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Review

The challenges in primary sclerosing cholangitis – Aetiopathogenesis, autoimmunity, management and malignancy☆

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Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease, characterized by progressive inflammation and fibrosis of the bile ducts, resulting in biliary cirrhosis and is associated with a high risk of cholangiocarcinoma. The majority of patients are young, male and have coexisting inflammatory bowel disease. PSC is found with a prevalence of 10/100,000 in Northern European populations. The pathophysiology of PSC is a complex multistep process including immunological mechanisms, immunogenetic susceptibility and disorders of the biliary epithelia. The diagnosis is primarily based on endoscopic cholangiography although magnetic resonance imaging is increasingly used; biochemistry and immunoserology as well as histology play only a minor role. Due to the high risk of developing cholangiocarcinoma and also other tumours of the GI tract, surveillance strategies are essential, however they have yet to be established and evaluated. Biochemical parameters, clinical risk factors, endoscopic procedures and imaging techniques contribute to the early identification of patients at risk. Since medical therapy of PSC with ursodeoxycholic acid does not improve survival, to date, liver transplantation is the only option with a cure potential; if transplantation is accurately timed, transplanted PSC patients have an excellent rate of survival. However if cholangiocarcinoma is detected, a curative treatment is not possible in the majority of cases. The present review critically summarizes the current knowledge on the aetiopathogenesis of PSC and gives an overview of the diagnostic approaches, surveillance strategies and therapeutic options. Primary sclerosing cholangitis is a disease of unknown aetiology and without any further curative treatment options apart from liver transplantation. Therefore it may be regarded as the greatest challenge in hepatology today.

***Keywords*: PSC; Primary sclerosing cholangitis; Aetiology; Pathogenesis; Immunology; Surveillance; Diagnosis; Therapy; Transplantation; Malignancy; Cholangiocarcinoma**

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Abbreviations: PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; UC, ulcerative colitis; MHC, major histocompatibility complex; HLA, human leukocyte antigen; MIC, MHC class I chain-like; CR5Δ32, 32-bp deletion of the chemokine receptor 5; ICAM-1, intercellular adhesion molecule-1; CFTR, cystic fibrosis transmembrane conductance regulator; ANA, antinuclear antibodies; p-ANCA, perinuclear-staining, antineutrophil cytoplasmic antibodies; AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; p-ANNA, peripheral antineutrophil nuclear antibodies; TNF-α, tumour necrosis factor-α; VAP-1, vascular adhesion protein-1; MadCAM-1, mucosal addressin cell adhesion molecule-1; BEC, biliary epithelial cells; MDR, multidrug resistance protein; UDCA, ursodeoxycholic acid; IL, interleukin; TLR, toll-like receptors; IFNγ, interferon γ; CC, cholangiocarinoma; iNOS, inducible nitric oxide synthase; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; MRC, magnetic resonance cholangiography; MRCP, magnetic resonance cholangiopancreatography; AMA, antimitochondrial antibodies; sdPSC, small-duct PSC; IgG, immune globulin G; MELD, model for end-stage liver disease; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; MRI, magnetic resonance imaging; CT, computed tomography; FDG-PET, positron emission tomography with ^{18}F-fluorodeoxyglucose; US, ultrasound; IDUS, intraductal US; IGF-I, insulin-like growth factor I; CRC, colorectal cancer; OLT, orthotopic liver transplantation; PDT, photodynamic therapy.

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1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic and progressive cholestatic liver disease, which is characterized by inflammation and fibrosis of mainly the large bile ducts leading to biliary cirrhosis in a high percentage of patients. It is associated with inflammatory bowel disease (IBD) in the majority of cases and is associated with a high risk of hepatobiliary as well as extrahepatic malignancies.

In 1929, J.A. Bargen described a case of a biliary cirrhosis in a patient with ulcerative colitis (UC); this was the first description of this disease in English [1] and subsequently he observed further cases of hepatic lesions in UC. In a series of 93 patients with UC, Kimmelstiel et al. reported in 1950 an increased frequency of liver damage [2], including bile casts and interlobular hepatitis. The term "Primary sclerosing cholangitis" was first coined in the early 1960s, when the diagnosis of this disease was based primarily on findings at laparotomy; but it was not until retrograde cholangiography by fiber duodenoscope introduced in 1970, that this disease became easier to diagnose and later also easier to treat. During the last three decades significant progress was made regarding the diagnostic and therapeutic methods, but still we are facing important challenges: the aetiopathogenesis of PSC remains poorly understood, the medical treatment of PSC is insufficient and the early detection of malignant complications to allow timely therapy, namely, liver transplantation is difficult.

Data on the epidemiology of PSC are rare and originate from a few major tertiary referral centres in Northern Europe or North America. In addition, the studies available mostly have methodological limitations [3]. Furthermore, PSC obviously does not occur with the same frequency worldwide. In Northern Europe, Canada or Minnesota incidence rates between 0.9 and 1.3/100,000/year and prevalence between 8.5 and 13.6/100,000 have been reported [4–7], while in southern Europe, Asia or Alaska this disease is seen much less frequently [8–11]. Between 55% and 71% of the patients are male and the mean age at diagnosis is around 40 years; a concomitant IBD can be found in 62–73% of patients and conversely 3–4% of patients with IBD have also PSC [3,12]. Ulcerative colitis (UC) is most common, but an association with Crohn's disease has been described in 1–14% of all PSC patients. However, in Japan [10] and Singapore [9] patients appear to be older at diagnosis and an associated IBD is less frequent. As numerous studies demonstrated, PSC is a disease of non-smokers, since current smokers have a decreased risk with an odds-ratio of 0.13–0.17 for the development of PSC [13,14].

The clinical course of PSC is characterized by recurrent episodes of cholangitis, during which the disease slowly progresses. While patients are initially often asymptomatic, they suffer over the years from jaundice, pruritus, fever and finally all the symptoms of end-stage liver disease can appear. Nevertheless in some patients the disease can also rapidly progress when after a period of stability septic biliary complications occur. The main causes of death are cholangiocarcinoma and liver failure. The mean time from diagnosis to death or liver transplantation ranges from 9.6 to 12 years and cholangiocarcinoma develops in 8–13.2% [15–17].

2. Aetiology and pathogenesis

While the cause of PSC still remains unknown, there are currently numerous approaches evolving that help us to understand the multiple mechanisms involved in aetiopathogenesis [18]. Based on an adequate immunogenetic background, immunopathogenetic mechanisms occur, which cause inflammatory changes of the bile ducts possibly triggered or intensified by infectious pathogens [19,20]. The following review describes several aspects of the aetiopathogenesis of PSC, i.e. PSC as a genetic disease, as an autoimmune disease, as an inflammatory disease triggered by infectious agents and as a cholangiopathy (Table 1).

2.1. PSC as a genetic disease

First-degree relatives of PSC patients have a PSC prevalence of 0.7% and siblings have an even higher prevalence of 1.5% [21]; this approximately 100-fold increased risk of PSC between genetically related individuals illustrates the importance of a genetic predisposition for the development of the disease. However, PSC is a complex non-mendelian disorder and the susceptibility to the disease is probably based on a combination of certain alleles of the major histocompatibility complex (MHC) and other non-MHC gene-polymorphisms.

The MHC encodes among others the human leukocyte antigen (HLA) class I and HLA class II molecules, which are involved in T-cell response, as well as the MHC class I chain-like (MIC)α-molecules, which play a role for the innate immune response, especially as ligands for natural killer cells [18,19,22]. MHC-haplotypes with an increased risk of PSC include several risk alleles like MICA * 008, DRB1 * 0301, DRB1 * 1301 or DRB1 * 1501; the strongest association was found for the MICA * 008-homozygosity with an odds-ratio of 5.01. Other haplotypes like DRB1 * 0701, DRB1 * 0401 and MICA * 002 are found in lower frequency in patients with PSC compared with controls and hence they are designated as protective haplotypes with an reduced risk of PSC development [23–25].

