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REVIEWS

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Pathogenesis, diagnosis and treatment of premalignant and malignant stages of cholangiocarcinoma in primary sclerosing cholangitis

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Abstract

Patients with primary sclerosing cholangitis (PSC) confer a high risk of cholangiocarcinoma (CCA). The molecular mechanisms of CCA development in PSC are incompletely understood, but pro-oncogenic processes resulting from chronic biliary inflammation are presumably of central importance. Distinguishing benign from malignant biliary strictures in PSC patients is challenging and accurately diagnosing CCA in PSC often requires a multifaceted approach involving imaging, serological testing, biliary brush cytology and fluorescence in situ hybridization (FISH). Lack of early detection tools leads to a late diagnosis in the majority of cases. Surgical resection or liver transplantation represent the only curative intent treatments in PSC-CCA, but is only an option for the small subset of patients where CCA is detected at an early stage. Current palliative treatment modalities result in only a modest increase in survival. Overall, PSC-CCA carries a dismal prognosis with a 5-year survival less than 20%. Advances aiming at improving strategies for early detection, treatment and surveillance of CCA will be essential to provide better future patient care for PSC patients. Herein, we review the pathogenetic mechanisms for PSC-CCA as well as strategies for diagnosing and managing premalignant and malignant stages of CCA in PSC.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated liver disease characterized by multifocal inflammatory and fibrotic strictures of the large intra- and extrahepatic bile ducts.[1] The estimated prevalence of PSC is in the range of 1-16 per 100 000, with significant regional differences in prevalence across Europe.[1] The disease primarily affects young individuals (median age of onset 30-40 years) with concurrent inflammatory bowel disease (IBD) (approximately 2/3 of patients).[1] In absence of any effective medical treatment, progressive bile duct disruption leads to cholestasis and hepatic injury with liver transplantation representing the only curative intervention.[1] Outcome after liver transplantation is good with a 5-year survival rate above 70%, but biliary tract cancers

Abbreviations: BTC, biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CT, computed tomography; EASL, European Association for the Study of the Liver; ERCP, endoscopic retrograde cholangiopancreatography; ESGE, European Society of Gastrointestinal Endoscopy; FISH, fluorescence in situ hybridization; GBC, gall bladder carcinoma; HCC, hepatocellular carcinoma; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; LGD, low-grade dysplasia; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; OLT, orthotopic liver transplantation; PET/CT, positron emission tomography computed tomography; PSC, primary sclerosing cholangitis; US, ultrasound.

(BTC), predominated by cholangiocarcinoma (CCA), represents a dreaded complication of PSC with major negative impact on life expectancy.[1,2]

The risk of CCA in PSC is approximately 160- to 400-fold greater than in the general population and PSC currently represents the main established risk factor for CCA in Western countries.[2,3] The annual incidence of CCA in patients with PSC is estimated to be 0.5%-1.5% with a reported lifetime incidence up to 20%.[3,4] Geographical differences in CCA risk are present, with lower observed CCA frequencies in PSC populations in Southern Europe and Asia compared to Northern Europe and the United States.[5]

Long duration of symptomatic PSC does not appear to increase the risk of CCA as up to 50% of PSC-CCA are diagnosed concurrently with, or within 1 year of, PSC diagnosis.[1] This suggests that subclinical PSC precedes the development of CCA, and that the workup performed because of the symptoms primarily related to CCA lead to the diagnosis of PSC.[1,2] Accordingly, PSC patients are most often young when diagnosed with CCA with mean age of CCA diagnosis in the fourth decade of life, as compared to seventh decade in sporadic CCA.[3]

Detecting CCA in PSC is challenging, and current diagnostic means for CCA in PSC are restricted by low accuracy. Multiple modalities, including serological testing, imaging and biliary cytology in combination, are most often needed to establish the diagnosis of CCA.[1] Detection of CCA at an early stage is crucial to allow for curative surgical treatment, but the lack of effective surveillance modalities leads to a late diagnosis in the majority of cases. As a consequence PSC-CCA carries a dismal prognosis with a median survival of 5 months where curative treatment is unavailable, with CCA

