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Title
Primary Sclerosing Cholangitis, Part 2: Cancer Risk, Prevention, and Surveillance.

Permalink
https://escholarship.org/uc/item/1d81v9rc

Journal
Gastroenterology & hepatology, 14(7)

ISSN
1554-7914

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Publication Date
2018-07-01

Peer reviewed

Primary Sclerosing Cholangitis, Part 2: Cancer Risk, Prevention, and Surveillance

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Abstract: Primary sclerosing cholangitis (PSC) is a chronic, fibro-inflammatory, progressive cholangiopathy. In a clinically significant proportion of patients, the disease course of PSC is punctuated by carcinogenesis, namely cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, and/or colorectal carcinoma. Indeed, malignancy is arguably the most consequential sequela and the cause of nearly 50% of deaths in patients with PSC. This statistic is multifactorial, relating partly to the premalignant nature of PSC, challenges in diagnosis due to obscuration of cancer by the inflammation and fibrosis inherent to PSC, and the unpredictability of which type of cancer will develop in PSC and when. Here, in the second of a 2-part series, we review cancer risk, prevention, and surveillance in patients with PSC. We also discuss potential cancer surveillance strategies in PSC and, where evidence is limited, make pragmatic recommendations based on current data and expert opinion.

Primary sclerosing cholangitis (PSC) is an idiopathic, cholestatic liver disease characterized by stricturing of the intra- and/or extrahepatic ducts.[1-4] PSC represents an important cause of morbidity and mortality worldwide, with a clinically significant proportion of patients ultimately developing one or more of various cancers, among other potentially lethal complications.[5] PSC is considered a prototype disorder, linking chronic inflammation to carcinogenesis.[6] Nevertheless, due to a variety of pathobiological, technological, and practical factors, predictors of cancer in PSC are lacking, preventive measures are unproven if not near-nonexistent, surveillance strategies have proven difficult to justify and implement, and management—both diagnosis and treatment—of cancer poses considerable clinical challenges and unknowns.[7]

Here, in the second of a 2-part series, we provide a review on cancer risk, prevention, and surveillance in patients with PSC. We also discuss potential cancer surveillance strategies, and, where high-quality evidence is limited, we offer clinically feasible algorithms and approaches based on current disease understanding, available evidence, and expert opinion.

Cancer Risk in Primary Sclerosing Cholangitis

Compared with the general population, the risk of any cancer in patients with PSC is double, and the risk of a primary hepatobiliary cancer is increased 40-fold.[8] The major malignancies for which patients with PSC are at the most increased risk are cholangiocarcinoma (CCA), gallbladder carcinoma, hepatocellular carcinoma (HCC), and colorectal carcinoma.

Cholangiocarcinoma Risk

The estimated annual incidence of CCA in patients with PSC is 0.5% to 1.5%, with a lifetime incidence approaching 15%, which is orders of magnitude above that of the general population.[5,9-12] Robust estimates of the magnitude of burden related to hepatobiliary cancer in PSC come in large part from an international, multicenter PSC cohort study (7121 patients from 37 countries); the prevalence of hepatobiliary cancer was 10%, with CCA being the most common hepatobiliary cancer (n=594).[13] In particular, nearly one-third of all-cause mortality in patients with PSC is specifically from CCA.[14] Indeed, PSC confers a 400- to 1500-fold increased risk for CCA (mainly hilar CCA) compared to matched healthy controls.[14,15] Furthermore, in the approximately 70% of patients with PSC who also have inflammatory bowel disease (IBD), the risk of developing cancer is even greater, particularly for CCA and colorectal carcinoma.[6,16,17]

More than one-half of patients with PSC complicated by CCA are diagnosed with already advanced-stage CCA, in part due to the challenges in achieving early diagnosis.[18] Therefore, the diagnosis of CCA in patients with PSC requires a high index of suspicion and active surveillance. Abdominal pain, weight loss, jaundice, fatigue, pruritus, acute and/or progressive worsening of liver enzyme abnormalities, and/or an unexplained rise in serum carbohydrate antigen 19-9 (CA 19-9) should prompt the clinician to rule out CCA. A multidisciplinary approach that involves clinical, laboratory, imaging, endoscopic, and surgical data is often necessary.