Genes outside the MHC-region also contribute to the susceptibility to PSC or influence the disease progression; most of them are involved in immune regulation. Unfortunately, most of the studies describing an influence of

Table 1
Summary of the current pathogenetic concepts possibly involved in the aetiology of primary sclerosing cholangitis

Pathogenetic concept	Pros	Cons
PSC as genetic disease	– Increased prevalence of PSC among first-degree relatives [21] – Association with certain MHC- and non-MHC-alleles [23–31]	– Association with HLA-haplotypes is only weak and not mandatory – Studies on non-HLA polymorphisms are not reproducible or contradictory
PSC as an autoimmune disease	– Increased incidence of co-existing autoimmune diseases [20] – Presence of multiple autoantibodies [33]	– No response on immunosuppressive treatment – Male predominance – Antibodies are not specific and do not correlate with clinical parameters
PSC as inflammatory reaction on infectious agents	– Co-expression of VAP-1 and MadCAM-1 in the gut and the liver of patients with PSC and IBD allows an enterohepatic lymphocyte circulation [41,42,44,45] – In a rat model small intestinal bacterial overgrowth lead to biliary strictures and portal inflammation [48] – Helicobacter species can be found in 24–75% of PSC livers [50,52]	– In PSC patients without IBD enterohepatic lymphocyte circulation is not a conclusive concept – No evidence of sign. bacteraemia in UC [46] – No evidence of small intestinal bacterial overgrowth or disturbed intestinal permeability in PSC patients [49] – Helicobacter species are not found more often in livers of PSC patients than in non-cholestatic liver diseases [51]
PSC as a cholangiopathy	– Knockout of the Mdr2 gene which encodes a canalicular phospholipid transporter in mice, results in a sclerosing cholangitis [61,62] – Sera of PSC patients contain autoantibodies against a shared peptide in biliary and colon epithelium [65] – Biliary epithelial cells that are activated by serum-autoantibodies produce cytokines and trigger inflammation [66,67]	– In human PSC patients a significant variation of the corresponding MDR3-gene could not be found [63]

genetic alterations on PSC development are not reproducible. For instance a 32-bp deletion of the chemokine receptor 5 (CR5Δ32), which is frequently found in Northern European countries, results in a reduced receptor expression on T-cells; a recent study on a Belgian population showed a significant lower frequency of this mutation compared with healthy control subjects suggesting a protective effect [26]. However, this is in contrast to a previous study from Australia, which found a higher frequency of CR5Δ32 in PSC patients [27]. E469E-homozygosity of the intercellular adhesion molecule (ICAM)-1 was associated with protection against PSC in one study [28], but again this finding was not reproducible in a bigger subsequent study [29]. Another polymorphism with an increased PSC-susceptibility is the G to A substitution at position 308 in the TNF-α promoter [30].

The findings regarding a role of the cystic fibrosis transmembrane conductance regulator (CFTR) are also contradictory; while one study demonstrated an increased prevalence of CFTR abnormalities in PSC patients, these results were not confirmed by others [31,32].

2.2. PSC as an autoimmune disease

The described strong association of PSC-susceptibility and progression with certain HLA-haplotypes as well as with other immune-regulating gene-polymorphisms (e.g. ICAM-1, CR5Δ32) underlines the fundamental role of immunogenetic mechanisms in the pathogenesis of PSC. The hypothesis of PSC as an autoimmune disease is supported by the high frequency of inflammatory bowel disease in PSC patients, the increased incidence of other coexisting autoimmune diseases [20] and the presence of multiple autoantibodies [33]. Nevertheless, because of its male predominance, its non-response on immunosuppressive treatment and the missing evidence of an PSC-specific autoantigen, PSC must be regarded with caution as an autoimmune disease [18,19].

In PSC multiple non-specific autoantibodies, which are rather an epiphenomena to chronic inflammation, can be found; these include antinuclear antibodies (ANA) in 7–77%, anticardiolipin antibodies in 4–66%, anti-smooth-muscle antibodies in 13–20%, anti-thyroid peroxidase (TPO) antibodies in 16% and rheumatoid factor in 15% [19,33]. Atypical perinuclear-staining, antineutrophil cytoplasmic antibodies (p-ANCA) can be found in 60–93% of patients with PSC but also in patients with AIH, PBC or UC [34–36]. Terjung et al. identified a 50-kDa nuclear envelope protein as target antigen in 92% of atypical p-ANCA and proposed the more accurate term "peripheral antineutrophil nuclear antibodies" (p-ANNA) [37]; nevertheless it is still questionable, whether this target protein or p-ANNAs are

involved in pathogenesis. The same group attributed a significant diagnostic role to ANCAs as the only antibodies in PSC; however, there is no clear correlation of ANCA-serum-titers and clinical parameters, so they are not helpful in clinical management.

Further hints of an involvement of humoral immunity are the early observations of elevated circulating immune complexes [38] as well as the complement activation with elevated C3d and C4d in PSC compared with obstructive cholestasis [39].

The finding of a T-cell predominant portal infiltrate indicates the role of cellular immunity in PSC [19]. Indeed the function of liver derived T lymphocytes of PSC patients seems to be considerably altered by a TNF-α dependent mechanism with impaired cytokine production and reduced proliferative responses to mitogens [40].

In consideration of the strong link between PSC and IBD, the hypothesis of an enterohepatic circulation of lymphocytes generated in the gut occurred, which persist as long-lived memory cells and upon activation trigger hepatic inflammation; this concept explains why PSC sometimes develops even many years after proctocolectomy [41,42]. The recirculation could be facilitated by the co-expression of vascular adhesion protein (VAP)-1 [43] and mucosal addressin cell adhesion molecule (MadCAM)-1 [44] in both organs in patients with PSC and IBD, while under normal conditions their expression is restricted to the gut (MadCAM-1) resp. the liver (VAP-1). Livers of patients with PSC showed strong expression of CCL25, a chemokine normally expressed only in the gut and thymus; it allows $CCR9^+$ T-cells, which are generated during colonic inflammation, to infiltrate the liver by adhesion to MadCAM-1 [45].

2.3. PSC as an inflammatory reaction to infectious agents

Some authors see PSC as an immune-mediated inflammatory disease rather than as an autoimmune disease. This would be consistent with a role of bacterial or viral antigens, which enter the portal circulation through the mucosa in IBD and trigger as molecular mimics an immune reaction leading to PSC. However, in a study on eight patients with UC no significant bacteraemia was verified in specimens of mesenteric and peripheral venous blood obtained during surgery for uncontrolled disease [46]; moreover in histological studies portal phlebitis in PSC was usually mild and did not differ from patients with UC without PSC [47]. Small intestinal bacterial overgrowth lead to biliary strictures and portal inflammation in a rat model [48], but it does not seem to contribute to the pathogenesis of PSC in humans; in a study on 22 PSC patients only one showed significant small intestinal bacterial overgrowth and the intestinal permeability was normal in all patients [49].

Current data concerning a possible role of helicobacter species in the pathogenesis of PSC are controversial. In a first study using PCR techniques to identify helicobacter in liver biopsies, 9 of 12 (75%) samples from PSC patients and 11 of 12 samples from PBC patients were positive, while all the normal livers and 92% of non-cholestatic cirrhotic livers were negative; furthermore PSC patients with UC were more likely to be positive [50]. Nonetheless, a subsequent study could detect helicobacter species only in 5 of 13 PSC livers as well as in 10 of 29 non-cholestatic livers and therefore disclaimed an influence of helicobacter on PSC [51]. A recent study also found helicobacter positive PCR in only 24% of PSC livers and 9.7% of non-biliary liver diseases [52].

Some authors suspected viruses like Cytomegalovirus or Reovirus type 3 played a role in PSC pathogenesis, however, more comprehensive studies did not support this hypothesis [53,54].

Numerous studies analyzed bile obtained during ERCP and found enteric bacteria [55,56] or even fungal infections with *Candida* [57]; yet these findings were more frequent in patients with previous ERCP and/or with dominant stenoses so that bile duct infections seemed to be more relevant for PSC progression rather than for aetiopathogenesis and primary manifestation of the disease.

Altogether, infectious agents probably do not directly cause PSC but could activate an immune reaction by the above mentioned enterohepatic lymphocyte circulation or could accelerate disease progression when leading to a biliary infection.

2.4. PSC as a cholangiopathy

PSC is a disease mainly of the large bile ducts and belongs to the cholangiopathies, a group of various hereditary or acquired diseases of the biliary tree with cholestasis as a common symptom and with cholangiocytes as primary target cells of the disease process [58,59].