Keypoints

- The lifetime risk of cholangiocarcinoma (CCA) in primary sclerosing cholangitis (PSC) is in the range 6%-20%.
- Current diagnostic means for CCA in PSC are restricted by low accuracy, and multiple modalities including serologic testing, imaging, biliary cytology and FISH need to be interpreted together to establish the diagnosis.
- Early detection of CCA is difficult, but critical to allow for curative surgery.
- PSC-CCA carries a dismal prognosis with a 5-year survival rate of less than 20%.
- There is no established evidence-based surveillance strategy for CCA in PSC, but many centers have implemented surveillance algorithms that may prove to be effective.

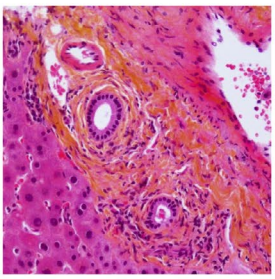
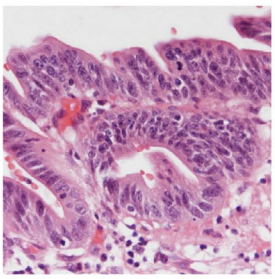
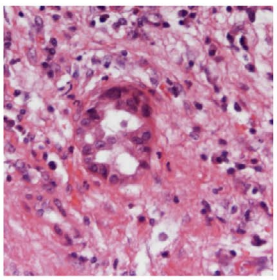
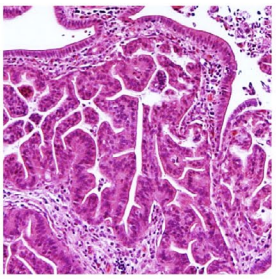
Histological images				
	Benign PSC →	**Low-grade dysplasia** →	**High-grade dysplasia** →	**CCA**
Cytological findings	Sheets of cells in monolayer with even, relatively dense, chromatin pattern and no nucleoli.	Sheets and clusters of cells with nuclear overlapping, smooth nuclear shape and moderately increased nuclear/cytoplasmic ratio. No dissociation of single cells. Nuclear chromatin shows mild clumping, and there are small, but clearly visible, nucleoli.	Atypical cell clusters with marked increase in nuclear/cytoplasmic ratio, nuclear overlapping and crowding. The nuclear membranes are irregular with signs of moulding. The nuclei show coarse chromatin with distinct and prominent nucleoli.	The same cytological findings as in high-grade dysplasia. Additional histological finding: Tumor invasiveness beyond the basement membrane of the bile ducts.

FIGURE 1 Cholangiocarcinoma (CCA) in primary sclerosing cholangitis is considered to develop through a stepwise premalignant to malignant transformation of the biliary epithelium, whereby inflammatory epithelial damage leads to a sequence of low-grade dysplasia (LGD), high-grade dysplasia (HGD) and ultimately to invasive CCA. In the clinical setting, the presence and grade of dysplasia are commonly based on biliary cytology obtained from the bile ducts during endoscopic retrograde cholangiography. Illustrated are histological images and cytological criteria to classify biliary brush cytology into the following categories (i) benign/non-dysplastic PSC, (ii) LGD, (iii) HGD and (iv) CCA. The main criterion for invasiveness is histological; tumour growth beyond the basement membrane.[15]Histological images are kindly provided by pathologist Krzystof Grzyb at the Department of Pathology, Oslo University Hospital Rikshospitalet (Oslo, Norway). Abbreviations: PSC, primary sclerosing cholangitis; CCA, cholangiocarcinoma

currently representing the most frequent cause of PSC-associated death, exceeding 30%.[3]

For the purpose of this review, we will give a short overview of the pathogenesis of PSC-CCA and the strategies for diagnosing and managing premalignant and malignant stages of CCA in patients with PSC.