The only curative option for CCA is surgery, but it is mainly reserved for patients with early-stage CCA and adequate hepatic reserve.[19] Liver transplantation is an option for a select group of patients with hilar CCA in highly specialized centers that utilize a protocol of neoadjuvant radiosensitizing chemotherapy, external beam radiotherapy, and endoscopic retrograde cholangiography–delivered transluminal brachytherapy followed by oral capecitabine (Xeloda, Genentech) up to the time of staging laparotomy (performed immediately prior to liver transplantation to reconfirm candidacy).[20,21] Liver transplantation is the only potentially curative treatment for PSC and has 1- and 5-year survival rates surpassing 90% and 80%, respectively[22]; however, recurrent PSC (or CCA[23]) can develop and become problematic, occurring in up to 34% of deceased donor liver transplantations[24] and in 67% of living-related donor liver transplantations.[25,26] Palliative therapies (usually systemic chemotherapy using a combination of gemcitabine [Gemzar, Eli Lilly and Company] and cisplatin) are reserved for patients who are not surgical candidates and/or who have metastatic disease.

Gallbladder Carcinoma Risk

Patients with PSC are at increased risk for gallbladder carcinoma, although at a lower rate than for CCA. The estimated lifetime incidence of gallbladder carcinoma in patients with PSC is 3% to 14%.[27] Gallbladder carcinoma most often appears on imaging as a mass within the lumen of the gallbladder or as eccentric thickening of the gallbladder wall.[28] Gallbladder polyps in patients with PSC should be closely monitored, and there is general agreement that cholecystectomy should be considered in all patients with PSC for gallbladder polyps between 5 to 8 mm in size and for gallbladder masses of any size,[29-31] especially if a change in the size and/or the number of polyps is observed. This agreement is based on the difficulty in distinguishing benign from malignant lesions of the gallbladder, the frequency with which adenocarcinoma is harbored within gallbladder lesions in PSC, and the increased risk of eventual malignant progression of such lesions (if they are not already malignant at the time of initial discovery).[29-31]

Hepatocellular Carcinoma Risk

Cirrhosis is a known major risk factor for HCC. HCC occurs with less frequency than does CCA in patients with PSC; the estimated lifetime incidence of HCC in patients with PSC is 0.3% to 2.8%, although comprehensive data have historically been scant.[32,33] We recently reported on 23 cases of HCC in a cohort of 830 patients with PSC; all cases of HCC occurred in patients with cirrhotic-stage disease.[34] Based on these and other data, patients with cirrhotic-stage PSC are indeed at increased risk for HCC, similar to patients with cirrhosis due to other underlying diseases.

Colorectal Carcinoma Risk

The association between PSC and IBD has been recognized for years, but the exact etiopathogenic mechanisms are yet to be fully elucidated. Patients with IBD, for reasons that remain unclear, are at significantly increased risk for colorectal carcinoma. The presence of PSC heightens the risk for colorectal carcinoma in patients with IBD by

severalfold. The cumulative risk of developing colorectal neoplasia has been reported to be 50% after 25 years of disease in patients with PSC-IBD compared to only 10% after 25 years of disease in patients with IBD alone.[35] In addition, male sex, extensive colitis, and use of immunosuppressive agents following liver transplantation for PSC have all been proposed as risk factors for developing colorectal neoplasia in patients with PSC-IBD.[36] More recently, an international, retrospective study including 1911 patients with IBD (among whom 293 had PSC) showed that PSC remained a strong risk factor for high-grade colonic dysplasia and colorectal carcinoma following the diagnosis of colonic low-grade dysplasia.[37] Although the risk for colorectal carcinoma is well established in patients with PSC and ulcerative colitis, the risk of colorectal carcinoma development in patients with PSC and Crohn's disease appears to be less clear (unless the patient has extensive Crohn's colitis).[38] Of note, the risk of colorectal carcinoma development among patients with PSC-IBD is additionally increased, essentially as soon as the diagnosis of this combination is made.[39] Interestingly, the risk of colorectal carcinoma remains elevated even after liver transplantation for PSC; this risk has been associated with worse survival if patients are not under surveillance for colorectal carcinoma.[36]