The complex osmotic secretory process of bile formation depends on a number of membrane transport systems including ion transporters and organic-solute transporters. These transporters are differentially expressed on the sinusoidal and the canalicular membrane of hepatocytes and on biliary epithelial cells (BEC) [60]. Knockout of the Mdr2 gene, which encodes a canalicular transporter for phospholipids in mice, causes absence of phospholipids in bile and leads to a sclerosing cholangitis with hepatobiliary changes that resemble PSC in humans. Interestingly enough, feeding of ursodeoxycholic acid (UDCA) in these mice lowered alkaline phosphatase levels but increased alanine aminotransferase levels and led to bile infarcts, while 24-nor-UDCA improved liver tests and liver histology [61,62]. Although in human PSC patients significant variations of the corresponding MDR3, the human equivalent of

the mouse Mdr2 gene, have not been found [63], this mouse model directs attention to a possible role of hepatobiliary transporters and changes of bile composition and may help to understand some pathogenetic and therapeutic principals in PSC.

Das et al. looked into the issue of how BEC become the target of an immune reaction in patients with PSC and UC. They developed murine monoclonal antibodies against a colonic protein that reacts with IgG from colon specimens solely of UC patients. This antibody reacted additionally with mucosal or epidermal epithelial cells of the gall bladder, the bile duct, the hepatic ducts and the skin, but not with other organs such as synovia, eye tissue or the small intestine [64]. In contrast to patients with PBC, other liver diseases or normal controls, approximately two-thirds of the sera of patients with PSC contained autoantibodies against this epitope [65], and therefore, it might be a candidate as a target protein for immune reaction on biliary epithelia in patients with UC.

The group from the Karolinska Institute in Sweden found antibodies against isolated BEC in the sera of 63% of PSC patients which induced BEC to produce high levels of interleukin (IL) 6 and increased the expression of the adhesion molecule CD44 [66]. A recent study from the same group demonstrated that the stimulation of BEC with these antibodies induced the expression of Toll-like receptors (TLR), extracellular signal-regulated kinase and transcription factors. When further stimulated with lipopolysaccharide the TLR expressing BEC produced high levels of cytokines such as IL8, interferon γ (IFNγ) and tumour necrosis factor α (TNF-α) [67]. As previous studies from Spirli et al. showed, each combination of IL6, IL1, TNF-α or IFNγ stimulated biliary epithelia to generate NO and thus inhibited cAMP-dependent fluid secretion of isolated bile duct units [68,69]. In summary, these findings clarify how antibody-activated BEC further stimulated by bacterial products, trigger chronic inflammation which leads to ductular cholestasis.

2.5. Aetiopathogenesis of malignancies in PSC

Chronic inflammatory diseases such as PSC are frequently linked with an enhanced risk for cancer. A very large study compared the risk of extra- and intrahepatic malignancies during a median follow-up period of 5.7 years (0–27.8) in 604 PSC patients with that of the general Swedish population [15]. The frequency of hepatobiliary cancer in PSC patients was 13.3% and 37% of these malignancies were diagnosed less than one year after PSC was diagnosed. It has been estimated that the incidence of cholangiocarinoma (CC) in PSC patients is 1–1.5% per year. In addition to the 161-fold increased risk for hepatobiliary cancer, PSC patients showed a 10-fold risk for colorectal cancer and a 14-fold risk for pancreatic cancer compared to the general population.

CC can arise at any stage of PSC and is the leading cause of death in these patients. It develops either as a mass lesion in the liver or as a ductal carcinoma in the biliary tree with a ratio of 1:4 to 1:7 in different studies [70]. In patients with PSC, cholangiocarcinoma occurs approximately in 15% in the liver, 20% in the distal common biliary duct, and in 65% in the hilar region. The risk factors for cholangiocarcinogenesis in PSC patients are poorly defined. Smoking and alcohol consumption have been suggested as risk factors while duration of PSC or inflammatory bowel disease appears not to be associated with an increased risk for CC in PSC patients.

The pathogenesis and molecular mechanisms of CC development in PSC are poorly understood. In experimental models, bile has been shown to induce oxidative stress and to up-regulate genes involved in carcinogenesis [71]. In PSC patients, the cholangiocytes are exposed to cytokines of inflammatory pathways such as interleukin-6 which prolongs survival of malignant cholangiocytes [72]. In addition, several investigations have suggested that inflammatory cytokines cause inducible nitric oxide synthase (iNOS) expression in cholangiocytes with peroxynitrite formation, oxidative DNA damage and inhibition of DNA repair. Subsequent accumulation of mutations in tumour suppressor genes and oncogenes as well as development of genetic instability finally leads to dysplasia of biliary epithelia and CC. Little is known about a characteristic pattern or hierarchy of different molecular alterations in PSC-associated CC. There are few data regarding molecular alterations in k-ras, an important oncogene, and p53 one of the most important tumour suppressor genes. Oncogenic k-ras mutations are present in approximately 30% of the PSC-related CC, and overexpression of p53 or p53 mutations has been observed in 30–80% of these tumours [73,74]. p53 mutations seem to occur only in malignant tissue, while k-ras mutations are also observed in dysplasia of bile duct epithelia in PSC patients, which suggest that, in contrast to p53 mutations, k-ras mutation is an early event in PSC-related cholangiocarcinogenesis. The p16INK4a is a major regulator of the cell cycle and also frequently altered in different tumour types. Several studies showed that p16INK4a inactivation by chromosome 9p21 loss, mutations within the coding gene and mutations or methylation of the p16INK4a promoter is common in PSC-associated cholangiocarcinoma [75,76].

On the whole, PSC appears to be caused by a complex interaction between deregulated immune mechanisms in genetically predisposed persons and environmental factors such as infectious agents. However, this multitude of possible pathogenetic processes should allow the question, as to whether PSC is perhaps

just a common clinical end-stage syndrome of a number of similar diseases with different aetiologies. Tumour development of the liver, CC but also HCC, and extrahepatic tissues such as pancreas and colon in PSC still is a black box. However, bringing light into this complex area may give significant clues to this overall poorly understood and mysterious disease.

3. Diagnosis of PSC

The clinical symptoms described in PSC as well as the laboratory tests are not specific but result in further diagnostic steps such as cholangiography, magnetic resonance imaging or liver biopsy. The definite diagnosis of PSC cannot be confirmed until secondary causes of cholangitis are ruled out.

3.1. Clinical presentation

At the time of diagnosis, a considerable proportion of the patients (21–44%) is asymptomatic [6,17,77] and is identified just through incidental or selective (in case of IBD) testing of the liver enzymes. One recent study showed that in contrast to the period 1984–1998, patients in the following 6 years (1998–2004) were more often asymptomatic and older when first diagnosed or diagnosed in earlier pre-cirrhotic stages and presented less frequently with associated IBD [78].

Symptomatic patients present frequently with abdominal pain (33–37%), jaundice (27–30%) or pruritus (20–40%) and with fever (11–35%). Other common findings in clinical examinations and abdominal ultrasound are hepatomegaly (44–55%) or splenomegaly (29–30%). Only 2–4% patients have ascites and 2.6–6% have a history of variceal bleeding prior to diagnosis [16,17,78,79]. The general prevalence of esophageal varices diagnosed by upper endoscopy varies from 7% to 36% [17,80]. Fatigue was described as a common symptom in PSC. However, a sophisticated study addressing this issue demonstrated that fatigue did not differ in PSC patients and patients with IBD alone, and that its prevalence was even lower than in age- and sex-matched subjects from the general population [81].

Cholangiocarcinoma is found in 3.3% of PSC patients within the first 3 months after diagnosis, and in 5% within the first year. These patients tend to be more symptomatic on initial diagnosis; therefore, the first clinical evaluation is of particular importance [15,17,82].

Apart from the well-known association with IBD more than 20% of PSC patients display at least one additional extraintestinal autoimmune feature: most frequently, insulin dependent diabetes mellitus was found in 10.1%, thyroid disorders in 8.4% and psoriasis in 4.2% [20].

Another frequent finding in more advanced stages of the disease is an osteopenic bone disease with 50% of the patients having a bone mineral density below the fracture threshold [83].

