Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease resulting in stricturing and destruction of the intra- and extrahepatic bile ducts and associated with cholangiocarcinoma (CCA) in 10-15% of patients. The pathogenesis of PSC remains unknown and there are currently no universally agreed upon medical therapies for treatment, with liver transplant representing the only available cure. Endoscopic therapy has proven vital in both diagnosis and management of the disease. A strategy of surveillance is recommended to enhance early detection of CCA to improve the possibility of resection and/or liver transplant, ultimately leading to increased survival. The combined use of magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology and newer modalities such as fluorescence in situ hybridization (FISH) have increased the sensitivity of detected CCA. Advances in cholangioscopy, endoscopic ultrasound (EUS), fine needle aspiration (FNA), and ancillary cytologic testing will further improve our ability to detect CCA at an early stage.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease characterized by fibrosis, inflammation, stricturing and destruction of the intra- and extrahepatic bile ducts. Typical age at presentation is around 40, ranging from 15 to 85 years of age, with men being affected at twice the rate of women.\textsuperscript{1,2} Disease progression is highly variable, but ultimately the development of widely distributed bile duct strictures can lead to cholestasis with the median survival to death or need for liver transplantation ranging from 12 to 18 years.\textsuperscript{3,4}

The pathogenesis of PSC is currently unknown. There is a strong association with inflammatory bowel disease, primarily ulcerative colitis (UC), in up to 80% of patients suggesting an autoimmune process; PSC has not, however, been demonstrated to respond to immunosuppressants.\textsuperscript{1,5} There is also a significantly heightened risk for hepatobiliary malignancy in patients with PSC with cholangiocarcinoma (CCA) occurring in 10-15% of patients.\textsuperscript{6} Incidence rate of CCA in PSC patients is 1.5% per year and carries a dismal prognosis with a median survival of 6 months in the absence of curative surgery including liver transplantation. To date, there are no established medical therapies universally agreed to be beneficial in the treatment of PSC.

Endoscopic therapy plays a vital role in the diagnosis and management of patients with PSC.
Endoscopic Retrograde Cholangiopancreatography (ERCP) is used to confirm the diagnosis in patients with questionably noninvasive imaging, obtain tissue, and decompress obstructed bile ducts due to strictures via balloon dilation and/or stents. ERCP and Endoscopic ultrasonography (EUS) play a role in the diagnosis of cholangiocarcinoma in patients with PSC. This article will review the role of endoscopy in the management of PSC and discuss its potential application for the surveillance of progression of PSC to CCA.

**INDICATIONS FOR ENDOSCOPIC INTERVENTION**

**Stone Removal / Decompression**

Cholelithiasis is a common finding in PSC, occurring in 19% to 51% of patients. Stricturing of extrahepatic ducts in PSC can also lead to biliary obstruction. Endoscopic intervention is indicated for patients with lab abnormalities or symptoms concerning for obstruction such as jaundice, pruritis, cholangitis or right upper quadrant abdominal pain.

**Tissue Acquisition**

PSC patients have a 10-15% lifetime risk of developing cholangiocarcinoma (CCA). Distinguishing between benign strictures and CCA can also lead to biliary obstruction. Endoscopic intervention is indicated for patients with lab abnormalities or symptoms concerning for obstruction such as jaundice, pruritis, cholangitis or right upper quadrant abdominal pain.

**Cholangiocarcinoma Surveillance**

Up to 50% of CCA cases are diagnosed either at the time of or within the first year of diagnosis of PSC, with an incident rate of 1.5% each year thereafter. Median survival associated with CCA is only 6 months. Despite this dismal prognosis, there are currently no evidence-based screening guidelines for CCA in PSC. A strategy of endoscopic surveillance has been employed at various institutions to enhance early detection which improves...
the possibility of resection and/or liver transplant for increased survival.

