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REVIEW

Review of incidence and outcomes of treatment of cholangiocarcinoma in patients with primary sclerosing cholangitis

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Abstract

Primary sclerosing cholangitis (PSC) is a premalignant condition and a well-documented risk factor for cholangiocarcinoma (CCA) which is the most common malignancy in this setting and the leading cause of deaths in the recent years, with an increasing incidence. PSC-associated CCA has a geographical distribution that follows the incidence of PSC, with an observed ascending gradient from the Eastern to the Western and from the Southern to the Northern countries. It may arise at any location along the biliary tree but is most common in the perihilar area. Patients with PSC and intrahepatic or perihilar CCA are typically not suitable for liver resection, which is otherwise the treatment of choice with curative intent in patients with resectable tumours, providing a radical resection with clear margins can be achieved. This largely relates to the commonly advanced stage of liver disease at presentation, which allows consideration for liver resection only for a very limited number of suitable patients with PSC. On the other hand, remarkable progress has been reached in the last decades with the implementation of a protocol combining neoadjuvant chemoradiation and orthotopic liver transplantation (OLT) for the treatment of perihilar CCA, within specific criteria. Excellent results have been achieved particularly for PSC patients with this cancer, who seem to benefit the most from this treatment, having converted this into an accepted indication for transplantation and the standard of care in several experienced centres. Intrahepatic CCA as an indication for OLT remains controversial and has not been accepted given disappointing previous results. However, as recent studies have shown favourable outcomes in early

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intrahepatic CCA, it may be that under defined criteria, OLT may play a more prominent role in the future. Distal CCA in the context of PSC requires aggressive surgical treatment with curative intent, when feasible. This review provides insight about particular features of CCA in the setting of PSC, with a main focus on its incidence, considerations relating to its anatomical location and implications to treatment and outcomes, through the viewpoint of historical evolution of management, and future perspectives.

Key Words: Cholangiocarcinoma; Primary sclerosing cholangitis; Liver resection; Liver transplantation; Neoadjuvant therapy; Adjuvant therapy

Core Tip: Cholangiocarcinoma (CCA) in primary sclerosing cholangitis (PSC) has become the leading cause of death. Major hepatic resection is commonly not possible in PSC patients to treat CCA, but overwhelming progress with excellent results in the last two decades has established an increasing role of protocolised combination of neoadjuvant chemoradiation and orthotopic liver transplantation. We review in detail, the incidence, as well as aspects of treatment and outcomes according to the different anatomical locations of CCA in PSC, through the viewpoint of historical evolution of treatment paradigms.

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INTRODUCTION

Cholangiocarcinoma (CCA) is a highly malignant and commonly fatal cancer originating from the bile ducts[1]. Three decades ago, the association between primary sclerosing cholangitis (PSC) and CCA was not clear and the question remained as to whether PSC is a premalignant condition[2]. Towards the end of the last century, the premalignant nature of PSC had been ascertained[3]. CCA is the most common malignancy in PSC patients and a major cause of mortality, accounting for 24%-58% of deaths[4-8]. Effective management options are known to be limited[9]. When CCA is diagnosed early, the prognosis appears to be better. However, patients with CCA are frequently diagnosed at an advanced stage, when surgical options are no longer available[7,9-12]. This appears to be the case for more than 50% of PSC-associated CCAs[13-15]. Different locations of CCA along the biliary tree have direct implications to treatment and outcomes, and this is particularly applicable in PSC patients who have distinct features in this regard, dictating different approaches and resulting in partly different outcomes compared to the general population. This review provides insight about various aspects of CCA in the setting of PSC, with a main focus on its incidence, particular considerations relating to its anatomical location and implications to treatment and outcomes, through the viewpoint of historical evolution of management, and future perspectives.

