represents a possible indication for liver transplantation. Surveillance includes imaging such as ultrasound (US), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), computed tomography (CT) scan, cholangiography, or endoscopic retrograde cholangiopancreatography (ERCP). Serologic screening is limited but usually relies on CA19-9, a glycolipid expressed by cancer cells that can be used as a circulating marker to detect malignancies.[18–20] CA19-9 is the most common serum marker associated with cholangiocarcinoma. Limitations of CA19-9 include the variability in sensitivity and specificity of the marker, depending on the cut-off value used. A cut-off value of 129 U/mL showed a sensitivity of 78% and a specificity of 98%,[21] whereas a cut-off value of 20 U/mL showed a sensitivity of 78% and a specificity of 67%.[22] Among PSC patients with increased CA19-9 levels, up to one third may not have cholangiocarcinoma.[18] Importantly, expression of CA19-9 requires the presence of the Lewis blood group antigen, which is lacking in up to 10% of the population.[23] In addition, genotypic variants of fucosyltransferases 2 and 3 influence levels of CA19-9, and utilization of different cut-off values based on fucosyltransferase 2 and 3 genotype may improve the tumor marker sensitivity.[24]

Imaging studies allow noninvasive evaluation of the biliary tree, however, when used alone, sensitivity and specificity are suboptimal.[22] Detection of hepatobiliary malignancies in PSC patients is variable across modalities, including US (sensitivity, 57%; specificity, 94%), MRI/MRCP (sensitivity, 89%; specificity, 75%), and ERCP (sensitivity, 91%; specificity, 66%).[22] The combination of serum tumor markers and imaging is associated with an improvement in sensitivity, including MRI/MRCP plus CA19-9 with a cut-off value of 20 U/mL (sensitivity, 100%; specificity, 38%; diagnostic average, 89%) and US plus CA19-9 with a cut-off value of 20 U/mL (sensitivity, 91%; specificity, 62%; diagnostic average, 93%).[22,25] A CT scan, as opposed to US and MRI, is used less commonly because of exposure to radiation and contrast. ERCP is performed frequently in patients with PSC for diagnostic cholangiogram stricture treatment and sampling by brushings and/or treatment of choledocholithiasis. When combined with CA19-9 at a cut-off value of 20 U/mL, ERCP reaches 100% sensitivity for diagnosing cholangiocarcinoma, but with a low specificity of 43%, and a risk of pancreatitis, cholangitis, bleeding, and hospitalization.[22]

Best Practice Advice 2 and 3

A rational approach for screening PSC patients for cholangiocarcinoma is interval radiologic assessment using imaging of the biliary tree with either US or MRI/MRCP in combination with CA19-9 every 6 to 12 months.[25,26] Because of the superior sensitivity of MRI compared with US to detect cholangiocarcinoma, MRI is the imaging mode preferred by many experts for cholangiocarcinoma surveillance. ERCP should not be used for routine surveillance because of its procedural risks. Evaluation of abnormalities including dominant strictures (see later), mass lesions, or increasing CA19-9 levels identified during surveillance, particularly within the first year of diagnosis, should include ERCP with brush cytology, biopsy specimens, and fluorescence in situ hybridization (FISH) for further evaluation of cholangiocarcinoma.[27,28]

Effectiveness of Diagnosis of Cholangiocarcinoma in Cases With a High Index of Suspicion