2 | PATHOGENESIS AND RISK FACTORS FOR CCA IN PSC

The molecular mechanisms of CCA development in PSC are incompletely understood, but a combination of pro-oncogenic processes resulting from chronic biliary inflammation and accumulation of bile acids during chronic cholestasis in PSC together with cocarcinogenic stimuli from the genetic and/or environmental factors causing PSC are all likely to be of importance.[1]

PSC-CCA is predominantly believed to originate from the large cholangiocytes lining the biliary tree, topographically, perihilar CCA is the most common PSC-CCA subtype (approximately 65%), but primary tumours may also arise in the intrahepatic (15%) - and distal extrahepatic (20%) bile ducts.

CCA in PSC is considered to develop through a multistep process preceded by preneoplastic often multifocal lesions, where a sequence of inflammatory epithelial damage and biliary metaplasia,

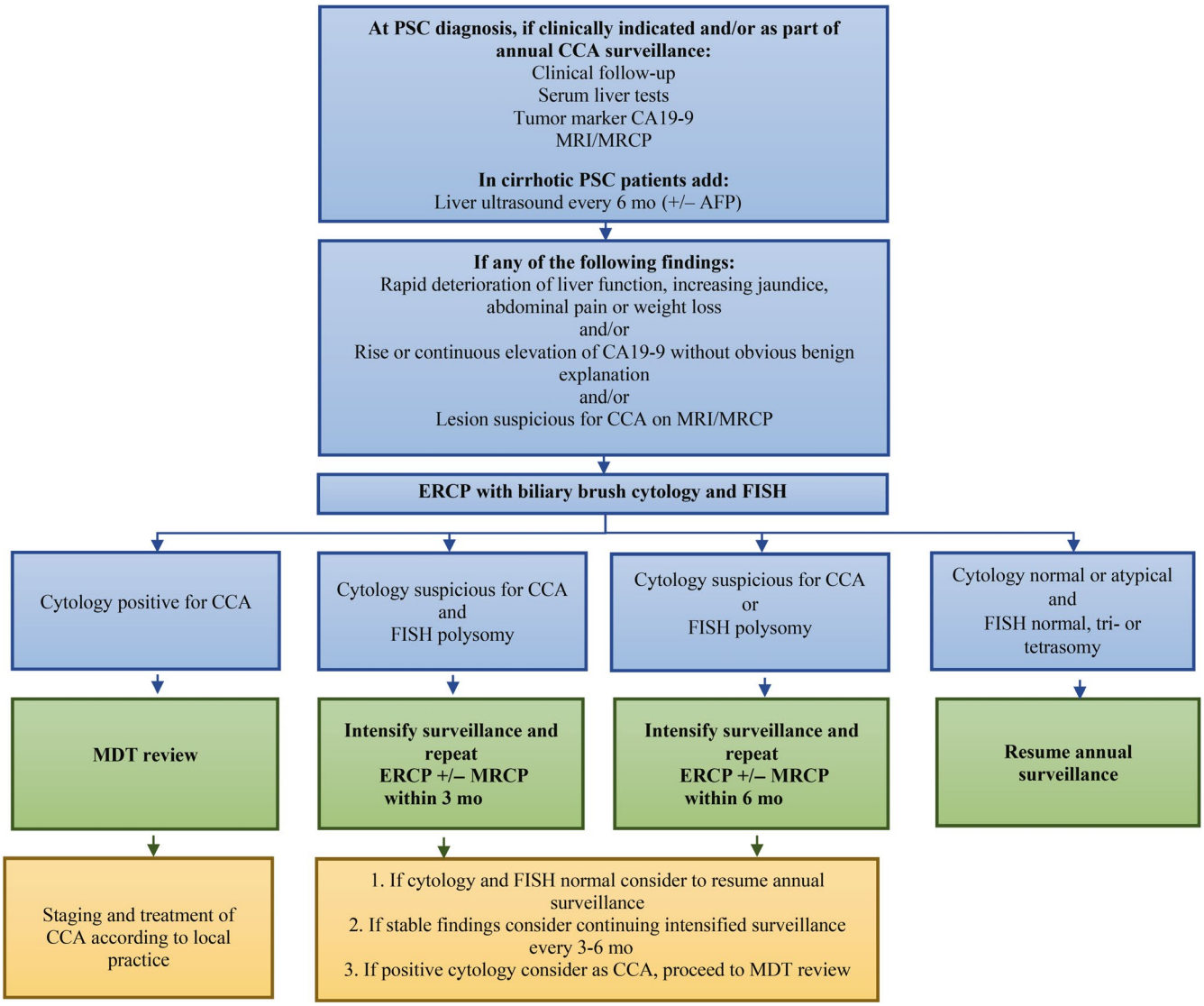


FIGURE 2 Suggested diagnostic evaluation of suspected cholangiocarcinoma (CCA) in patients with primary sclerosing cholangitis (PSC) The algorithm requires that ERCP with brush cytology and FISH assessments is available. In cases where insufficient biliary brush material is obtained at ERCP, a new ERCP procedure with biliary brushing needs to be considered to enable acquisition of sufficient material for diagnostic workup (cytology and FISH). Individual risk assessments are required in patients with cytology suspicious for CCA and/or polysomy after initial ERCP with brush cytology and FISH to determine the extent and frequency of further workup with new imaging, ERCP with brush cytology/FISH and possibly ductal biopsy. Abbreviations: PSC, primary sclerosing cholangitis; CCA, cholangiocarcinoma; CA19-9, carbohydrate antigen 19-9; MRI/MRCP, magnetic resonance imaging/magnetic resonance cholangiopancreaticography; AFP, alpha-fetoprotein; FISH; fluorescent in situ hybridization; ERCP, endoscopic retrograde cholangiopancreatography; MDT, multidisciplinary team