3.2. Biochemistry and immunoserology

PSC patients typically present with a cholestatic biochemical profile with 3–10 times of the upper limit increased levels of the serum alkaline phosphatase (AP). However, this finding is neither specific nor mandatory [79,84]. Slight increases of the serum aminotransferase values are also frequently found. Serum bilirubin levels are usually normal at the beginning, but with progression of the disease they increase with fluctuations due to choledocholithiasis or dominant stenoses. Since hepatic synthesis function is initially unimpaired, parameters like albumin, cholinesterase or prothrombin time are normal at early stages.

As mentioned above, multiple autoantibodies can be detected in PSC [33] however, as Terjung et al. [36] stated, only p-ANCA might play some diagnostic role and there is no correlation with clinical parameters or the clinical spectrum of the disease.

3.3. Endoscopy

The most important diagnostic tool in the establishment of PSC are the cholangiographic features of the biliary tract. So far, endoscopic retrograde cholangiography (ERC) remains the current gold standard for imaging of the biliary tract in patients with PSC. The intra- and/or extrahepatic bile ducts show localized or multifocal strictures and intervening segments of normal or dilated ducts. The cholangiographic appearance of PSC includes a broad spectrum of features. While some patients may have primarily extrahepatic bile duct alterations, others might represent with normal common bile duct but significant intrahepatic changes. Li-Yeng and Goldberg proposed a classification of biliary tract alterations in PSC. This classification has been slightly modified by Majoie et al. and amended by Rajaram et al. (Table 2) [85,86]. The classification separately grades extra- and intrahepatic affections of the bile ducts. Alterations range from strictures with minimal dilatations to basically complete loss of peripheral ducts. Examples of radiographic PSC-associated alterations are shown in Fig. 1. Endoscopically detectable alterations of the bile ducts and biliary tree are limited to patients with large bile duct PSC. Patients with small bile duct PSC present with similar biochemical and histological features as PSC, but with a normal cholangiogram [87]. Therefore, a normal cholangiogram in a patient with cholestasis cannot rule out PSC and requires additional diagnostic tests, such as a liver biopsy. Vice versa, other cholestatic liver diseases present with ERC features similar to PSC

Table 2
Cholangiographic classification system for primary sclerosing cholangitis (modified from [112,146])

Intrahepatic	
Type 0	No abnormalities
Type I	Multiple strictures with normal caliber of the bile ducts or minimal dilatations
Type II	Multiple short, bandlike strictures, saccular dilatations, decreased arborisation
Type III	Despite adequate filling pressure only central branches filled; severe pruning, one or more outpouchings
Extrahepatic	
Type 0	No abnormalities
Type I	Irregularities of extrahepatic duct contour, without distant narrowing
Type II	Segmental stenosis of extrahepatic duct, with smooth or irregular margin
Type III	Irregular stenosis and beading of almost entire length of the common duct
Type IV	Extremely irregular margin of the extrahepatic duct, diverticulumlike outpoutchings

[88]. Especially ischemic lesions and secondary biliary cholangitis may present with similar bile duct lesion in the cholangiogram. Over recent years, various groups reported an ischemic-like cholangiopathy with secondary sclerosing cholangitis and biliary cast formation in patients who had survived prolonged intensive care treatment (Fig. 2) [89–91]. Therefore, in addition to ERC the patient's history, laboratory tests and histology have to be taken into account before the diagnosis of PSC can be established. The risk of post ERCP pancreatitis is not increased in PSC patients if compared to non-PSC patients [92,93]. While various studies found the incidence of ERC-induced cholangitis to be approximately 1% in unselected patient cohorts, van Milligen et al. reported a 10% incidence of cholangitis in PSC patients [94–97]. The increased risk of cholangitis supports the concept of antibiotic prophylaxis and addition of antibiotics to the contrast agent. Stiehl et al. for example, reported an ERC-related cholangitis in only 3.3% in their cohort of PSC patients, however, they consequently administered peri-interventional i.v. antibiotics and added antibiotics to the contrast agent [93]. Unfortunately, prospective and comparative data have not been reported so far concerning this specific issue.

3.4. Magnetic resonance cholangiography (MRC)

Considering the inevitable risks of ERC for serious complications such as cholangitis, pancreatitis, perforation or bleeding, alternative imaging procedures for diagnosing PSC have become more desirable. Hence, in recent years, magnetic resonance cholangiography (MRC) as a non-invasive technique has increasingly been used in the diagnosis of PSC.

A number of studies comparing both procedures found that MRC showed a sensitivity of 80–91%, a specificity of 85–99% and an accuracy between 83% and 93% [98–103]. These results were only a little inferior to those obtained with ERC-techniques with a sensitivity 89–96%, specificity 8–100% and accuracy 85–97% [100,102].

Despite similar accuracy, the findings leading to the diagnosis of PSC differ for both modalities. ERC depicts more bile duct stenoses and pruning while MRC finds more skip dilatations together with bile duct occlusions [103] (Fig. 3).

MRC has the advantage of visualizing bile ducts proximal to a complete bile duct obstruction and of providing additional diagnostic information on the liver parenchyma [100]. With the exception of some contraindications such as claustrophobia or the existence of metallic implants, diagnostic quality images can be obtained by MRC in nearly all patients, particularly in those individuals with biliary-enteric anastomosis or gastric bypass as well.

However, because of inferior spatial resolution, severe stenoses may appear as complete occlusions in MRC and mild wall irregularities can be easily overestimated [103]. Furthermore, in cirrhotic patients and if PSC is limited

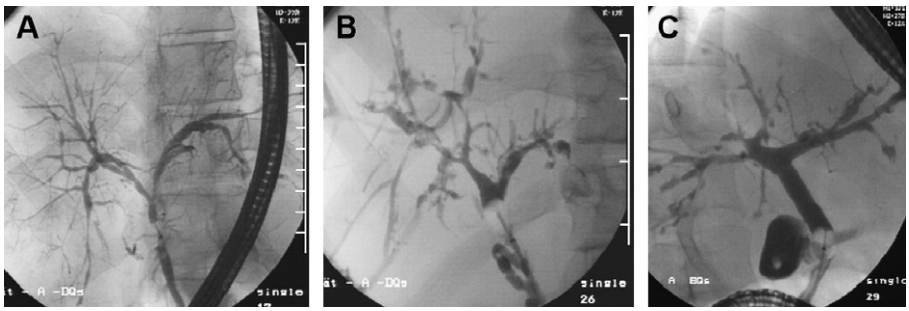

Fig. 1. Typical examples of PSC cholangiograms. (A) Type I intrahepatic alterations, (B) Type II intraheptic alterations, (C) Type III intraheptic alterations.

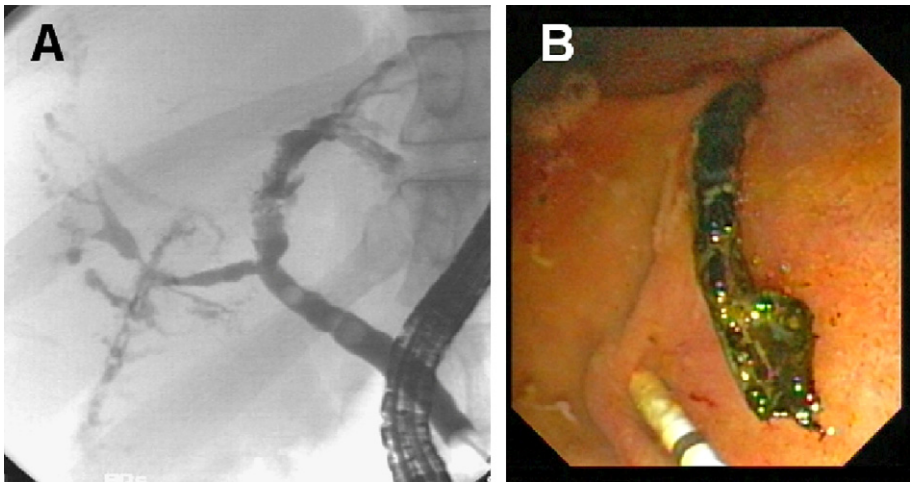

Fig. 2. Secondary biliary sclerosis can mimick cholangiographic features of PSC. (A) The cholangiogram of a patient with ischemic-like cholangiopathy and biliary cast formation after prolonged anamnestic polytrauma with sepsis and mechanical ventilation. (B) A biliary cast that had been removed from the hepatic duct in this patient.

to peripheral ducts, the disease appears to be more difficult to detect with MRC [99]. Naturally, one considerable limitation of MRC is the fact that further diagnostic (i.e. brush cytology) or therapeutic (i.e. dilatation) interventions are not possible, but very necessary in the majority of cases according to one study [100].