Best Practice Advice 4

PSC patients with increasing cholestatic biochemistry values or who develop jaundice, fever, right upper-quadrant pain, or pruritus no longer fit within the paradigm of cholangiocarcinoma surveillance and should undergo appropriate evaluation for cholangiocarcinoma. This includes patients with dominant strictures, which typically refer to strictures of the common bile duct and right and left confluence of the hepatic ducts, and has been defined on the basis of stenoses with a diameter of 1.5 mm or less in the common bile duct and/or 1.0 mm or less in a hepatic duct within 2 cm of the main hepatic confluence by ERCP.[29] However, the importance of these strict criteria compared with the clinical relevance of strictures of the common bile or hepatic ducts is unclear. Notably, 6.2% to 26.3% of PSC patients with a dominant stricture will be diagnosed with cholangiocarcinoma over a 6.2- to 9.8-year follow-up period.[30] In addition, benign and malignant strictures can have a similar appearance on imaging, warranting a high index of suspicion for cholangiocarcinoma in any patient with worsening cholestasis and a stricture of the common bile duct, and/or right, left, or confluence of hepatic ducts. Direct sampling of the stricture should be considered to rule out underlying cholangiocarcinoma.

Bile duct brushings can be obtained safely and are specific (84%–89%), but lack sensitivity (8%–100%), which limit its performance as a screening tool.[22,31] A recent meta-analysis found bile duct brushings to be 43% sensitive and 97% specific.[32] FISH from bile duct brushings uses DNA probes to identify chromosomal abnormalities such as aneuploidy and polysomy.[28,33] FISH can increase the sensitivity of standard cytology with an overall sensitivity of 64% to 68% and a specificity of 70% to 94% to detect cholangiocarcinoma.[28,34]

Best Practice Advice 5

In addition to ERCP with brushings, endoscopic ultrasound, intraductal ultrasonography, and cholangioscopy may be used to direct biopsy sampling.[35] Cholangioscopy has been shown to differentiate IgG4-related sclerosing cholangitis from PSC.[36] In addition, a prospective study of 47 PSC patients found that 4 of the target lesions could not have been reached without the cholangioscopic visualization of the bile duct.[37] However, despite similar sensitivity, specificity, and accuracy for cancer diagnosis in PSC and non-PSC patients, cannulation failure with cholangioscopy is more frequent in PSC (15% vs 2% in controls; $P = .015$).[38] Fine-needle aspiration through any imaging modality should be pursued with great caution in transplant candidates because of the risk of tumor seeding.

Cholangiocarcinoma Surveillance in Special Populations

Best Practice Advice 6

Among patients undergoing liver transplantation, the rate of cholangiocarcinoma has been reported to be 9% to 36%.[39–42] In pediatric PSC patients, cholangiocarcinoma is very rare, with only 8 of 781 (1%) pediatric PSC patients developing cholangiocarcinoma.[43] The development of cholangiocarcinoma among patients with small-duct PSC also is rare, with no cases identified in 254 patients.[13] A multicenter study of 193 African American PSC patients estimated the incidence of cholangiocarcinoma to be 0.55 per 100 person-years (95% CI, 0.26–1.16).[5] On this basis, routine cholangiocarcinoma surveillance should not be performed in patients younger than age 20 years or those with small-duct PSC.

Prevalence and Risk Factors for Gallbladder Cancer in Primary Sclerosing Cholangitis

Gallbladder cancer develops in an estimated 2% of PSC patients over their lifetime.[44] Two recent reports found gallbladder polyps in 10% and 17% of patients with PSC, with a mean size of 10 mm and median size of 4 mm.[45,46] In the latter study of 366 PSC patients, the incidence of gallbladder cancer among PSC patients with a gallbladder polyp was 1.6 per 100 person-years. No significant growth in polyp size was observed among those with a polyp smaller than 8 mm after a median of 5 years of follow-up evaluation.

The optimal modality for diagnosis of gallbladder polyps in PSC remains unknown. A recent Cochrane analysis found that transabdominal US has a sensitivity and specificity for the detection of gallbladder polyps of 0.84 (95% CI, 0.59–0.95) and 0.96 (95% CI, 0.92–0.98), respectively.[47] A single study found that CT scans with oral contrast detected only 76 of 96 (79.2%) surgically confirmed gallbladder polyps, although all missed lesions were smaller than 5 mm.[48] There are no data on the ability of MRI to identify gallbladder polyps.