INCIDENCE AND PREVALENCE

PSC is an immune-mediated chronic cholestatic liver disease characterised by chronic inflammation, patchy peribiliary fibrosis causing regional cholestasis and damage to the intra- and/or the extrahepatic bile ducts, which leads to multifocal bile duct stricturing and liver fibrosis[16-18]. The disease is generally progressive and can eventually result in liver cirrhosis and the related complications[19-22]. PSC is considered a rare disease, with an estimated prevalence of around 1 per 10000, which

appears to be increasing over time, and an increasing geographical gradient from South-East towards North-West. The incidence of the disease, in population-based studies, ranges between 0.4 and 2.0 per 100000 person-years in Northern Europe and the United States[23-31]. PSC is more common and usually more severe in male sex (male to female ratio of approximately 2:1), and the mean age at diagnosis is 32-41 years[19,25,27,32,33]. Up to 80% of PSC patients have concomitant inflammatory bowel disease (IBD), in the majority of cases ulcerative colitis (UC)[23]. Patients affected by concomitant Crohn's disease seem to have a better prognosis compared to those with UC[32]. In 6%-16% of PSC patients, only the small intrahepatic bile ducts are affected by the disease. This variant is called small duct PSC and is characterised by milder disease course and better prognosis, but may eventually progress towards large duct disease, in about 20-25% of cases[34-36]. The natural history of PSC is variable and unpredictable; the disease may present with a longstanding indolent course or have a more aggressive and rapidly progressive phenotype[22]. Unfortunately, no effective medical treatment has been identified so far[37], and orthotopic liver transplantation (OLT) remains the only available curative option for these patients[33]. Reported mean time from diagnosis to death or OLT differs between population-based studies and transplant centre cohorts, and ranges between 10 and 22 years[19,23,27,31,38,39]. Furthermore, the disease recurs after OLT in up to 47% of cases[40,41].

PSC patients have a well-established increased risk of developing malignancy, in particular CCA, colorectal cancer, hepatocellular carcinoma, gallbladder cancer, and pancreatic cancer[42-47]. While this risk is double compared to the general population, for primary hepatobiliary cancer, in particular, is as higher as 40 times[48]. In the largest multicentre PSC cohort, which included subjects from European and American centres, hepatobiliary malignancy was diagnosed in 10.1% of cases[32]. Lower prevalence rates have been reported in Southern Europe and Asia (3.3%-5.7%)[45,49-51].

CCA is the second most common malignancy in the liver after hepatocellular carcinoma (HCC) and has generally a poor prognosis[52], with a median survival of less than 24 mo[53,54]. Its incidence varies between geographical areas, with 0.35-3.36 cases per 100000 a year in the western countries, where PSC is the leading risk factor [42,55-58], and increases dramatically in Asian endemic regions, such as Thailand, where the incidence is 50-113 per 100000 person-years[59-62]. The incidence of CCA appears to be increasing over time[52,61,63-68]. Most patients have advanced-stage disease at presentation[61], which limits the therapeutic options[69].

CCA represents a major threat to PSC patients, who have a reported 400-fold increased lifetime risk compared to the general population[23,70]. In fact, being the most common malignancy in PSC, it occurs in 6-20% of cases, has a generally poor prognosis and a very high rate of mortality at 1 year (up to 80%)[69], representing the most frequent cause of death in PSC patients[19,23,32,43,71]. The incidence of PSC-associated CCA ranges from 0.5 to 1.5 per 100 person-years, and varies between geographical areas[7,33,42,55,72]. CCA is detected within the first year of PSC diagnosis in approximately one third of cases[19,33,73], but in a European multicentre study of almost 400 PSC patients followed up for a median of 18 years, 50% of CCAs were diagnosed within the first year[56]. CCA can also occur late in the course of the disease, although the risk reduces 2-10 years after the diagnosis of PSC (7%)[74]. The estimated cumulative risk at 5 and 10 years from diagnosis is 7% and 8-11%, respectively[7]. After the first year of PSC diagnosis, the estimated yearly incidence of CCA is 0.5%-1.5%, the prevalence 6-13%, and the lifetime risk reaches 20%[22,42,55,56,75]. The reported prevalence of CCA seems to be higher in liver transplant series than in population-based studies, suggesting that patients with more advanced disease may have a higher risk of developing CCA[42]. In up to 30%-42% of cases, PSC-associated CCA is found incidentally, on autopsy or liver explants following OLT[76,77]. CCA may even develop de novo in the liver following OLT[78-80], or in the native common bile duct (CBD), when this has been preserved[4,81,82]. CCA occurs in up to 20% of patients with post-transplant recurrent PSC[83,84].

Studies reporting on incidence and prevalence of CCA in PSC patients are shown in Table 1. The geographical distribution of incidence risk of CCA in PSC patients, based on available studies, is depicted in Figure 1.

