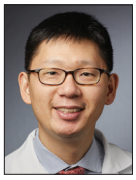
ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Screening for Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis



Joseph K. Lim, MD
Professor of Medicine
Director, Clinical Hepatology
Vice-Chief, Section of Digestive Diseases
Yale University School of Medicine
New Haven, Connecticut

G&H What is the risk of developing cholangiocarcinoma in patients with primary sclerosing cholangitis?

JL Primary sclerosing cholangitis (PSC) is a rare chronic autoimmune and cholestatic liver disease that is characterized by strictures and progressive fibrosis within the intra- and extrahepatic biliary tree. The disease is associated with significant morbidity and mortality owing to cirrhosis, liver failure, and hepatobiliary malignancies. Cholangiocarcinoma (CCA) represents a well-established complication of PSC, with an estimated incidence of approximately 1% to 1.5% per year and a lifetime risk of up to 20%. CCA can occur at any stage of liver disease with or without cirrhosis. Natural history studies reveal significant long-term risk of CCA in patients with PSC, estimated to be 6% at 10 years, 14% at 20 years, and 20% at 30 years, translating to approximately 400-fold the risk of CCA in the general population. Of note, population-based studies suggest that 27% to 37% of incident cases of CCA occur within the first year of PSC diagnosis. This may stem from the overlap of diagnostic radiology findings between PSC and CCA and the fact that CCA may represent the presenting complaint of PSC, thus resulting in concurrent diagnoses.

It is important to highlight that patients with PSC are also at increased risk of non-CCA malignancies, including hepatocellular carcinoma, gallbladder cancer, and colorectal cancer, for which screening is warranted in select individuals.

G&H What explains the increased risk of CCA in patients who have PSC?

JL The molecular pathogenesis of CCA remains incompletely elucidated, but is believed to be mediated through a combination of pro-oncogenic processes stimulated by chronic inflammation and cholestasis in the context of genetic and environmental risk factors. Chronic hepatocellular inflammation and cholestasis have been demonstrated to result in increased exposure of cholangiocytes to various inflammatory mediators, such as interleukin-6, tumor necrosis factor–α, cyclooxygenase-2, and Wnt. This, in turn, may activate multiple genetic mutations in tumor-suppressor genes, proto-oncogenes, and DNA mismatch repair genes, as well as pathways that stimulate cellular proliferation in association with other mediators, such as transforming growth factor–β, vascular endothelial growth factor, and hepatocyte growth factor. This is an area of active research, and more is still being learned that will help support the development of novel biomarkers and molecular diagnostic markers to improve early detection and diagnosis of CCA as well as identify therapeutic targets for treatment.

G&H Which patients with PSC are at greatest risk of developing CCA?

JL There are 3 primary risk factors for CCA in the context of chronic PSC. First, substantial epidemiologic data suggest that the individuals at highest risk are

those with advanced age (>60 years). Second, there is a male predominance both for the diagnosis of PSC and for developing CCA among patients with PSC. Third, individuals with active and/or long duration of ulcerative colitis concurrent with PSC are more likely to develop CCA compared with individuals with PSC alone. The presence of advanced liver disease or cirrhosis, history of colorectal cancer, alcohol use, and tobacco consumption may represent additional risk factors. Outside the specific context of PSC, bile duct stones, choledochal cysts, liver fluke infections, and viral hepatitis (hepatitis B virus/hepatitis C virus) are additional established risk factors for CCA. Importantly, CCA is viewed as rare in children, as well as in adult patients with small-duct PSC.

> … there are subtle differences in the advice statements with regard to the choice of imaging modality, frequency of surveillance, role of serum CA 19-9, age cutoff for screening, and role of … FISH analysis during ERCP to facilitate CCA diagnosis.

G&H What are the current screening recommendations for CCA in patients with PSC?

JL There is general consensus from recent guidance documents from major specialty societies, including the American Gastroenterological Association (AGA) in 2019, European Association for the Study of the Liver (EASL) in 2022, and American Association for the Study of Liver Diseases (AASLD) in 2023, that patients with PSC should undergo regular surveillance for CCA with abdominal imaging beginning at the time of initial diagnosis. This can include abdominal ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) with or without magnetic resonance cholangiopancreatography (MRCP) with or without the tumor marker serum carbohydrate antigen 19-9 (CA 19-9).

Furthermore, in individuals who have abnormalities identified on imaging (US/CT/MRI/MRCP), there are consensus recommendations for selective use of endoscopic evaluation with endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic US for patients with worsening clinical symptoms, cholestasis, or dominant stricture. In addition, fine-needle aspiration of perihilar biliary strictures should be performed with great caution because of the concern for tumor seeding.

G&H What are the key differences among the guidance documents?