In a study of 53 PSC gallbladder specimens, 2 had high-grade dysplasia and 7 had low-grade dysplasia without masses.[49] In a separate study, among 72 cholecystectomies performed before or during liver transplantation in PSC patients, 37% contained dysplasia and 14% contained adenocarcinoma.[50] However, patients with PSC are at increased risk for complications from cholecystectomy. Forty percent of patients in 1 series had early postoperative complications, especially in patients with more severe liver disease. Gallbladder polyps smaller than 0.8 cm did not contain dysplasia, and lesions smaller than 1.2 cm did not contain carcinoma in this small group. When combined with other cases in the literature (52 cases) and using a cut-off value of 0.8 cm for any lesion found on US, a sensitivity of 96% and a specificity of 53% for neoplasia detection was found.[51]

Best Practice Advice 7

Because of the high risk of malignancy in gallbladder mass lesions and a 5-year survival rate of 5% to 10% for gallbladder cancer, patients should undergo annual US screening.[17,26,52] The indications for cholecystectomy remain a debated area in patient management. In the European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines for diagnosis and management of PSC, cholecystectomy is recommended in PSC patients regardless of gallbladder lesion size,[17,52] whereas the American College of Gastroenterology clinical guideline suggests cholecystectomy for patients with gallbladder polyps greater than 8 mm,[26] and other society guidelines have concluded insufficient data are available to support cholecystectomy in all PSC patients with gallbladder polyps. Smaller lesions may be at lower risk for gallbladder cancer, but rare cases of rapid growth have been observed in PSC patients. Guidelines should be applied cautiously to individual circumstances, and with consideration of benefits and risks.