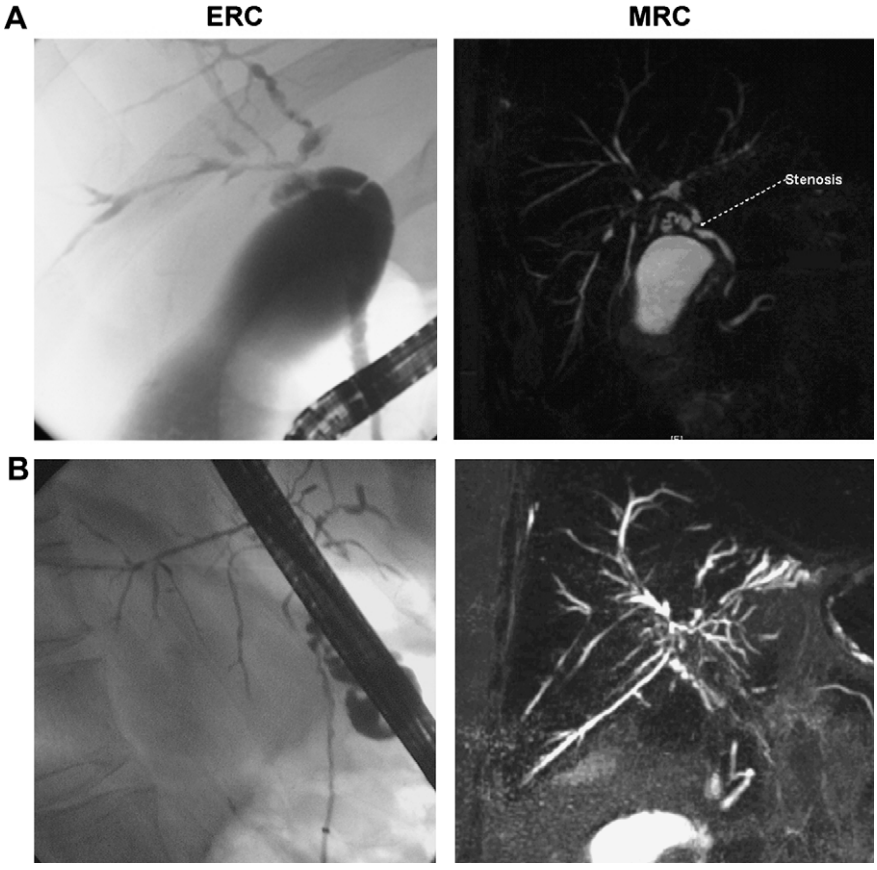

Fig. 3. ERC with the corresponding MRC of two patients with PSC. Patient A presents with multifocal strictures of the intrahepatic bile ducts and with a high-grade stenosis at the cystic duct junction. Patient B features a long-segment filiform stenosis of the common bile duct; the intrahepatic ducts seem to be profoundly narrowed in ERC while MRC accentuates the dilated bile ducts in intervening segments.

Altogether, MRC seems to be a good initial approach in the diagnosis of PSC in asymptomatic patients without cholestasis or with only moderate cholestasis. It should be considered for follow-up studies or when a complete visualization of the biliary tract is necessary. However, ERC remains the gold standard at least for initial diagnosis and PSC management including exclusion of malignancy of stenotic bile ducts; in particular when diagnostic or therapeutic interventions are expected, then ERC is the procedure of choice [100,101,103].

3.5. Histology

The main histopathological findings in PSC are less specific and include portal fibrosis (60–80%) and portal lymphocyte infiltration (69%), even cirrhosis is present in 9–33%. The more specific periductal fibrosis with the typical "onion skin"-pattern resulting in ductopenia as well as bile duct proliferation is found in 8–55% and cholestasis can be observed in 7–50% [47,104].

Ludwig et al. classified histological features in PSC in four stages [47]: At stage I, changes such as cholangitis or portal hepatitis are confined to the portal tracts, at stage II fibrosis or hepatitis are also periportally found, septal fibrosis and/or bridging necrosis indicate stage III, while biliary cirrhosis defines stage IV.

However, because of the merely non-specific changes percutaneous liver biopsy is rarely diagnostic in PSC and is used primarily to exclude other coexisting diseases or to support the diagnosis in doubtful cases. A retrospective study revealed that liver biopsy in patients with a known PSC (assured by ERC) added new information and affected clinical management in only 1.3% [105]. Moreover, serial liver biopsies demonstrated a high degree of sampling variability [104], since PSC is a focal disease, so the usefulness of liver biopsy for staging, as some authors proposed, has to be questioned. Therefore, histology is no longer included in current survival models for PSC [17,106].

3.6. Differential diagnosis and variant syndromes

Other cholestatic liver diseases that feature similar cholangiographic findings as PSC have already been mentioned. In case of an AMA-negative cholestatic disease with a normal cholangiogram, liver biopsy is recommended as the next diagnostic step, to rule out, among others, an AMA-negative PBC, an autoimmune cholangitis and sarcoidosis or cholestatic hepatitis [107]. If the histology is compatible with PSC and IBD is present, small-duct PSC (sdPSC) can be assumed.

Ludwig et al. [47] coined the phrase small-duct PSC instead of the obsolete term "pericholangitis" as designation for a chronic hepatitis associated with IBD, a normal cholangiogram and with biochemical and histological features compatible with PSC. The question of whether IBD presence is mandatory for the diagnosis has not yet been definitively resolved. According to current studies, only 3–17% of patients with sdPSC die or undergo liver transplantation compared with 42–47% in the group of patients with large-duct involvement. In addition, up to the present time cholangiocarcinoma (CC) has not been reported in patients with sdPSC [108–111]. Approximately 12–16% of patients develop features of large-duct PSC during follow-up. UDCA therapy appears to improve liver biochemistry, however does not delay disease progression [111].

An overlap syndrome of PSC and autoimmune hepatitis (AIH) is presumed in patients with PSC, who also fulfil the diagnostic criteria for AIH. Based on the revised AIH scoring system [112], overlap was found in 1.4–8% of PSC patients [17,113,114]. Paediatric AIH patients showed an overlap with primary sclerosing cholangitis in 49% [115]. Patients with overlap syndrome exhibited higher serum levels of aminotransferases, IgG, total globulins and higher titers of autoantibodies. These patients were younger at presentation, association with IBD was less common [116] and their median histological score was higher than in patients with PSC alone [114]. Immunosuppressive therapy appears to be beneficial with a significant reduction of aminotransferases and the transplant-free survival appears to be higher than in PSC alone [113,116].

Patients with IgG4-related autoimmune pancreatitis (sclerosing pancreatitis) often feature sclerosing cholangitis as an extrapancreatic manifestation. This type of sclerosing cholangitis resembles PSC in the cholangiogram but responds well to steroid therapy. It is characterized histologically by a marked lymphoplasmacytic infiltration with IgG4-positive plasma cells and $CD4^{+}/CD25^{+}$ regulatory T-cells [117–119]. On the other hand, a recent study from the Mayo clinic found elevated IgG4-levels in 9% of PSC patients [120]. These patients had in addition significantly higher levels of total bilirubin and of alkaline phosphatase, a lower frequency of IBD and a shorter time to liver transplantation. There were no differences in age, gender or in history of pancreatitis. The authors speculated that this special subset of PSC patients may behave similar to patients with autoimmune pancreatitis and that treatment of these patients with corticosteroids should be considered.

4. Surveillance

One of the major challenges for clinicians, with regard to the limited long-term prognosis of PSC, is an effective surveillance strategy in the medical care of these patients in order to select the optimum time for

liver transplantation and to identify biliary tract malignancies as early as possible. Thus a number of studies attempted to figure out clinical, biochemical, endoscopic or imaging parameters which may help physicians to identify the patients with reduced long-term prognosis due to hepatic decompensation or cholangiocarcinoma (CC). However, all the surveillance strategies described are neither prospective nor are they based on patients of differing ethnicity enrolled by multiple centres from various parts of the world.