low-grade dysplasia (LGD) and high-grade dysplasia (HGD) eventually leads to CCA (see Figure 1).[6] In a study evaluating 100 formalin-fixed PSC liver explants (including 30 with PSC-CCA), PSC-CCA livers more frequently showed the presence of biliary dysplasia of any grade (83% vs 36%, $P < 0.0001$) and HGD (60% vs 11%, $P < 0.0001$) than PSC livers without CCA, supporting an association between the presence of biliary dysplasia and CCA in PSC.[6] In the same study, presence of both biliary metaplasia, LGD and HGD significantly predicted CCA, but with increasing strength (intestinal type metaplasia vs CCA ($P = 0.013$), LGD vs CCA ($P = 0.0004$) and HGD vs CCA ($P < 0.0001$)), suggesting that PSC-CCA develops through a sequence of gradually accentuating biliary dysplasia.[6]

Although biliary dysplasia serves as a significant predictor for CCA, dysplasia is a relatively frequent finding also in absence of CCA (observed focally in 36% of benign PSC explants.[6] The natural course of biliary dysplasia in PSC in terms of the fraction of patients that will eventually progress from dysplasia to CCA and the time interval involved is not well established.[6] PSC-CCA are often mucin producing tumours characterized by peribiliary gland involvement and high expression of stem/progenitor cell markers.[7] The carcinogenesis shows aspects of 'field effects' with widespread and progressive inflammation and thickening of the bile duct wall, resulting from both activation of the stem cell niche within the peribiliary glands and expansion of the peribiliary vascular plexus.[7]

At the cellular level, the pathogenic metaplasia-dysplasia-carcinoma sequence in peribiliary glands is characterized by the acquisition of epithelial to mesenchymal transition features, absence of primary cilia, and the increase of autophagy and senescence. [7] Local secretion of pro-inflammatory cytokines such as TNF-α and inducible nitric oxide synthase in the microenvironment have been shown to promote nitric oxide and IL-6 production from surrounding cells which putatively further facilitate oncogenesis via DNA damage, cholangiocyte proliferation and inhibition of apoptosis.[8]

Knowledge on predisposing risk factors for PSC-CCA is limited, but reported risk factors include older age at PSC diagnosis, smoking, alcohol consumption, history of variceal bleeding or of colorectal neoplasia, presence and duration of concurrent IBD and polymorphisms of the *NKG2D* gene. However, these factors only confer small increments to risk and are not helpful in defining subgroups of PSC patients who are more likely to develop CCA.