**THE ROLE OF ERCP**

**Risk of ERCP in PSC Patients**

Given the potential for adverse events associated with endoscopic intervention, consideration must be given to the risks associated with ERCP. As with any endoscopic procedure, there is risk of cardiopulmonary depression, aspiration, hypoxia or perforation. Adverse events specifically associated with ERCP include infection, post-ERCP pancreatitis, cholangitis, acute cholecystitis, occlusion or migration of biliary stents, and bile duct injuries. Intraprocedure and post-procedure antibiotics are recommended for patients undergoing ERCP for PSC.

Previous studies have demonstrated that in patients without PSC, the rate of ERCP-specific adverse events is between 3 to 11%, higher than that in average patients undergoing ERCP. ERCP in PSC patients may carry more risk as these patients may have more complex ductal anatomy, multiple strictures, suboptimal biliary drainage, and increased risk for post-ERCP infectious complications. The rate of reported post-ERCP adverse events in PSC patients ranges from 7 to 18%.

Specific risk factors that have been identified for PSC patients include: operator experience, duration of the procedure, therapeutic as opposed to diagnostic ERCP, the need for urgent ERCP based on acute signs or symptoms, and the number of therapeutic maneuvers and/or interventions performed during ERCP.

In the largest published study of post-ERCP adverse events in patients with PSC undergoing ERCP, the most significant risk factors were found to be existing co-morbid conditions (cirrhosis, Crohn’s disease, and autoimmune hepatitis), endoscopist experience (with the most experienced endoscopists having the best outcomes), and ERCP maneuvers including dilation and sphincterotomy (which were associated with poor outcomes). Gender, stenting, presence of a dominant stricture, and cholangitis were not found to be predictive for post-ERCP adverse events. This study highlighted the fact that stenting can be done without increasing the risk of the procedure and argued against the conventional wisdom that stenting was to be avoided in patients with PSC.

In terms of the actual complication rate of ERCP in PSC patients, one retrospective study of 168 PSC patients and 981 patients without PSC concluded that the overall complication rate between the two groups was not significantly different (18/168 (11%) vs. 76/981(8%), P=0.2), although the two groups were not well matched in terms of size.

The only prospective multicenter study available that addresses adverse post-ERCP events in PSC patients found that diagnostic ERCP led to adverse events in only 2% of asymptomatic patients. The post-ERCP complication rate reached as high as 14% in symptomatic patients; however this rate was felt to be justified by the benefits of endoscopic intervention.

**Dominant Strictures**

Over the course of the disease, a reported 35% to 57% of patients with PSC will develop a “dominant stricture.” The term “dominant stricture” is somewhat variable in its definition. Some in the literature have defined this as a stenosis of ≤ 1.5mm diameter in the common bile duct, or ≤ 1.0mm diameter stenosis of the common hepatic duct close to the bifurcation. The problem with these definitions is that they are somewhat technical in nature and may be less than valuable in patients with severe PSC and multiple diffuse strictures or in patients who have a stricture of concerning appearance that does not meet the dimensions of note. One of the authors (DGA) defines a dominant stricture as “the cholangiographic finding of a stricture that stands out amongst all others in a patient with primary sclerosing cholangitis.” This definition, while somewhat less precise, is more intuitive when interpreting cholangiograms in patients with PSC and is more broadly applicable although also somewhat subjective. Dominant strictures are associated with increased episodes of cholangitis, stone formation, cirrhosis, and may serve as a primary indicator of concomitant cholangiocarcinoma.

**Stenting versus Dilation for Strictures**

It is currently recommended that patients with symptomatic and/or dominant strictures with symptoms such as pruritus, jaundice, cholangitis, or increasing LFTs, be evaluated and potentially treated with endoscopic therapy. Although a randomized controlled study has not been performed to evaluate the effectiveness of endoscopy, there have been a number of large retrospective studies that demonstrated clinical improvement and increased survival following endoscopic treatment. A study by Baluyut et al. followed...
63 PSC patients who underwent repeated balloon dilation for dominant strictures and found their observed 5-year survival rate to be significantly higher (83% versus 65% as predicted by the Mayo Risk Score, $P = 0.027$). The mean number of dilations per patient during the study period was $2.33 \pm 2.0$ with 16 of the patients undergoing more than 4 dilations and 36 who had between 2 and 4 dilations.