JL Although the guidance documents are largely in alignment regarding the need for surveillance with abdominal imaging, there are subtle differences in the advice statements with regard to the choice of imaging modality, frequency of surveillance, role of serum CA 19-9, age cutoff for screening, and role of fluorescence in-situ hybridization (FISH) analysis during ERCP to facilitate CCA diagnosis. First, whereas the AGA and EASL suggest the use of abdominal imaging of any form (US/CT/MRI/MRCP), the AASLD designates MRI/MRCP as the preferred imaging modalities. Second, whereas the AASLD recommends a surveillance interval of once-yearly imaging, EASL advises at least yearly imaging, and the AGA suggests imaging every 6 to 12 months. Third, whereas the AASLD and AGA suggest an adjunctive role for serum CA 19-9 testing (abdominal imaging with or without serum CA 19-9), EASL recommends that serum CA 19-9 should not be used for routine surveillance but reserved for diagnostic testing in patients with suspected CCA on the basis of new symptoms, rising serum alkaline phosphatase or bilirubin levels, increase in liver stiffness measurement on transient elastography greater than 1.5 kPa per year, or ductal progression. Fourth, all societies concur that CCA is rare in children with PSC but differ on the age above which imaging surveillance is warranted. Whereas the AGA suggests no CCA surveillance in patients under age 20 years, the AASLD recommends against surveillance in patients under age 18 years. Although an age cutoff is not specified in its document, EASL also recommends against routine surveillance imaging in children with PSC, although it notes that some experts suggest using adult screening recommendations for individuals over 15 years of age. Finally, whereas the AASLD recommends routine performance of intraductal tissue sampling for cytology and FISH analysis during ERCP for relevant strictures, the AGA suggests using brush cytology with or without FISH, and EASL recommends more selective use of FISH (in the presence of equivocal findings from brush cytology and/or histology). Importantly, all

3 society documents are aligned in support of routine surveillance for hepatocellular carcinoma among patients with PSC and cirrhosis.

G&H Are the current screening recommendations for CCA in PSC effective and sufficient?

JL The societies provide valuable, pragmatic, and actionable guidance to clinicians with regard to the need for CCA surveillance in all adult patients with large-duct PSC, and the appropriate time interval and use of serum and imaging modalities to facilitate detection. However, an optimal evidence-based surveillance approach remains elusive, as no current screening strategies have been validated in prospective studies. Furthermore, available data do not suggest that CCA surveillance improves survival or other liver-related clinical outcomes in patients with PSC. This includes a recently published cohort study that revealed that annual MRI/MRCP surveillance imaging and serum CA 19-9 in a large unselected cohort of patients with PSC from Sweden was not associated with an improvement in long-term survival. A more personalized approach to surveillance based on the presence of select risk factors would be desirable. This must also be supported by research and validation studies confirming the diagnostic test performance of novel biomarkers and molecular diagnostic markers to improve early identification of CCA, such as DNA methylation markers in bile.

G&H How is clinician adherence to these recommendations, particularly in the long term?

JL Although most clinicians are aware of the association between PSC and CCA, there remains a wide disparity in how surveillance for CCA is performed in real-world clinical practice. Having strong evidence-based guidance statements by major specialty societies formally advocating for routine screening is important and impactful in influencing clinical practice. Of note, the 2010 AASLD guideline addressing PSC did not include a recommendation for routine CCA surveillance; therefore, further examination of screening practices following the publication of the updated 2023 guideline, as well as methodologies that enhance surveillance (eg, screening reminders, best practice alerts, and performance measures), would inform future strategies to improve CCA surveillance.

G&H What are the biggest challenges associated with screening for CCA in patients with PSC?

JL My view is that there remain important gaps at multiple steps in the care cascade of patients with PSC (including screening, diagnosis, linkage to care, and treatment) independent of the specific risk of CCA. Given the high incidence of CCA concurrent with initial PSC diagnosis, enhancing early detection represents an important priority linked to screening for CCA. Among patients with a known diagnosis of PSC, an ongoing challenge is timely local access to imaging tools and adequate imaging, endoscopic, laboratory, and pathology expertise within an institution to effectively establish the diagnosis of CCA; these are not universally available across institutions.

G&H What are the next steps in research in this area?

JL As previously mentioned, there is significant clinical value in improving the ability to personalize management of PSC and CCA. Ultimately, this will likely require the capability to access and interpret molecular profiling of patients with PSC that can identify risk factors for the development of CCA, individualized predictors of natural history and prognosis, and clinical phenotyping that can guide approaches to both CCA surveillance and treatment.

Disclosures

Dr Lim has no relevant conflicts of interest to disclose.

Suggested Reading

Bowlus CL, Arrivé L, Bergquist A, et al. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology*. 2023;77(2):659-702.

Bowlus CL, Lim JK, Lindor KD. AGA clinical practice update on surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis: expert review. *Clin Gastroenterol Hepatol*. 2019;17(12):2416-2422.

European Association for the Study of the Liver. EASL clinical practice guidelines on sclerosing cholangitis. *J Hepatol*. 2022;77(3):761-806.

Villard C, Friis-Liby I, Rorsman F, et al. Prospective surveillance for cholangiocarcinoma in unselected individuals with primary sclerosing cholangitis [published online November 19, 2022]. *J Hepatol*. doi:10.1016/j.jhep.2022.11.011.