3 | DIAGNOSIS OF PREMALIGNANT BILIARY LESIONS AND CCA IN PSC

The tools currently available to diagnose biliary dysplasia and/or CCA in PSC patients include a combination of radiographic imaging, endoscopic retrograde cholangiopancreatography (ERCP) with cholangioscopy, brush cytology and fluorescent in situ hybridization (FISH) analysis, in addition to tumour serum markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) (see Figure 2 for diagnostic approach to PSC-CCA).[9] In addition more recent developments utilizing genetic, epigenetic, proteomic and metabolomic technologies may prove valuable in future diagnostics of PSC-CCA, but have yet to be validated in larger, prospective cohorts.

3.1 | Clinical manifestations

Symptoms of CCA in PSC are unspecific and overlap with those observed in benign PSC. Rapid deterioration of liver function, increasing jaundice, abdominal pain and/or weight loss should raise suspicion of CCA development in PSC, but is frequently also observed in benign PSC disease progression and would in case of malignancy often imply advanced, incurable stages of CCA. In the majority of cases of biliary dysplasia or early stage CCA in PSC, no clinical alterations are observed, but in patients showing signs of progressive biliary obstruction, one should be aware of the possibility of underlying or co-occurring biliary dysplasia and/or early stage CCA.[10]

3.2 | Radiographic features

Non-invasive imaging may, in the case of CCA, visualize typical malignant appearing mass lesions with delayed venous phase enhancement, polypoid lesions or thickening of the bile duct wall, but most early stage CCA have a ductal location that makes them difficult to define using current imaging techniques. Ultrasound (US) and magnetic resonance imaging (MRI) in a study following 230 PSC patients, of which 23 developed CCA, have shown a similar sensitivity for CCA detection of 57% and 63%, respectively, with US having a slightly better specificity of 94% compared to 79% in MRI.[10] Magnetic resonance cholangiopancreatography (MRCP) and computed tomography (CT) showed a high sensitivity of 78% and 75%, respectively, and an acceptable specificity of 76% and 80%.[10] Magnetic resonance imaging is generally preferred for the detection of small lesions and may provide additional information, including typical signal intensity and enhancement of the lesion, while MRCP has the advantage of portraying structural changes inside of the biliary ducts.[10,11] Combined MRI/MRCP is considered superior in monitoring biliary tract changes in PSC with a sensitivity of 89% and specificity 75%.[10] Positron emission tomography/computed tomography (PET/CT) scans do not appear to add to the diagnostic accuracy compared to combined MRI/MRCP, but PET/CT is valuable in determining the extension, spread and stage of established CCA.[12]

No specific or definite imaging features have been defined that differentiate benign from premalignant or malignant strictures. Detection of a dominant stricture (stenosis with diameter of ≤1.5 mm in the common bile duct and/or ≤1.0 mm in the hepatic duct within 2 cm of the main hepatic confluence) by MRCP is frequent in PSC. It does not per se indicate development of malignancy, but is associated with an increased risk of CCA with approximately 5% of dominant strictures harbouring CCA.[13]