A more recent study by Gluck et al. reported an observed survival rate of 82.8% among 84 endoscopically treated PSC patients after 4 years vs. 71.3% survival as predicted by the Mayo Clinic natural history model ($P = 0.021$). These patients were followed for an average of 8 years and underwent 291 ERCP procedures for symptoms including 160 balloon dilations of strictures and 84 temporary stents placed with an average of 3.46 ERCPs per patient.

To date, there have been conflicting results from published studies regarding the optimal approach for endoscopic management of strictures. Balloon dilatation both with and without stent placement has demonstrated efficacy for clinical and biochemical improvement of dominant strictures. Stenting of the biliary tract can prevent rapid re-occlusion of strictures, however, the stent itself can be subject to occlusion over the course of time. One retrospective study of 71 patients with dominant strictures reported a higher rate of post-ERCP adverse events in patients treated with dilatation followed by stenting compared with treatment by dilatation alone. This helped to create the impression that stenting was “risky” in patients with PSC. A more recent retrospective study of 30 patients with PSC found no significant difference when balloon dilatation was performed with or without stents, arguing in favor of stenting when clinically indicated.

In the largest retrospective study to date examining post-ERCP adverse events in PSC, a total of 185 procedures were performed on 75 PSC patients and found the use of temporary plastic biliary stents to treat strictures was not associated with post-ERCP adverse events when compared to dilation alone. This study strongly suggested that the use of stents in patients with PSC was, in fact, associated with better outcomes and argued that the use of stents should not be avoided.

**Tissue Acquisition**

As primary sclerosing cholangitis is associated with the development of cholangiocarcinoma in 10–20% of PSC patients, tissue sampling should be performed at the time of ERCP of any concerning sites in the biliary tree such as strictures or areas of concerning duct wall appearance. Endoscopic sampling is preferred over a percutaneous approach, as it is less invasive, has fewer complications, does not alter the bile duct anatomy and induce adhesions of the liver capsule (which are important considerations given the indication for liver transplantation in PSC patients).

Tissue sampling can be carried out by bile duct forceps biopsy and/or brush cytology after localization of a stricture or ductal lesion. Currently, brush cytology is most commonly used method for tissue sampling in ERCP as some lesions are not amenable to biopsy (i.e. high intrahepatic or angulated ducts) whereas low-profile brush cytology catheters can access most sites in the biliary tree, including very proximal locations. Brush cytology is a highly specific means (97-100%) to detect malignancy in the biliary tract. It is somewhat limited by its moderate sensitivity when used as an independent testing modality, reported as 52.6 – 68% based on numerous studies. Also, a significant proportion of brushings can be reported as “atypical.” Atypical brushings need to be evaluated in the appropriate
clinical context, and those suggestive for malignancy should be further investigated. In a study by Volmer et al, it was reported that out of 1118 specimens from bile and pancreatic duct brushings, 101 specimens (10.4%) were atypical/inconclusive; of those atypical brushings, 43.6% were later found to be malignant. It has recently been proposed by Witt et al that patients with atypical brushings can be further stratified into “high risk” and “lower risk” based on a variety of factors, with a history of PSC being a major factor associated with malignancy. Based on this information, the authors derived a weighted scoring system termed the Atypical Biliary Brushing Score (ABBS) to help identify patients at high risk for malignancy in the setting of an atypical brushing (Table 1).36

**Biopsy**

When a suspicious lesion or narrowed duct is amendable to biopsy, a direct sample can be obtained using forceps under fluoroscopic and/or endoscopic guidance. Although less far-reaching than brush cytology, a prospective study evaluating bile duct strictures reported a 91% success rate in obtaining biopsies out of 86 patients.37 Earlier studies demonstrated an increased risk of bile duct perforation with biopsy, however the risk in current practice is felt to be quite small.38,39 Similar to brush cytology, specificity of biopsy is quite high (97-100%) but also found to have poor to moderate sensitivity (30-80%).38,39,35