4.1. Biochemical and clinical parameters for surveillance

Due to the fact that the prognostic scores for cirrhotic diseases such as the model for end-stage liver disease (MELD) or the Child–Pugh score do not assess survival in PSC well, to date a couple of prognostic scores which estimate survival of PSC patients have been developed, e.g. the well known Mayo survival model [106]. Age and bilirubin were identified as independent predictive parameters in all of these scores [16,17,106,121], whereas the histological stage was only included in older scores. Low albumin proved to be of prognostic relevance in the two current scores [17,106], while aspartate aminotransferase could be identified as an independent prognostic parameter only from the Mayo group. Other clinical parameters which evolved as independent prognostic factors in one or two of the scores were splenomegaly, hepatomegaly or variceal bleeding. Another recently published study identified an aspartate to alanine aminotransferase ratio $\geqslant 1$ as predictor of liver-related death with an almost 4-fold higher risk [122].

Multiple studies looked for risk factors or predictive parameters for CC; however the fact that most of the results of these studies were not reproducible, and in some cases even contradictory, demonstrates the enormous difficulty of predicting hepatobiliary malignancy in PSC. Parameters found to be predictive only in single studies which could not be verified in other studies were: history of variceal bleeding and history of proctocolectomy (mostly due to refractory UC) [123], smoking [82,124], alcohol consumption [125], higher bilirubin levels on admission, previous colorectal cancer, and no UDCA treatment [126]. Three studies identified a longer duration of IBD as a risk factor [124,126,127] and several studies identified a recent diagnosis of PSC as a predictor of malignancy [124,126–128]. At the time of cancer diagnosis, patients with hepatobiliary carcinoma present more often with abdominal pain according to three studies [82,124,127]. Hence a patient with a recently diagnosed PSC with severe symptoms and a long history of IBD should be examined very carefully in order to rule out the possibility of CC.

The detection of serum tumour markers such as carcinoembryonic antigen (CEA) or carbohydrate antigen 19-9 (CA19-9) was regarded initially as a helpful diagnostic tool in diagnosing CC in PSC. Preliminary retrospective studies found sufficient accuracy for a combined score of CA19-9 and CEA [129] respectively significantly higher levels of CA19-9 in PSC patients with CC [82]. Also, three current retrospective studies which used higher cut-off values between 100 U/ml and 200 U/ml [124,125,130] found significant correlations with CC. However, the results of two prospective studies in which serial tests of tumour markers were performed were disappointing in predicting CC [125,131]. The main disadvantage of tumour markers is their unspecific increase in case of acute cholangitis or dominant stenoses [132]. Furthermore, only advanced cases seem to be detectable by CA19-9 which makes it inappropriate for surveillance [130]. Serum trypsinogen-2 was recently found to be superior to CA19-9 in differentiating patients with PSC and CC from patients with PSC alone [133]; further studies are needed to support these promising results.

4.2. Imaging techniques for surveillance

Imaging techniques too are of restricted value in the early detection of CC in PSC due to the fact that they are unable to detect CC at a stage which allows for curative resection or liver transplantation. Indeed, in a retrospective study on 30 PSC patients with biliary tract carcinoma, CT and MRI were able to detect CC in about 85% [134], however this non-blinded retrospective study had several limitations and did not provide information on the patients' outcome. In another study on 48 patients with PSC and CC, the diagnosis of CC was suspected in only 63% by CT and in 46% by ultrasound (US) [127] and the majority of cases were too far advanced for curative treatment.

Dynamic positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) was found to be useful for screening of CC in PSC patients, since in a study on 24 patients it detected (in contrast to CT) correctly 3 of 4 CC/high-grade-dysplasia and was false positive in only 1 of 20 patients [135]. However, other studies did not confirm these results [70], so that the value of FDG-PET as a surveillance method in PSC should be evaluated in prospective studies.

The sensitivity of ultrasound in detecting CC in PSC is low; nonetheless, it might be useful to assess cirrhotic complications of advanced disease. Furthermore, US allows to detect gallbladder polyps, which are in about 50% of cases malignant in PSC [136] which would indicate a cholecystectomy. Furthermore, due to the fact that the risk of pancreatic carcinoma appears to be increased more than 10-fold in PSC [15], ultrasound might be useful for screening in this high-risk population.

4.3. Endoscopic methods for surveillance

Unfortunately, ERC alone has a low sensitivity and specificity to discriminate between benign and malignant bile duct stenoses [82,137]. Therefore, routine surveillance ERCs have not been shown to be of significant benefit for the patients. Increase in cholestasis however, should trigger endoscopic examinations [124]. In addition to radiographic delineation of the biliary tree, ERC can be complemented by brush cytology, forceps biopsy, intraductal ultrasound and direct visualization of the biliary tree using 'through the scope' cholangioscopy (Fig. 4). Depending on the various studies, the published sensitivity of ERC guided biliary brush cytology can be very low [138–140]. However, brush cytology has a high specificity for CC [138–140]. The low sensitivity requires repeat examinations, if cytology is negative while the cholangiogram is suspect of CC. ERC can be performed to advance forceps in the bile duct and obtaining histological samples. Advancing of rigid biopsy forceps in the common bile duct can induce perforations in particular in the hand of the unskilled physician. Unfortunately, to date no wire guided biopsy forceps has been introduced, so that performing a biopsy in the hepatic ducts remains difficult. However, the combination of forceps biopsy and brush cytology increases sensitivity [141]. Cholangioscopy enables direct visualization of the biliary epithelium. In a recent study from our department, Tischendorff et al. demonstrated that cholangioscopy is superior to ERC alone in discriminating between malignant and benign strictures (Fig. 5) [142]. With the development of a 4-way deflecting cholangioscope and cholangioscopy guided biopsies further improvement in the diagnosis of early CC may be achieved [143].

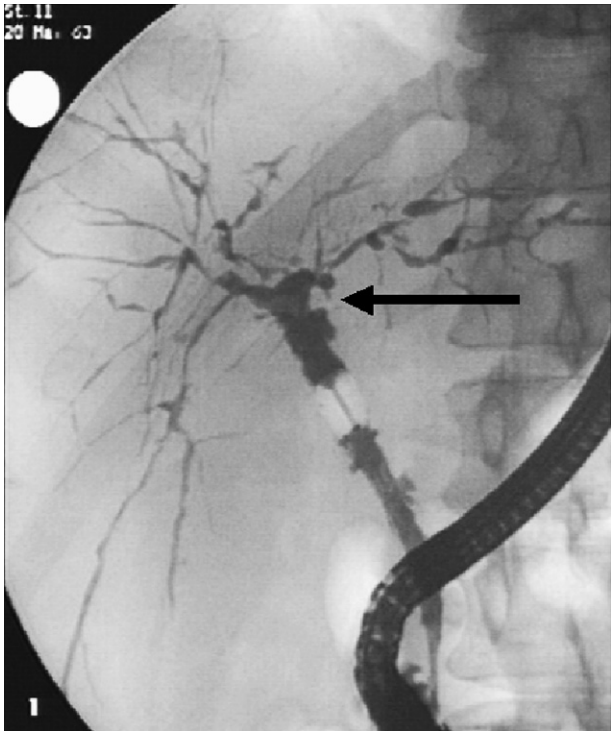

Fig. 4. Cholangiogram of a PSC patient. The arrow indicates a polypoid mass in the hilar region. Forceps biopsy revealed CC.

Intraductal ultrasound may be another important technical addition for differential diagnosis of dominant strictures. In addition to cholangioscopy, Tischendorff et al. studied the role of intraductal ultrasound to discriminate between benign and malignant strictures. In comparison to solely ERC, intraductal ultrasound (IDUS) significantly increased sensitivity from 62.5% to 87.5% and specificity from 53.1% to 90.6% [144]. In addition to the above mentioned methods, ERC can be used to aspirate bile fluid. Kubicka and colleagues measured mutations in the K-ras oncogene in epithelia derived from bile fluid of PSC patients [145]. While k-ras mutations can be detected in the bile of PSC patients without CC, however, patients that were positive for k-ras mutations were at a significantly higher risk to develop CC. Biliary insulin-like growth factor I (IGF-I) is significantly increased in patients with CC and can distinguish between carcinoma and benign strictures [146]. Whether these promising data can be applied for PSC patients, still needs to be investigated.