3.3 | ERCP, biliary brush cytology and FISH

ERCP is considered complementary to non-invasive imaging modalities for PSC-CCA detection with a reported sensitivity of 91%

and specificity of 66%,[10] but is rarely used as a surveillance modality as it represents an invasive procedure associated with severe complications such as pancreatitis and cholangitis (4%-18% of PSC patients undergoing ERCP) and need of post-procedure hospitalization in up to 10% of patients. However, according to the guidelines from the European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) 2017, ERCP with ductal sampling (brush cytology and/or endobiliary biopsies) is recommended as part of initial investigation for diagnosing and staging in patients where CCA is suspected based on clinical, biochemical or radiological features. This especially if a new or progressive dominant stricture and/or an enhancing mass lesion is present.[13]

Bile duct brushing is the standard method used for obtaining biliary tissue/cells in order to evaluate if biliary dysplasia or CCA is present in PSC strictures. A cytological brush sample, if containing sufficient cells for categorization, can reveal benign, reactive/inflammatory non-dysplastic changes, low-grade dysplasia or high-grade dysplasia/adenocarcinoma.[14] A meta-analysis (11 studies, 747 patients) has shown a pooled sensitivity of 43% and specificity of 97% for biliary brush cytology in detecting PSC-CCA.[15] Although biliary brush cytology represents a highly specific modality for detecting PSC-CCA, the modest sensitivity reduces its utility as an early detection tool for CCA.

Addition of FISH analysis (which uses labelled DNA probes to detect abnormal loss or gain of selected chromosomes or chromosomal foci in individual cells) performed on cytology specimens increases the sensitivity for PSC-CCA detection.[10,16] In a meta-analysis (8 studies, including 828 patients) the pooled sensitivity and specificity for positive FISH (trisomy, tetrasomy and polysomy) for CCA detection were 68% and 70% respectively.[16] If only definitely positive FISH results (measured as polysomy) (6 studies, 690 patients) were included, the pooled sensitivity decreased to 51%, while specificity increased to 93%.[16] FISH analysis is suggested to be of increased yield in cases of equivocal cytology (suspicious for, but not definitive for malignancy) compared to clear cases of benign cytology. Primary sclerosing cholangitis patients with polysomy detected in multiple sites of the biliary tree (i.e multifocal polysomy) or with a subsequent polysomy FISH result (i.e serial polysomy) are at enhanced risk of CCA compared to patients with non-serial, unifocal polysomy findings.[17] Presence of serial and/or multifocal polysomy can therefore aid in the diagnostic decision-making in challenging cases where FISH polysomy is present in absence of other diagnostic criteria for CCA.

Testing for specific methylation patterns in 4 genes (*CDO1*, *CNRIP1*, *SEPT9* and *VIM*) utilizing DNA extracted from biliary brushes (92 patients, 42 with CCA) has shown a sensitivity of 85% and a specificity of 98% and may potentially serve as a supplement to conventional brush cytology and FISH in diagnosing PSC-CCA in the future.[18]

3.4 | Cholangioscopy

Single-operator peroral cholangioscopy allows direct video-based visualization and targeted tissue sampling of extrahepatic bile duct strictures. In sporadic CCA, use of cholangioscopy appears to increase the diagnostic accuracy of CCA compared to ERCP-guided brushings or biopsies, but limited evidence is available on its utility in PSC-CCA.[13] In a case series from Sweden, including 47 PSC patients, cholangioscopy with visual assessment and targeted biopsies detected only one out of three CCA cases, but it is anticipated that newer digital versions of cholangioscopes will improve the diagnostic performance.[13]

3.5 | Serum tumour markers CA19-9 and CEA

Increasing CA19-9 levels may be associated with CCA development, but the diagnostic accuracy is suboptimal, and raised serum levels of CA19-9 should only be used as a supportive measure in combination with other modalities in diagnosing CCA. High CA19-9 levels can be observed in the presence of cholestasis and cholangitis resulting from benign PSC or in other gastrointestinal and gynaecological cancers.[19] Conversely, low levels may be observed in presence of advanced CCA, for instance in patients who harbour inactivating polymorphisms in *FUT3* (approximately 7% of PSC patients) leading to lack of the CA19-9 epitope.[19] A low cut off value for CA19-9 will increase test sensitivity at the expense of the test specificity and accuracy for CCA detection.[10] For instance a sensitivity of 78% and specificity of 67% for CCA detection has been reported for a CA19-9 cut off value of 20 U/mL, while increasing the cut off value to 129 U/ml led to a decrease in sensitivity to 13%, but optimized specificity to 100%.[10] Using low CA19-9 cut off values may allow detection of early stage CCA at cost of low test specificity.[10] Combining CA19-9 (≥20U/mL) with CT, MRI or MRCP increases the sensitivity to 100%, 96% and 100% respectively, but lowers the specificity to 38%, 37% and 38%.[10]