**Fluorescence in situ Hybridization**

Fluorescence in situ hybridization (FISH) utilizes fluorescently labeled DNA probes to detect sampled cells that have numerical or structural abnormalities. The probes target the centromeres of four chromosomal locations (CEP 3, CEP 7, CEP 17, and the locus of 9p21) to look for chromosomal abnormalities such as polysomy and trisomy (aneuploidy), which is indicative of malignancy. FISH has been determined to be more sensitive for the detection of malignancy in PSC patients than brush cytology.40 There have also been studies, however, that demonstrate a lower specificity (88%) for FISH compared to brush cytology when evaluating strictures in PSC patients.19,41,42 Given the increased sensitivity of FISH over routine cytology, FISH has been demonstrated to detect more patients with carcinoma than routine cytology and can significantly improve the chances of detecting malignancy of bile duct strictures at an early stage.43

**The Use of Cholangioscopy in PSC**

Cholangioscopy, usually performed in a per-oral manner via ERCP, allows direct visualization of suspicious lesions and can increase the accuracy of tissue acquisition. Traditional “mother-baby” cholangioscopes have been available for decades, but their use has been limited due to a number of factors including high-cost, fragility, the requirement for two-operators, increased procedure time, and lack of accessory channels needed to perform biopsy.44 Recently, a smaller single-operator cholangioscope has been introduced that offers greater durability, four-way tip deflection, disposability (the entire device is disposable except for the optical fiber, which can be cleaned and re-used), and for a working channel that allows both tissue acquisition (via biopsy forceps) and therapeutic interventions (such as laser or electrohydraulic lithotripsy). The single-operator cholangioscope, termed the Spyglass (Boston Scientific, Natick MA) has been the subject of several recent studies. Chen et al. reported being able to utilize the scope to obtain adequate tissue samples for analysis in 88% of 140 patients in evaluating indeterminate biliary strictures and a sensitivity of 78% in diagnosing malignancy based on visual impression alone.45 A retrospective study by Siddiqui et al demonstrated
Endoscopic Management and Therapy of PSC

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Table 1. Atypical Biliary Brushing Score (ABBS). *Witt et al*

*Patients with an ABBS score of ≥ 4 should be considered to be of increased risk of harboring malignancy despite an atypical brush cytology result.*

<table>
<thead>
<tr>
<th>Score</th>
<th>Age ≥ 60</th>
<th>Endoscopic impression malignant</th>
<th>Procedure indication pancreatic mass</th>
<th>Stricture in Common Hepatic Duct</th>
<th>Stricture in Distal Common Bile Duct</th>
<th>Presence of PSC</th>
<th>CA 19-9 above 300 U/ml</th>
</tr>
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<tr>
<td></td>
<td>+1</td>
<td></td>
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The Spyglass system had 77% accuracy (23 of 30) in diagnosing malignancies that were inconclusive on ERCP-guided brush or EUS-FNA analyses. The reported sensitivity of biopsy using the Spyglass system in detecting malignancy was lower than visualization (49%-76.5%), and was thought to be related to the small (1-mm) forceps size. The optical fiber can also be passed through a biliary catheter to reach very narrow and proximal locations in the pancreaticobiliary tree. Cholangioscopy can play a meaningful role in patients with PSC as it can allow for direct visualization of the biliary tree, and can help identify areas that would warrant tissue sampling by brush cytology, FISH, or cholangioscopic biopsy in an effort to detect cholangiocarcinoma.

**CHOLANGIOCARCINOMA IN PSC**

**Distinguishing Between Dominant Strictures and CCA**

The presence of a dominant stricture should heighten concern for cholangiocarcinoma, as the tumor itself may produce a dominant stricture either by extrinsic compression of the duct or by direct (intrinsic) tumor involvement. In one study 62% of patients with cholangiocarcinoma had a dominant stricture on cholangiography. Another study also reported that up to 25% of dominant strictures were found to be malignant. Given the poor prognosis of patients with cholangiocarcinoma, early detection is essential; however distinguishing between cholangiocarcinoma and dominant strictures can be difficult. Tumor markers such as CA 19-9 have a limited role in patients with PSC, as many will have an elevated CA 19-9 at baseline, although a CA 19-9 that is markedly elevated should prompt further investigation via imaging and/or ERCP with brushings. It should be noted that cholangiocarcinoma can occur in the absence of a dominant stricture, especially if it arises from a high intrahepatic duct.