Approximately 60–80% of patients with PSC suffer from IBD [17,147]. UC constitutes the biggest group with nearly 80% [17,147]. Chronic intestinal inflammation increases the risk of colonic neoplasms. A subsequent increase in colorectal cancer incidence has been reported in association with ulcerative colitis. A cancer incidence of approximately 9% and 30% after 20 and 30 years of disease has been reported [148]. Several studies have indicated that patients with UC and coexisting PSC may be at an even higher risk for the development of CRC [149–154]. Broome et al. reported an almost 5-fold increase in the absolute cumulative risks of developing colorectal cancer or dysplasia for UC patients with PSC after 20 years of colitis [154]. If possible, surveillance colonoscopy should be performed during remission in order to allow differentiation between reactive changes from dysplasia. Chromoendoscopy and zoom colonoscopy might be helpful to unmask intraepithelial neoplasia and guide biopsy [155,156].

5. Treatment

5.1. Medical therapy

Present day data and clinical experience do not suggest that PSC represents a disease which is curable by medical therapy [157]. A cure would include the improvement or normalization of abnormal cholestatic biochemical features but more importantly the improve-

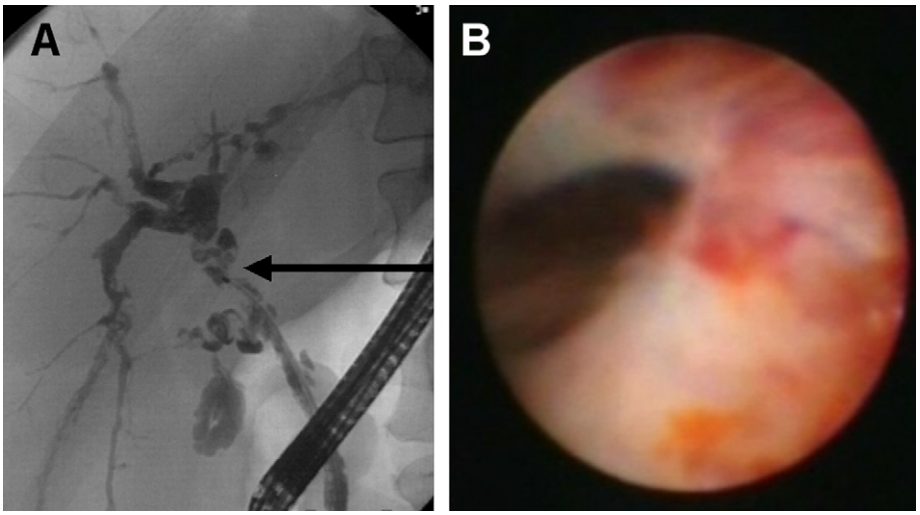

Fig. 5. Cholangiogram (A) and cholangioscopic appearance (B) of a benign stricture in a patient with PSC.

ment of sclerosing changes to the intra- and extrahepatic biliary tree, which ultimately lead to biliary cirrhosis, to episodes of cholangitis, and which carry the risk of cholangiocellular carcinoma. The only available drug that combines a favourable toxicity profile and can lead to a reduction of cholestatic serum parameters is currently ursodeoxycholic acid (UDCA). Predictive scores which have been developed to assess the progress of PSC in view of the clinical experiences of high interindividual variability and unpredictable acceleration episodes almost always contain serum bilirubin as a parameter [16,77,106,121,158,159]. Between 1998 and 2000 four such scores have been reported that employ bilirubin in addition to age, histology, variceal bleeding, hepatomegaly, inflammatory bowel disease, albumin, AST, and haemoglobin [16,77,106,121]. From this perspective, an improvement of the parameter bilirubin, common to these four scores, would be a plausible indicator of an improved prognosis. However, a number of controversies surround the use of UDCA. In two studies by Mitchell et al. and Harnois et al. published in 2001, an improvement was documented using 20 mg/kg body weight, and 25–30 mg/kg body weight, respectively [160,161]. Both use UDCA doses which are considerably higher than those common in the therapy of primary biliary cirrhosis (PBC) (15 mg/kg body weight). From these data a higher dose appeared to be more beneficial in PSC. However, a study analyzing UDCA in bile as a function of oral UDCA dose found that doses exceeding 25 mg/kg body weight are not likely to be useful since the maximum transport of UDCA into the bile levelled off at this dose with no further increase [162]. After these and other initial reports, a meta-analysis was published in 2002 [162] which concluded that UDCA therapy improved biochemical parameters but that the overall beneficial effect in patients with PSC, in particular survival benefit, was uncertain. In 2005 a large study was reported that appeared to confirm this view. Olsson et al. studied 219 PSC patients in a placebo-controlled trial [163]. Treatment was carried out with 17–23 mg/kg body weight of UDCA and a trend towards a better survival and less need for transplantation was seen which did not reach statistical significance. A difference in the incidence of CC was not observed. However, statistical analyses reported in this study concluded that 346 patients would have been required to reach statistical significance. Based on the body of the literature available, a positive effect of UDCA at present cannot be excluded and clearly larger placebo-controlled studies are required. This will only be possible in multi-centre approaches.

An additional effect of UDCA has been seen in two reports which observed a decrease of the dysplasia in colon polyps associated with UDCA doses as low as 10–15 mg/kg body weight [164,165]. Although this requires confirmation in larger studies, the association of PSC with ulcerative colitis in 75% of affected individuals would make this an interesting ancillary effect of UDCA therapy.

The issue of immunosuppression in PSC is controversial and the majority of centres and publications do not recommend the routine administration of corticosteroids and other immunosuppressants [157,166]. In PSC one of the most feared and unpredictable complicating factors is bacterial cholangitis and cholangiosepsis. Immunosuppression would be expected to aggravate this complication. In rare instances such as overlapping features of PSC and autoimmune hepatitis (AIH), immunosuppression may be of benefit but this requires rigorous documentation of AIH which includes biopsies, autoimmune serology and suggestive biochemistry [167,168].

5.2. Endoscopic therapy

Inflammatory alterations in PSC can lead to almost complete stenosis of the extrahepatic biliary tree and can cause acute deterioration of liver function and more rapid progression to biliary cirrhosis (Fig. 4). Such lesions are termed as dominant biliary strictures. Endoscopic treatment of strictures can improve cholestasis and pruritus [91,169–171]. Several modes of endoscopic treatment have been developed and applied successfully in PSC patients. Endoscopic treatment is especially aimed at strictures located in the common bile duct and main hepatic ducts. Current endoscopic therapy consists of either bougienage or balloon dilation of strictures with or without concomitant placement of endoprotheses [92,93,171–175]. Nasobiliary catheter drainage and lavage with or without instillation of corticosteroids have been successfully applied as well [176,177]. These endoscopic treatment modalities are all aimed at maintaining biliary patency and at inducing sustained improvement of clinical and biochemical variables. Baluyut et al. showed that endoscopic treatment has a beneficial effect on survival in PSC patients when applying the Mayo clinic survival model [175]. Cholangioscopy, as an additional diagnostic tool revealed biliary stones in 56% of PSC patients [178]. 30% were missed on cholangiography and detected only by cholangioscopy. Clinical improvement after removal of stones was achieved in 63% of patients. Unfortunately, no randomised trials have been published which compare the various endoscopic treatment options for their efficacy in maintaining biliary patency. The limited number of patients and the very heterogenous patient population hinders the realization of randomised endoscopic trials. Therefore, so far, no general recommendation can be given concerning the best endoscopic approach to dominant strictures. When dominant strictures are treated endoscopically, it is most important not to overlook the presence of CC. Therefore, repeated brush cytologies and/or forceps biopsies of suspicious areas should be obtained.