Cancer Prevention in Primary Sclerosing Cholangitis

Due to the rarity of PSC combined with the barriers to amassing sufficient patient-years to adequately power studies regarding cancer prevention (ie, chemopreventive studies), there is a dearth of data regarding the putative role of any particular pharmacologic agent in preventing cancer in patients with PSC. Currently, there are no pharmacologic agents that have been rigorously shown to prevent cancer development in patients with PSC. Agents such as ursodeoxycholic acid (UDCA) and curcumin, among others, have been studied to varying degrees as potential chemopreventive agents, with variable findings.

The use of UDCA remains a subject of debate and uncertainty, as some studies have shown that the use of UDCA in patients with PSC-IBD reduces the risk of colonic dysplasia or colorectal carcinoma development,[40,41] whereas other studies have shown an increased risk of colorectal carcinoma in patients with PSC-IBD using UDCA.[42-44] For example, data from a Scandinavian, long-term, randomized, placebo-controlled, high-dose UDCA clinical trial (patient follow-up, >10 years) did not show a statistically significant difference in the rate of colorectal carcinoma between the UDCA group and the placebo group.[43] Thus, the available data to date suggest that there is potential harm, or at least no benefit,

with high-dose UDCA, whereas intermediate- (or low-) dose UDCA may have some chemopreventive impact in a subset of patients with PSC. Therefore, the consensus at this time is that high-dose UDCA should be avoided, and that for intermediate- or low-dose UDCA, additional studies are needed to validate its putative chemopreventive properties in patients with PSC-IBD before it can be routinely recommended for this indication, although it may ostensibly be considered in select patients (eg, patients with a strong family history of colon cancer).[30,31]

Curcumin, a phytoextract from the turmeric (*Curcuma longa*) rhizome, has been shown to have anti-inflammatory, antifibrotic, and antineoplastic effects, although these effects have been less studied in the specific context of PSC.[45] Given the pleiotropic and multiple potentially beneficial effects of curcumin in both inflammatory and neoplastic disorders, it may merit further investigation as a chemopreventive agent and is currently under phase 1 and 2 study for treatment of PSC.[46]

Cancer Surveillance in Primary Sclerosing Cholangitis

Surveillance, particularly for cancers, is a programmatic strategy used to detect tumors in their early stages in order to increase the chances of curative therapy. For a surveillance program to be effective, there are certain points to consider: (1) the at-risk population should be identified; (2) surveillance methods should be highly sensitive, specific, and cost-effective; (3) surveillance should be available, accessible, and have acceptable risks; and (4) treatment modalities should be available and scientifically proven.[27] The following sections discuss strategies and recommendations for cancer surveillance for patients with PSC.