RISK FACTORS

Several risk factors have been reported to be potentially associated with CCA in PSC

Table 1 Studies on the incidence and prevalence of primary sclerosing cholangitis-associated cholangiocarcinoma

Ref.	Year	Country	No of PSC patients	Median/mean age (yr) of PSC patients	Percentage of male PSC patients	No of PSC patients with CCA[1]	Incidence of PSC-associated CCA (%)	Prevalence of PSC-associated CCA (%)	Median/mean age (yr) of the CCA cohort	Percentage of males in the CCA cohort	Study design
Stieber *et al*[171]	1989	United States	111	NS	NS	10	N/A	9	45	70	Retrospective (Tx cohort)
Broome *et al*[39]	1996	Sweden	305	39	63.9	24	1.5	7.8	NS	NS	Retrospective
Goss *et al*[173]	1997	United States	127	47	68.5	14	3.4	11	NS	NS	Retrospective (Tx cohort)
Ahrendt *et al*[8]	1999	United States	139	47	64.2	25	N/A	18	46	48	Retrospective
Björnsson *et al*[36]	2002	Sweden	260	41	72.3	28	1.2	10.8	NS	NS	Retrospective
Ponsioen *et al*[38]	2002	Netherlands	174	40	60.3	18	1.6	10.3	NS	NS	Retrospective
Brandsaeter *et al*[77]	2004	Scandinavian	255[a]	45	68.6	37	N/A	14.5	NS	Male preponderance	Multicentre retrospective
Burak *et al*[42]	2004	United States	161	41	67.7	11	0.6	6.8	NS	NS	Retrospective
Tischendorf *et al*[19]	2007	Germany	273	32	71.4	36	2.1	13.2	NS	NS	Retrospective
Bjornsson *et al*[35]	2008	International	176	38	55.1	20	1.1	11.4	NS	NS	Retrospective
Tanaka *et al*[92]	2008	Japan	391	50	58[b]	14	0.7	3.6	NS	57.1	Retrospective
Charatcharoenwitthaya *et al*[136]	2008	United States	230	42	59.6	23	1.2	10	51	73.9	Retrospective
Morris *et al*[87]	2008	United Kingdom	370	49	71.6	48	2.7	13	50	75	Retrospective
Claessen *et al*[74]	2009	Netherlands	211	35	67.8	15	0.8	7.1	NS	NS	Retrospective
Ataseven *et al*[51]	2009	Turkey	35	42	60	2	1.2	5.7	72	0	Retrospective
Chapman *et al*[5]	2012	United Kingdom	128	49	63.2	21	1.7	16.4	NS	67	Retrospective
de Valle *et al*[88]	2012	Sweden	199	39	71.3	17	1.3	8.5	NS	NS	Retrospective
Fevery *et al*[43]	2012	Belgium	200	39	59	13	0.5	6.5	41	46.1	Retrospective
Ngu *et al*[46]	2012	New Zealand	79	49	62	7	1.1	8.9	NS	NS	Retrospective + Prospective
Boonstra *et al*[33]	2013	Netherlands	590	39	63.5	41	0.9	6.9	47	NS	Retrospective
Geramizadeh *et al*[78]	2015	Iran	181	37	67.2	16	N/A	8.8	49	75	Retrospective

											(Tx cohort)
Liang *et al*[58]	2017	United Kingdom	244	57	63.5	10	0.8	4.1	NS	NS	Retrospective
Liu *et al*[91]	2017	Australia	208	41	60.5	16	0.7	7.7	NS	NS	Retrospective
Weismuller *et al*[32]	2017	International	7121	39	65.4	594	1.1	8.3	NS	NS	Retrospective
Saffioti *et al*[47]	2018	United Kingdom	281	48	64	13	N/A	4.6	NS	NS	Retrospective
Ali *et al*[158]	2018	United States	830	NS	NS	56	N/A	6.7	55	66	Retrospective
Freeman *et al*[21]	2019	Australia	39	45	69.2	3	1.0	7.7	NS	100	Retrospective

[1]Incidences have been estimated by number of cholangiocarcinoma (CCA)/total person years, or number of CCA/[number of primary sclerosing cholangitis (PSC) × mean or median follow-up time (yr)].
[a]listed for transplantation.
[b]available data for 345 patients. Appropriate calculations were made where required. No studies with exclusively small duct PSC or studies in paediatric cohorts were included. PSA: Primary sclerosing cholangitis; CCA: Cholangiocarcinoma; N/A: Not applicable (where estimation is not feasible); NS: No significance; Tx: Transplant.

patients. The association of ageing with biliary tract cancer is well established[59,85]. With a median age at diagnosis of 38-54 years, PSC patients develop CCA at much younger age (20 years earlier, on average) than non-PSC patients. CCA in the non-PSC population (de novo) is commonly diagnosed in the seventh decade of life[43,86,87].