ERCP is widely employed to evaluate dominant strictures with concern for cholangiocarcinoma, with brush cytology being the common method to obtain tissue during ERCP. As previously mentioned, although highly specific, brush cytology alone has poor sensitivity. Greater specificity and sensitivity for detecting cholangiocarcinoma can be achieved by combining imaging, serologic markers, and ERCP findings (including cholangioscopy) with tissue acquisition. (Figure 2) Early identification of cholangiocarcinoma in patients with PSC should increase the number of patients who are candidates for primary resection or liver transplantation.

**Surveillance for Cholangiocarcinoma Imaging versus Endoscopy**

Currently there are no established and/or universally accepted guidelines regarding the surveillance of cholangiocarcinoma (CCA) in PSC patients. Clinical signs such as increased jaundice, weight loss and

(continued on page 19)
abdominal pain, and/or worsening liver chemistries generally represent an advanced stage of disease. It is recommended that surveillance for CCA be initiated before these symptoms present. It would be preferable to detect lesions at an earlier stage when surgical options were still available.

It has been advocated by some that routine surveillance utilizing MRCP be performed to enhance early detection of CCA, citing the increased complication rate associated with ERCP. In a large retrospective study, demonstration of a mass lesion on MRCP was 100% specific for the diagnosis of CCA (equivalent to ERCP), but mass lesions are often not present in early stage disease and were observed in only 35% of confirmed cancers, arguing for a more aggressive screening protocol beyond simple imaging, which some institutions have begun to practice. The overall positive predictive value of MRCP for CCA was 21% compared to 23% for ERCP, based on the cholangiographic findings of ERCP only and not incorporating cytology. This finding can be explained by the difficulty in evaluating dominant strictures with both MRCP and ERCP as independent modalities.

When compared to MRCP, ERCP is more sensitive for detecting extrahepatic dominant strictures (a retrospective study comparing MRCP with ERCP in 36 patients showed that extrahepatic and intrahepatic ductal visualization of MRCP was 64% and 66%, respectively, compared with 86% and 74% for ERCP). ERCP is also indicated in the setting of a suspicious finding or a dominant stricture in order to obtain cytology specimens and biopsies to evaluate for malignancy. To enhance the diagnosis of cholangiocarcinoma in the setting of a dominant stricture, combining ERCP with cholangioscopy and routine cytology results with newer modalities such as FISH and digital imaging analysis was demonstrated to increase the sensitivity of detecting CCA up to 64%. Further advancements in these techniques should significantly improve our ability to detect CCA at an earlier stage, thus improving the odds of survival.

Endoscopic Ultrasound
In cases where ERCP with cytology is inconclusive in evaluating for early stage cholangiocarcinoma, endoscopic ultrasound (EUS) has been explored as an additional modality to assist in the diagnosis. Endoscopic ultrasound is able to provide high quality images of the extrahepatic bile duct and can also be employed to guide fine-needle aspiration (FNA) of distal bile duct strictures. In a respective study, Ohshima et al recently evaluated 75 out of 225 patients with suspicious biliary strictures found to have negative results on endoscopic brush cytology and biopsy. EUS with FNA was performed on 22 of the 75 cases where additional imaging was also negative and malignancy was detected in 16 of these cases. Sensitivity and specificity of EUS-FNA for evaluation of biliary strictures has been reported from 43 to 86% and 95% to 100%, respectively. Sensitivity of EUS-FNA was also found to be significantly higher in detecting distal cholangiocarcinoma compared with proximal malignancy (81% vs. 59%). Although there have been case reports of tumor seeding due to the use of EUS-FNA, incidence is believed to be quite rare. Still, some liver transplant centers may not consider transplant in patients who have had transmural FNA of primary cholangiocarcinomas out of a concern of tumor seeding. Some institutions advocate only for looking with EUS and performing FNA only for evaluation of suspicious lymph nodes. While ERCP remains the preferred approach in the initial evaluation of biliary strictures, EUS-FNA is a promising modality for early detection of cholangiocarcinoma in distal strictures when ERCP with tissue acquisition is non-diagnostic.
COST ANALYSIS VS. RISKS OF INVASIVE PROCEDURES