Surveillance for Cholangiocarcinoma
CCA carries a dismal prognosis, in part because most patients are diagnosed when the cancer is already at least locally advanced, which itself is consequent to the fact that reliable methods for early detection and accurate tissue diagnosis (especially in the context of PSC) can be extremely challenging.[19,47] Nearly 80% of patients with CCA die within 7 years of the diagnosis of the disease.[14] Expert opinion has called for surveillance for hepatobiliary cancer (and colorectal carcinoma) in patients with PSC (Figure),[27,48,49] but there have been little data to support this or the specific methodologic approach (particularly regarding CCA). The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) recommend surveillance for gallbladder carcinoma annually[30,31]; however, surveillance for CCA and HCC
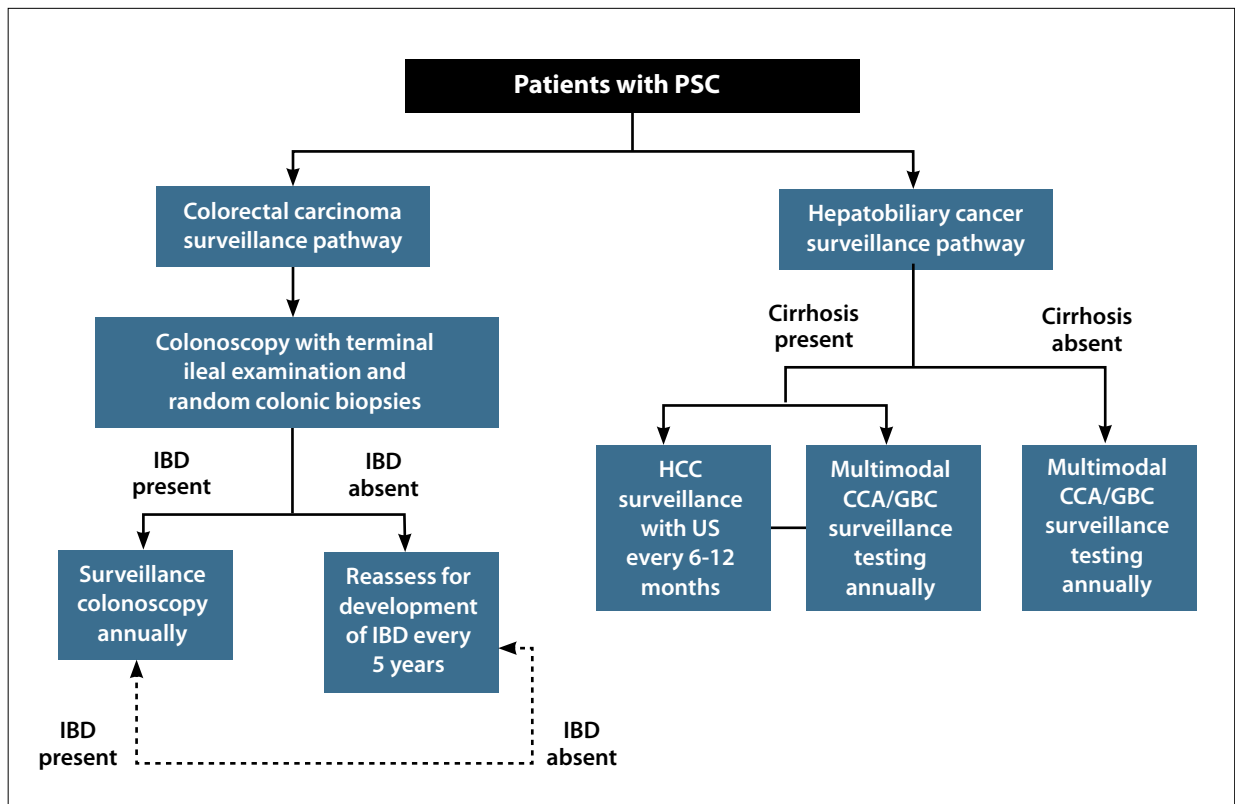
Figure. Overview of cancer surveillance in patients with primary sclerosing cholangitis (PSC), beginning at the time of PSC diagnosis, based on the American Association for the Study of Liver Diseases practice guidelines.[30]

CCA, cholangiocarcinoma; GBC, gallbladder carcinoma; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; US, ultrasound.

has been controversial, in large part owing to the paucity of data demonstrating survival benefit.

We recently reported the first-ever long-term surveillance and outcomes data in patients with PSC who developed hepatobiliary cancer.[34] The study found that surveillance for hepatobiliary cancer in patients with PSC was associated with a diagnosis of hepatobiliary cancer at earlier stages, a significantly lower 5-year probability of experiencing a hepatobiliary cancer–related adverse event (32% vs 75%; $P<.001$), and a significantly higher 5-year overall survival (68% vs 20%; $P<.001$) compared to no surveillance. These data have important implications in the management of patients with PSC, but care should be exercised when implementing such surveillance strategies for several reasons, including the hazards of false-positives and the aforementioned consideration regarding the limited availability of proven treatments for certain types of hepatobiliary cancer (eg, liver transplantation for early-stage hilar CCA only being available in select, highly specialized centers).