In the 7210-patient cohort from the international PSC Study Group, the incidence of CCA in patients younger than 20 years was 1.2 per 100 patient-years, and increased gradually for each decade of age, reaching 21.0 per 100 patient-years for patients older than 60[32]. On the other hand, age at PSC diagnosis[88] is an important risk factor for the development of CCA[32], while the duration of PSC does not appear to be relevant [42].

PSC-associated CCA is much rarer in children, with a reported incidence between 0.2 and 1.2%[89,90], as compared to 0.6%-2.7% in adults[35,36,38,42,43,87,91]. Male sex has also been reported as a determinant of risk for CCA[32,43,87,92]. Patients with small-duct PSC have a much lower risk of CCA, unless they progress to large-duct disease. The incidence in this group ranges between 0.6% and 1.7%[32,35,42,93,94].

In PSC patients, the presence of cirrhosis is not necessary for the development of CCA[4]. In fact, the majority of patients with PSC have not developed cirrhosis at the time of CCA diagnosis[8,69,86]. Furthermore, cirrhosis in patients with PSC has been reported to be associated with the absence of CCA[95]. On the other hand, the presence of concomitant liver diseases, such as HCV or HBV infection, may further increase the risk[7].

The presence of dominant strictures, increases the risk of biliary malignancy significantly[5] (estimated risk of any dominant stricture harbouring a CCA of about 5%[96]). In fact, most of PSC-associated CCAs develop from a dominant stricture (defined as a stricture with a diameter < 1.5 mm in the CBD or < 1.0 mm in the