5.3. Liver transplantation (OLT)

In PSC patients, survival has been shown to be reduced both in symptomatic and in asymptomatic patients [106,157], which is in part attributable to the inherent risk of CC affecting 10–20% of these patients and renders decision making for liver transplantation a formidable challenge. In addition, PSC patients with advanced destructive cholangiopathy frequently exhibit only mild signs of liver failure based upon coagulation abnormalities, hypoalbuminemia, or complications of portal hypertension [17]. The course of deterioration leading to liver failure is often observed after long periods of clinical stability and frequently proceeds rapidly following septic biliary complications. This is not well predicted by the aforementioned PSC scores and this is also true for the model of end-stage liver disease (MELD) which is used for organ allocation in the USA and as of 2006 in the Eurotransplant member countries.

Two major problems define the challenges involved in the indication for liver transplantation in PSC. Firstly, timing is difficult [179]. PSC patients are young and preemptive liver transplantation carries a higher short-term risk of OLT itself than the most likely short-term natural course of the disease. On the other hand, patients who urgently require OLT because of advanced biliary destruction frequently do not meet priority criteria calculated by the MELD system. Secondly, the 161-fold increase of CC risk [15] is an eventuality which may eliminate the option of liver transplantation altogether if evidence of CC is detected by diagnostic imaging procedures. The diagnosis of early CC is difficult and presently there is no single diagnostic procedure characterized by high sensitivity and specificity available [124]. Moreover, those patients at risk cannot be reliably identified.

In terms of practical management, the first point can only be addressed by careful clinical monitoring of PSC patients in transplant centres with an experienced hepatology team, where the likelihood of early complication diagnosis and management, as well as the individualized timing of listing for OLT is higher [17]. The second point has been addressed in two centres by establishing specific protocols for the management of hilar CC and OLT [180,181]. Rea et al. reported a rigorous algorithm for non-resectable hilar CC patients who were carefully selected and capable of surviving chemotherapy, radiation therapy and surgery. A multimodal approach including neoadjuvant chemo-/radiation therapy, brachytherapy, chemotherapy, laparotomy and OLT was employed resulting in a 5-year survival of 82%, which did not differ from results in PSC patients without CC [180]. However, although attractive, these interdisciplinary strategies are best limited to studies and experienced liver transplant and hepatology centres.

Overall, the results of liver transplantation in PSC are good (Fig. 6), leading to 10-year survival rates of approximately 70% [182]. In our centre, the median survival of PSC patients with CC was 12.7 months and all PSC patients irrespective of OLT had a mean survival of 112 months [124]. Recurrence after OLT is difficult to diagnose but appears to occur in up to 25% of patients [183]. Liver transplantation continues to represent the only curative option in PSC. Future developments will have to address the missing sensitivity and specificity of early CC detection, as well as the clinical prediction of the disease course and consequently, specific OLT allocation criteria for this group of patients.

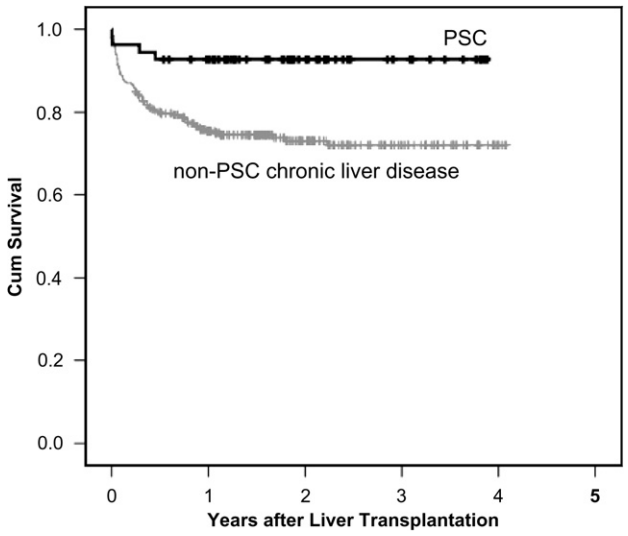

Fig. 6. Kaplan–Meier analysis of cumulative survival after liver transplantation from 01/2003 to 08/2007 at Hannover Medical School comparing 55 patients with PSC (incl. five patients with CC) and 318 patients with other chronic liver diseases (hepatitis B and C, alcoholic liver disease, hepatocellular carcinoma and others). The log-rank-test shows a significant better survival of patients with PSC ($p < 0.01$).

5.4. Treatment of cholangiocarcinoma in PSC

Surgical resection or liver transplantation is the only curative option for patients with PSC-associated CC. However, the prognosis of patients with CC is poor, even after surgical resection. A large population-based study recently showed that survival after surgery for extrahepatic CC has dramatically improved since 1973. However, patients with intrahepatic CC have achieved an improvement in survival largely confined to more recent years. This may be explained by innovative developments in imaging technology, improvements in patient selection and advances in surgical techniques [184]. In the therapy of hilar CC, the most favourable results with 5-year survival rates of 61% are achieved by no-touch-technique, en-bloc-resection and wide tumour-free margins [185].

Compared to patients with non-malignant diseases, patients with PSC-associated CC have a worse prognosis after liver transplantation. Due to the shortage of donor organs, liver transplantation for patients with CC has therefore been abandoned by most liver centres. The above mentioned non-randomised pilot study with neoadjuvant radiochemotherapy reported excellent 5-year survival rates of 80%, at least in a subset of patients with PSC-associated CC. In one study liver transplantation with neoadjuvant chemoradiation achieved an even better survival with less recurrence than conventional resection [180]. There are presently no randomised controlled studies using this neoadjuvant strategy and, therefore, the value of neoadjuvant radiochemotherapy and liver transplantation for patients with PSC-associated CC is still unclear. Obvious limitations of this strategy are a substantial drop out rate during the neoadjuvant therapy due to tumour progression and treatment-related complications, such as vascular complications after liver transplantation [186].

Palliative therapy of PSC-associated CC includes endoscopic management of biliary stenosis (dilatation, stenting), treatment of bacterial cholangitis and systemic chemotherapy. A randomised study with photodynamic therapy of CC resulted in prolongation of survival (493 days versus 98 days; $p < 0.0001$), improved biliary drainage and better quality of life for the patients compared with endoscopic stenting alone [187]. Although a randomised study investigating the combination of chemotherapy and PDT is still not available, there is evidence of synergistic antitumoural activity of local PDT and systemic chemotherapy in cell culture experiments and early clinical studies [188].

There is only a limited number of studies regarding the systemic treatment options for biliary cancers. To date, the best response rates have been achieved with combination chemotherapies containing platinum analogues and gemcitabine. In the absence of larger clinical phase III trials, a standard chemotherapy for biliary cancers does not exist today [189].

6. Conclusion

Primary sclerosing cholangitis represents in many ways one of the most intriguing challenges of current hepatology. Its aetiology is still mysterious though a number of promising experimental approaches enlighten the different aspects of pathophysiology. PSC is not a classical autoimmune disease but the increasing understanding of underlying immunological mechanisms stimulates further investigations; the interaction between biliary epithelial cells and cellular and humoral immunity and the search for triggers of a deregulated immunity is of particular interest in this context. At present, there is no effective pharmacotherapy available, thus new insights into pathophysiological mechanisms will hopefully lead to new therapeutic innovations. Advances of endoscopic techniques promise additional possibilities in diagnosis and treatment. Even though the clinical course of the disease is rather variable, the mean survival of PSC patients is markedly shortened. Cholangiocarcinoma is a frequent outcome of PSC with a very poor prognosis. Therefore clinical management is exceptionally demanding. Advances in new imaging techniques expand the diagnostic options and allow new views on the disease. Considering the high risk of malignancy effective and evidence-based surveillance strategies based on a combination of endoscopic, imaging and biochemical techniques are urgently required. These will be beneficial for the timing of liver transplan-

tation, the only curative treatment at present, and the current allocation systems should account for the special features of this disease.

Finally, significant progress in the management of PSC will depend on breakthroughs in the pathophysiological understanding of this mysterious disease. These studies will need to look at the site of action which is the biliary tree. Thus endoscopic management will go hand in hand with studies on aetiology and pathogenesis that rely on the investigation of biological materials obtained endoscopically from the site of action, e.g. the biliary tree with its pathological changes, in particular bile duct epithelium and the pathognomonic dominant biliary strictures. Hopefully, the years ahead will be interesting for the sake of our patients.

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