Carcinoembryonic antigen (CEA) represents another serum tumour marker with utility in PSC-CCA detection. Carcinoembryonic antigen is a commonly used marker for colorectal cancers, but significantly elevated levels of CEA in PSC-CCA compared to PSC patients without CCA have been reported.[20] Carcinoembryonic antigen appears not to be dependent on *FUT3* genotype or influenced by biliary obstruction or cholangitis, and could prove to be of additional value to CA19-9 when these factors are present.[20]

3.6 | Promising biomarkers for PSC-CCA

The development of innovative technologies has permitted the identification of several genetic, epigenetic, proteomic and metabolomic biomarkers with potential clinical usefulness in diagnosing PSC-CCA. Important examples include a proteomic analysis utilizing urine and bile resulting in an area under the curve of 0.96 for differentiation of CCA from benign biliary disorders.[21] Studies on concentration and protein content in extracellular vesicles in bile and serum have also demonstrated the ability to accurately separate patients with malignant vs non-malignant bile duct stenoses in PSC, and also to discriminate patients with PSC and CCA from healthy individuals.[22,23] Specific changes in serum concentration of certain metabolites or

gene expression patterns in mRNA isolated from biliary brushings may also provide potential sources for development of new biomarkers for the diagnosis of CCA in PSC [24,25] Mutational profiling of brush cytology specimens has also shown the potential of improving CCA detection compared to cytology assessments alone.[26]

4 | TREATMENT

The only potentially curative treatment method for PSC patients with established CCA is surgical treatment, either by resection or orthotopic liver transplantation (OLT). Resection of the affected segments or lobe is usually performed in intrahepatic CCA, pancreatoduodenectomy in extrahepatic CCA and, depending on the extent of tumour, resection of the involved intra- and extrahepatic bile ducts, the associated ipsilateral liver, the gallbladder and regional lymph nodes in perihilar CCA. Unfortunately, CCA tumours in PSC are often unavailable for complete resection because of the advanced and infiltrative growth, skip lesions, oncogenic field effect and reduced remaining liver function and volume.[11] When surgical treatment is performed with curative intent, and with negative tumour margins, it is still associated with an unfavourable prognosis with 3-year survival rates less than 20%.

If a CCA tumour is evaluated unresectable, OLT can still represent a curative treatment option, but careful selection of candidates for OLT is essential for acceptable outcomes. A study based on data from the Nordic Liver Transplant Registry (53 CCA patients, 34 with PSC-CCA) found that by selecting CCA patients with a TNM stage ≤2 and a CA19-9 ≤ 100 U/mL an acceptable 5-year survival of 58% was achievable, regardless of tumour localization (intrahepatic or extrahepatic).[27] OLT following neoadjuvant radiotherapy with chemosensitization may provide even better 5-year survival rates above 70% for patients with early stage perihilar CCA, but can be offered to less than 10% of a highly selected group of patients.[28]

For PSC-CCA patients presenting with unresectable or metastatic CCA, systemic chemotherapy remains the main palliative treatment. A meta-analysis performed in sporadic CCA combining the results from two randomized trials (ABC-02, phase III and BT22, phase II), provides supportive evidence for the use of gemcitabine combined with cisplatin as a first-line treatment.[29] Although this chemotherapy regimen improves the progression-free and overall survival, the median overall survival of 11.6 months in metastatic CCA is still modest.[29]

For inoperable patients, palliative endoscopic stenting can be used to relieve cholestasis symptoms and avoid cholangitis. The combination of photodynamic therapy and biliary stenting may improve the effect of biliary stenting and the overall quality of life in the palliative care setting.