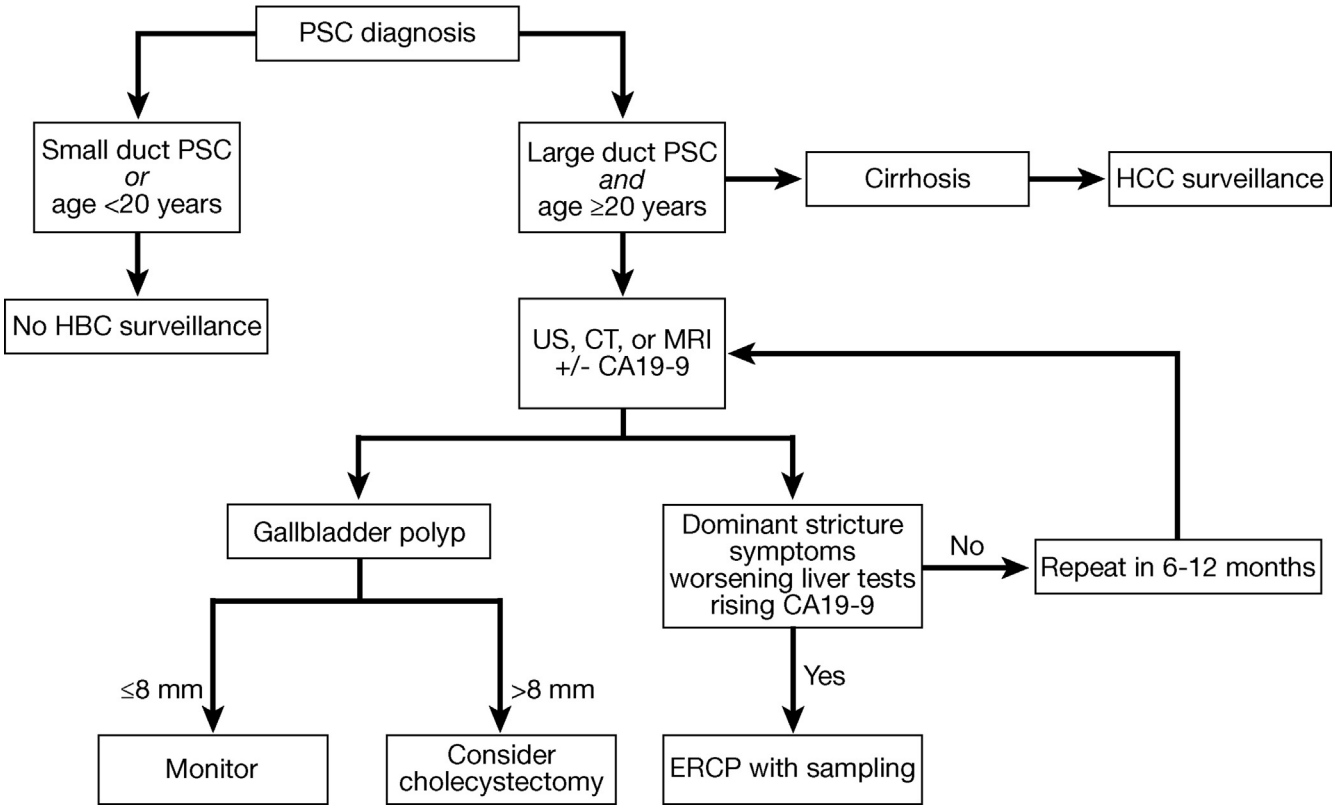

Figure 1. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis (PSC). PSC patients older than age 20 years should be considered for surveillance of hepatobiliary cancers (HBC), including cholangiocarcinoma and gallbladder cancer. Patients with cirrhosis also should be considered for surveillance of hepatocellular carcinoma (HCC). Surveillance should include imaging by ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI), with or without measurement of serum carbohydrate antigen 19-9 (CA19-9). Changes in imaging, symptoms, liver biochemistry values, or CA19-9 values should be followed up with direct sampling by endoscopic retrograde cholangiopancreatography (ERCP). Gallbladder polyps 8 mm or smaller have a low risk of malignancy and may be monitored, whereas cholecystectomy should be considered for gallbladder polyps greater than 8 mm. Dominant stricture refers to the strict definition of strictures of the common bile duct and right and left confluence of the hepatic ducts with a diameter of 1.5 mm or smaller in the common bile duct and/or 1.0 mm or smaller in a hepatic duct within 2 cm of the main hepatic confluence by ERCP, as well as strictures in these ducts associated with evidence of worsening cholestasis.

Prevalence of Hepatocellular Carcinoma in Primary Sclerosing Cholangitis

Best Practice Advice 8

HCC appears to be relatively rare in PSC.[9,53,54] However, there remains concern that once cirrhosis develops, the risk of HCC may be similar to other forms of cirrhosis, but existing studies have not specifically examined the risk of HCC in PSC patients with cirrhosis. In a retrospective study from 2 academic centers including 119 patients with cirrhosis and 292 patient-years of follow-up evaluation, no cases of HCC were identified with an upper limit of the 95% CI for the instantaneous risk of HCC of 1.03% in PSC patients with cirrhosis.[54] Current PSC guidelines do not address surveillance for HCC in PSC patients,[17,26,52] although HCC guidelines provide recommendations for the surveillance for HCC in all patients with cirrhosis, regardless of etiology.[55]

Conclusions

Herein, we provide clinical advice for the surveillance of hepatobiliary cancers in patients with PSC (Figure 1). The low prevalence and long duration of PSC present substantial barriers to better understanding risk stratification, developing biomarkers, and measuring the impact surveillance has on clinical outcomes. The management of this patient group is complicated further by the competing risks of liver disease progression and malignancies, primarily cholangiocarcinoma, which may preclude the only effective therapy for PSC, namely liver transplantation. With these limitations and consequences in mind, these practice advice points are based on the best available data and are meant to provide a reference point for clinicians to gauge their practice when making clinical decisions related to individual PSC patients. We anticipate that with the development of large patient cohorts, advances in uncovering genetic and other risk factors for cholangiocarcinoma, and development of

effective treatments for PSC, further refinement of this practice update will be required.

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Reprint requests
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Conflicts of interest
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