Given the potential for complications such as pancreatitis and cholangitis with ERCP, several studies have been conducted to determine if non-invasive techniques may prove beneficial in the diagnosis of PSC from a cost-analysis standpoint. In a cost-minimization analysis by Talwalker et al., it was determined that the average cost per correct diagnosis of PSC using a test strategy of initial MRCP was $724.00 versus $793.17 for initial ERCP yielding a comparable diagnostic accuracy and only a scant cost savings with MRCP.51 A separate cost-analysis by Scheiman et al concluded that the lack of specificity with MRCP in the diagnosis of biliary strictures led to further diagnostic testing in patients with a normal biliary tree, negating the lower cost associated with MRCP. This same study found that the use of EUS as the initial study was associated with the lowest overall cost per patient evaluated; however the authors also supported ERCP as the initial test when a stricture was likely given the therapeutic and diagnostic benefits of ERCP.62

CHANGING THE NATURAL HISTORY OF PSC VIA ENDOSCOPIC SURVEILLANCE

Unfortunately, the natural history of PSC is often years of progressive liver disease followed by either cirrhosis with end stage liver disease and/or the development of cholangiocarcinoma, or both. Transplant and resection are the only options to cure patients with cholangiocarcinoma. Surveillance of PSC patients is proposed as a means to detect cholangiocarcinoma at an early stage, allow for transplant, and thus (potentially) change the natural course of the disease and is being undertaken at centers around the nation.

At present there is no gold standard for the surveillance of PSC patients for the development of cholangiocarcinoma. Given the 10-15\% lifetime risk of developing CCA and the grim prognosis associated with this diagnosis, early detection allows the greatest potential for possible resection, consideration for liver transplant, and thus increased survival. As cholestatic changes often do not occur until the advanced stages of CCA, (and may be associated with liver decompensation and not obstruction) surveillance strategies based on clinical or liver chemistry findings alone cannot be uniformly recommended. MRCP, though associated with high specificity and sensitivity for the detection of PSC, has difficulty differentiating between benign and malignant strictures. It is recommended by the authors that PSC patients found to have concerning strictures, labs suggestive of obstruction, recurrent cholangitis, or other worrisome findings undergo surveillance with ERCP and brush cytology to assess for CCA.

It has been demonstrated that combining ERCP and routine cytology with newer modalities such as FISH and digital imaging analysis increases the sensitivity of detecting CCA, and it is expected that our ability to detect CCA at earlier stages will improve as these techniques are further refined. Tissue obtained via bile duct forceps or FNA can also improve detection of cholangiocarcinoma in distal strictures when ERCP is non-diagnostic. The direct visualization offered by cholangioscopy and EUS represent promising means to enhance tissue acquisition and will serve to further increase the sensitivity in detecting CCA.

CONCLUSIONS

The pathogenesis of PSC remains unknown and there are currently no available medical therapies for treatment, with liver transplant representing the only available cure. Endoscopic therapy has proven vital in both diagnosis and management of the disease. Given the heightened risk of cholangiocarcinoma in patients with PSC and the poor prognosis this conveys, a strategy of endoscopic surveillance is recommended to enhance early detection of CCA to improve the possibility of resection and/or liver transplant, ultimately leading to increased survival. The combined use of ERCP with brush cytology and newer modalities such as FISH have increased the sensitivity of detected CCA. Advances in cholangioscopy, EUS-FNA, and ancillary cytologic testing (e.g. FISH) will further improve our ability to detect CCA at an early stage.

References