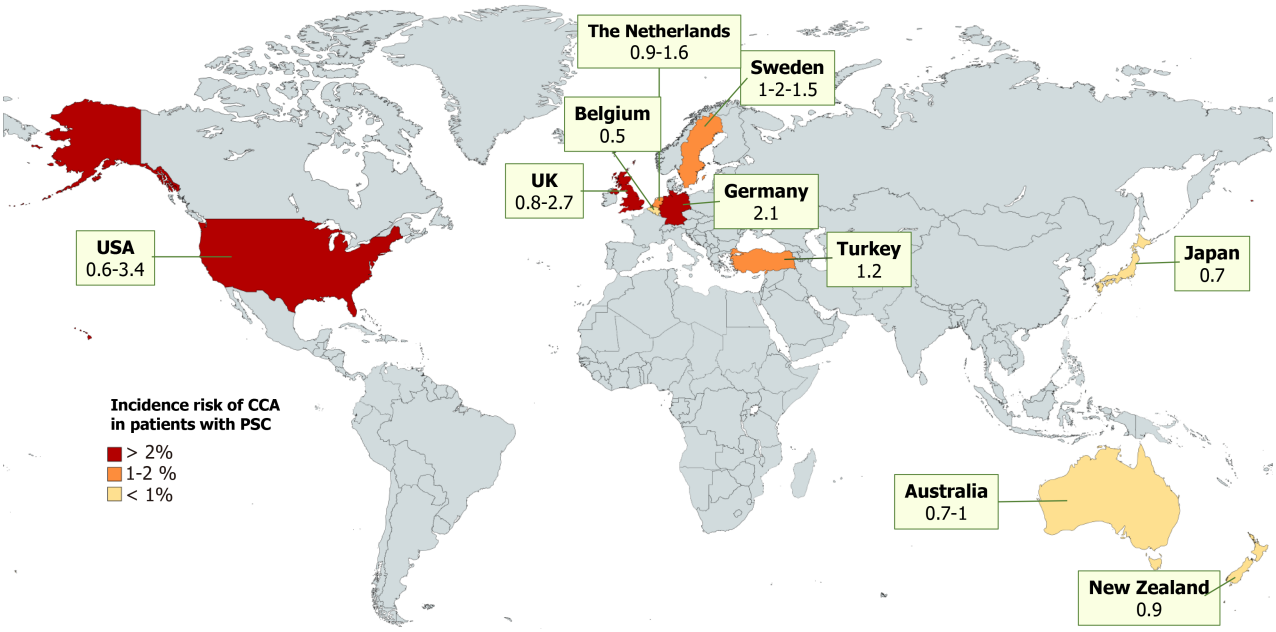

Figure 1 Geographical distribution of incidence risk of cholangiocarcinoma in primary sclerosing cholangitis patients, based on available studies[5,8,19,21,33,36,38,39,42,43,46,47,51,58,74,87,88,91,92,136,158,171,173].

intrahepatic ducts[97])[7,22,98]. Dominant strictures of the extrahepatic bile ducts are the most frequent (about 80% of cases) and associated with a higher mortality[5,45,86,99]. In a European single centre study of 128 PSC patients with a mean follow-up of 9.8 years, more than a 25% of patients with a dominant stricture developed CCA[5].

The impact of IBD severity on the risk of CCA in PSC remains controversial[39,42,56,100-103]. The largest multicentre retrospective study on PSC, with more than 20 years follow-up, revealed a CCA incidence of 1.25 (95%CI: 0.90-1.60) per 100 patient-years among patients with large-duct PSC. An increased risk of hepatobiliary malignancy (mainly CCA) was noted in PSC patients with concomitant UC. The risk in patients with Crohn's disease, instead, did not differ from that in patients without IBD [32]. A prolonged duration of concomitant IBD, as well as a history of colonic dysplasia or carcinoma, have been related to an increased risk of CCA[100].

Smoking and excessive alcohol intake have also been suggested as additional risk factors[76].

PATHOGENESIS

Although the pathogenetic mechanisms leading to the development of PSC-associated CCA are largely unknown, its origin is likely multifactorial and involves a combination of genetic background, chronic inflammation and immunological dysfunction[7,104,105]. Substantial differences exist in the molecular characteristics and biology of different anatomical subtypes of CCA[53]. It has been demonstrated that patients with chronic biliary disease have an impaired secretion of the potentially toxic bile acids, as well as a reduced efficacy of some protective mechanisms, such as the bicarbonate umbrella[106,107]. Episodes of bacterial cholangitis stimulate the release of nitric oxide and other reactive oxidant species[108], as well as the activation of the epidermal growth factor receptor (EGFR) and, subsequently, pathways such as cyclooxygenase-2 and K-ras, which are involved in the carcinogenesis process[6,109]. Moreover, cholestasis and, in particular, dominant biliary strictures, favour the accumulation of toxic bile acids in the biliary tree and subsequent prolonged exposure of cholangiocytes to bile, therefore promoting chronic inflammation, reduction of the biliary pH and damage to the cholangiocytic lining of the bile ducts, with subsequent DNA damage, metaplasia and low-grade dysplasia[6,7,108]. The persistence of those stimuli may lead to progression to high-grade dysplasia and cancer. The reduction of the biliary pH also favours apoptosis[110]. The fact that metaplasia and dysplasia of cholangiocytes are more frequently identified in PSC livers with rather than in those without CCA seems to support this hypothesis[111]. Several genetic and epigenetic

factors, as well as other molecular mechanisms are also involved and are discussed elsewhere[105,112-114].

ANATOMICAL LOCATION AND MACROSCOPIC MORPHOLOGY OF CCA

CCA can arise from any site along the biliary tract[115], namely, from the left and right hepatic ductal systems, their confluence, the common hepatic duct and its confluence with the cystic duct (CD), or the CBD[116]. In order to better characterise and manage CCA, it is commonly classified into three subtypes according to its anatomical location: (1) Intrahepatic (IHCCA), which is located proximally to the second order branches of the left or right hepatic duct; (2) Perihilar (PHCCA) or Klatskin tumour, which is located between the second order branches of the left or right hepatic duct and the CD confluence; and (3) Distal (DCCA), which is located between the CD confluence and the ampulla of Vater[4,117]. PHCCA is the most common type (50%), followed by DCCA (40%) and IHCCA (10%)[10]. According to its pattern of growth and macroscopic appearance, CCA may present in three different types: Mass-forming (which presents with a mass), periductal-infiltrating (growing along the wall of the bile duct) and intraductal-growing (with intraluminal growth)[117,118]. The mass-forming type is by far the most frequent[118](Figure 2).