Techniques for surveillance and early diagnosis of CCA in patients with PSC remain limited. The specificity of brush cytology for detecting malignant lesions is greater than 95%, but its overall diagnostic performance is hampered by low sensitivity.[50,51] CA 19-9 is the most extensively studied and utilized serologic tumor marker for CCA in patients with PSC; nonetheless, there is no agreement on the cutoff for diagnosis of CCA. Moreover, elevated CA 19-9 is seen in patients without CCA, whereas normal CA 19-9 levels can be seen in patients with advanced CCA.[34] Therefore, until superior methods are developed, combining imaging (ultrasound, computed tomography, and magnetic resonance imaging [MRI] or magnetic resonance cholangiopancreatography [MRCP]) with CA 19-9 is currently recommended.[12,27,48]

Regarding the choice of imaging, a recent consensus position by the International PSC Study Group recommends the use of MRCP as the first imaging modality in patients with suspected PSC, for surveillance of CCA in patients with PSC, and if CCA is suspected in patients with PSC.[52] In our published experience, ultrasound (when performed by ultrasonographers experienced in hepatobiliary imaging) and MRI/MRCP have the best overall performance characteristics, both being superior

to computed tomography.[34] Longitudinal studies as well as comparative performance studies are needed to further elucidate the clinical utility of these imaging modalities with or without the use of traditional and novel tumor markers for surveillance and early diagnosis of CCA (and other hepatobiliary cancers) in patients with PSC.

Surveillance for Gallbladder Carcinoma

Gallbladder disease is common among patients with PSC; adenocarcinoma is found in more than 50% of patients with PSC with gallbladder mass lesions.[53] For this reason and others, cholecystectomy is recommended in patients with PSC with gallbladder masses of any size or with gallbladder polyps greater than 5 to 8 mm in diameter. The AASLD and EASL recommend annual abdominal ultrasonography to screen for gallbladder cancer in patients with PSC.[30,31]

Surveillance for Hepatocellular Carcinoma

Patients with PSC who have cirrhosis are at risk for HCC.[33] We recently found that among 830 patients with PSC, 2.8% (n=23) developed HCC.[34] All patients had cirrhotic-stage PSC at the time of HCC diagnosis.[34] Therefore, patients with PSC-related cirrhosis should undergo annual or semiannual surveillance for HCC, as should patients with cirrhosis due to other underlying diseases.[30,31]

Surveillance for Colorectal Carcinoma

PSC is an important risk factor for colorectal carcinoma.[14,54-56] Surveillance for colorectal carcinoma in patients with PSC (Figure) has been found to be associated with improved colorectal carcinoma–related survival compared to no surveillance.[14] All leading societies currently recommend beginning aggressive surveillance for colorectal carcinoma in patients with PSC at 1- to 2-year intervals after the diagnosis of PSC[30,31,57] given the high risk for colorectal carcinoma.[39,58] Reports regarding the risk of colorectal carcinoma in patients with PSC and coexisting Crohn's disease are conflicting[55,59]; further research is needed to examine the risk of colorectal carcinoma in patients with PSC and Crohn's disease, and, more broadly, to identify optimal (ie, efficacious, cost-effective, and patient-centered) surveillance techniques and intervals.[43,44,60]

Summary

PSC is a premalignant, chronic, fibroinflammatory disease of the bile ducts. Patients with PSC are at significantly increased risk for hepatobiliary and colorectal cancers compared to the general population; this risk is particularly the case among patients with PSC-IBD.

There are no proven medical therapies for the treatment of PSC or for the prevention of associated hepatobiliary and/or colorectal cancers. Leading national and international societies recommend screening PSC patients for colorectal carcinoma and gallbladder carcinoma; however, screening for CCA has been a subject of debate, although it has been recommended by many experts in this field, and the evidence in its support continues to grow. Currently, a common surveillance practice for CCA in patients with PSC is annual cross-sectional imaging (ultrasound or MRI/MRCP) coupled with tumor marker CA 19-9. The roles of imaging studies and tumor markers for the surveillance of CCA (and other hepatobiliary and colorectal cancers) in patients with PSC and the identification of high-risk patients who might benefit from closer surveillance need to be better defined in large, multicenter, long-term studies.

The authors have no relevant conflicts of interest to disclose.

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