Unlike the situation in many other cancers, there are no targeted treatment options yet approved for CCA. Preliminary data from a targeted sequencing effort of established oncogenes and tumour suppressor genes (50 patients with PSC-associated CCA or gallbladder carcinoma) detected potentially actionable mutations in 76% of the patients, including alterations in genes affecting actionable pathways such as P13K/AKT/mTOR- (eg *PIK3CA*), RAS/RAF/MEK/ERK- (*KRAS*, *BRAF*) and tyrosine kinase receptor signalling (eg *EGFR*, *ERBB2*, *FGFR2*).[30] These findings could be of direct relevance for molecular testing for targeted therapies and planning of clinical trials for personalized medicine approaches in PSC-CCA in the future.

The clinical approach to LGD or HGD detected in biliary brush cytology or biopsy without other signs of CCA is challenging. Segmental resection is considered an insufficient strategy for the removal of dysplasia as LGD and HGD often represents a field effect in the biliary tree. However, as dysplasia is closely associated with CCA risk, pre-emptive OLT is advocated for and practiced at some centres in cases of findings of LGD.[6] This policy is also supported by the EASL guidelines for management of PSC, but both the indication for, and timing of, OLT remains controversial.[9,11] However, at most centres these patients are not prioritized for OLT, but redirected to diligent monitoring at short time intervals with repeated ERCP-directed brush cytology/FISH/ductal biopsies until CCA can be detected and managed accordingly.

5 | SURVEILLANCE FOR CCA IN PSC

In order to carry out systematic and effective cancer surveillance, several criteria should ideally be met. In PSC, the criteria of a clearly defined at-risk surveillance population for CCA and presence of an available, affordable and acceptable surveillance modality (MRI/MRC with CA19-9) are met. However, the criterion of an available and beneficial (in terms of increased survival) treatment modality when early stage CCA is first detected through initial screening is currently only accessible for the subset of patients that are candidates for curative resection or OLT. In addition, the cost-effectiveness of any systematic surveillance strategy in PSC-CCA has not been defined.

In absence of evidence and clear support for systematic surveillance in current guidelines for management of PSC, several local management proposals in PSC advise for an interval surveillance strategy most often including annual imaging (preferably MRI and/or MRC) in combination with CA19-9 every 6-12 months, proceeding to second-line evaluation with ERCP with biliary brushings for cytology and FISH (if available) in cases of CCA suspicious findings on initial imaging or a continuously elevated CA19-9.[11] Despite lack of evidence, implementation of pragmatic surveillance approaches is likely to provide better patient care, moreover, by continuously evaluating different surveillance strategies, future evidence of the benefit of such strategies may ultimately be provided.

6 | SUMMARY

CCA development represents a major determinant for poor prognosis in PSC, and lack of accurate diagnostic methods for early detection of CCA and the limited therapeutic options for advanced stages

of CCA are among the main challenges in current handling of PSC patients. Although the majority of PSC patients does not develop CCA, awareness of their increased risk of developing a potentially incurable cancer represents an immense psychological burden to PSC patients.

In addition to the existing imaging modalities and cytological analyses, there is a need for new diagnostic tools that can reveal PSC-CCA at an early stage. Discoveries of potential early detection biomarkers in bile and serum are likely to play an important role in the future, but have yet to be validated in prospective cohorts before implementation into clinical use. A well-defined, evidence-based surveillance strategy that can aid in establishment of earlier diagnosis is also required. New treatment options are needed, where molecular-targeted tailored therapies, already in use for other cancer types, are likely to be developed in the future, and could help improve prognosis of the disease. A combination of improved modalities for early detection and treatment would be of great importance for the future care of this patient group.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

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