LOCATION OF CCA IN PSC PATIENTS

As more than 80% of dominant strictures develop in the extrahepatic ducts, it is not unexpected that most PSC-associated CCAs affect the hilum and CBD[7,22,98,119]. Studies reporting features of PSC-associated CCA by location are very limited and there is marked heterogeneity as regards the various definitions and classifications, which limits the ability of meaningful comparison[4]. The incidence of various locations of PSC-associated CCA is variable among different studies and, while there are series reporting no distal[1,8] or intrahepatic tumours[1,5], other studies conclude that intrahepatic tumours appear to be more frequent in the setting of PSC[4]. Nevertheless, among series with all types of CCA, there seems to be a clear prevalence of PHCAA (57%-76%)[5,6,22], followed by DCCA (20%-43%)[5,6] and IHCCA (15%)[6].

DIAGNOSIS

In PSC patients, CCA may present as clinical and biochemical deterioration and signs of obstruction or progressive biliary stricturing (*e.g.*, weight loss, persistent abdominal pain, intractable pruritus, fever, night sweats, worsening of the cholestatic enzymes compared to the baseline, jaundice) or, as previously mentioned, as an incidental finding at surgery or transplantation, or during endoscopic or radiological investigations/follow-up[76]. As the symptoms often overlap with those of PSC itself, the diagnosis of CCA can be particularly challenging in this setting and a high index of suspicion and routine surveillance are required to increase the chance of CCA diagnosis[120]. CCA should be suspected in all PSC patients with a sudden clinical and/or biochemical deterioration or with a new dominant stricture[97]. However, at the time of the diagnosis of PSC, 15%-20% of patients present with biliary strictures, which can be malignant in 10%-15% of the cases[121].

In a cohort of 370 PSC patients followed up at a British tertiary centre during the period 1981-2004, 48 patients (13%) were diagnosed with a CCA within a median time of 0.51 mo from the initial presentation. Among these, 29% had inoperable tumours at diagnosis, 19% presented as dominant strictures in the context of follow-up investigations for PSC, 10% during transplant work-up and 10% during surveillance whilst on the transplant waiting list. In 27% of cases, CCA was an incidental finding in the liver explant, and in one case an incidental finding at cholecystectomy (tumour arising from the CD)[87]. At the time of CCA diagnosis, no specific clinical or biochemical characteristic could distinguish patients potentially eligible for radical treatment from those with more advanced disease. Accordingly, all newly-diagnosed PSC patients should be screened for CCA[33], especially as early detection of CCA is associated with significantly better outcomes.

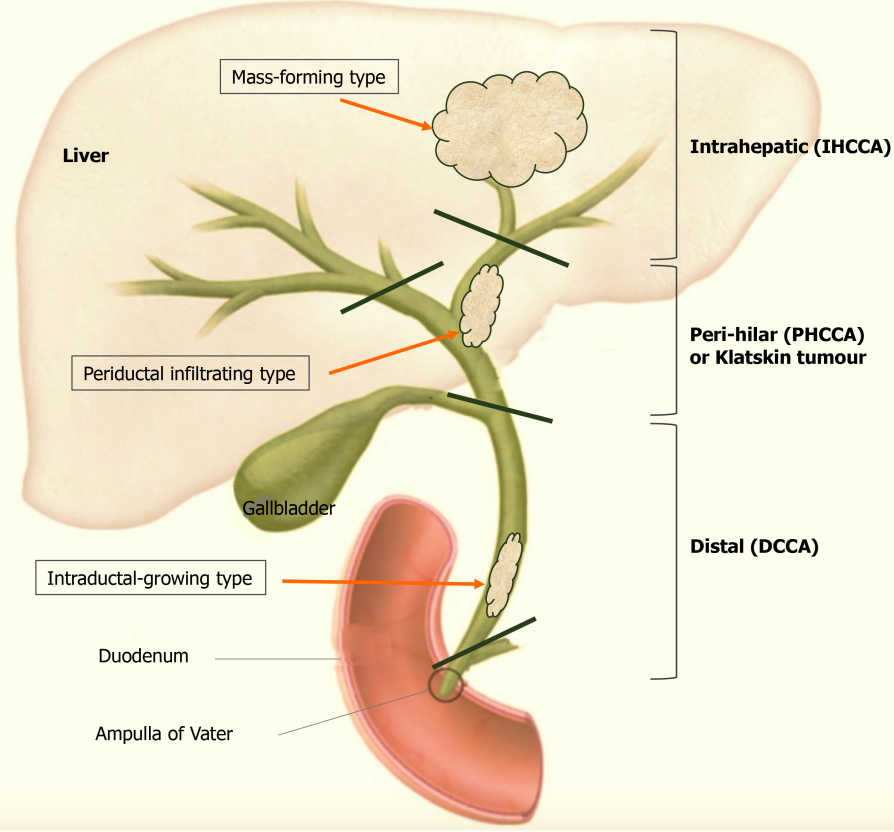

Figure 2 Types of cholangiocarcinoma according to anatomical location along the biliary tree and macroscopic morphology/pattern of growth. Thick black lines delimit the tree anatomical sections of the biliary tree corresponding to the anatomical locations of cholangiocarcinoma. IHCCA: Intrahepatic cholangiocarcinoma; PHCCA: Perihilar cholangiocarcinoma; DCCA: Distal cholangiocarcinoma.

Abnormal liver biochemistry, and in particular an elevation of ALP, GGT, bilirubin and/or transaminases, can be an early indicator of CCA in PSC[7]. A normalisation of the ALP has been reported to be associated with a reduced risk of developing CCA, in some studies[122,123], but not in others[124]. Other currently used biomarkers, such as serum carbohydrate antigen (CA) 19-9 (the most widely used tumour marker in patients with PSC) and carcinoembryonic antigen (CEA), have low positive predictive value and are inadequate for CCA surveillance in PSC patients[15,70,119]. CA 19-9 has limited utility in the diagnosis of CCA both in PSC and non-PSC patients. In fact, it lacks specificity for the diagnosis of CCA or other biliary tract cancers, it can be elevated in other malignancies and is not adequately synthesised in some individuals, depending on their fucosyltransferase 2 and 3 genotypes. Furthermore, CA 19-9 can be raised in benign biliary obstruction or in the presence of bacterial cholangitis, both not uncommon conditions in PSC[61]. A CA 19-9 cut-off of 129 U/mL (corresponding to 3 times the upper limit of normal) has been reported to have a 79% sensitivity and a 99% specificity by Levy *et al*[125], although the adjusted positive predictive value (PPV) was only 57%. However, in the study conducted at the Mayo Clinic by Sinakos *et al* [95], more than one third of PSC patients with a CA 19-9 higher than 129 U/mL, did not have CCA. The presence of cirrhosis and a total bilirubin lower than 34 μmol/L (2 mg/dL) at the time of initial detection of elevated CA 19-9 were associated with the absence of CCA during follow-up. Other authors advocated the utility of the ratio of the fold-increase of CA19-9 to the fold-increase of total bilirubin for the diagnosis of CCA[126].

CEA has a lower performance than CA 19-9 for the diagnosis of CCA, with levels > 5 ng/mL having a sensitivity of 33%-68% and specificity of 82%-89%[15].

The pancreatic autoantibody against glycoprotein 2 (anti-GP2) has been recently proposed as a novel prognostic/diagnostic tool for PSC-associated CCA. In two independent cohorts, anti-GP2 IgA was associated with a more severe PSC phenotype, reduced transplantation-free survival and a high frequency of CCA[127]. A combination of biomarkers containing pyruvate kinase M2, cytokeratin 19 fragment, mucin 5AC, and GGT allowed to distinguish CCA from PSC with a sensitivity of 82% and a specificity of 90%[128]. Proteomic analyses on serum extracellular vesicles[129],

metabolomics studies analysing changes in serum concentrations of certain metabolites potentially useful for the differentiation between CCA and PSC[130] and, more recently, studies of micro-RNA expression[131] have also been performed[120]. However, the utility of these markers for the differentiation of PSC and PSC-associated CCA requires further validation, in particular as the above mentioned studies included patients without PSC[120]. A number of bile and urine biomarkers are also under current evaluation and have shown, alone or in combination, good sensitivity and specificity profile for CCA, although most of those studies have been done in heterogeneous groups of patients and did not explicitly focus on the difference between PSC and PSC-associated CCA, and also included patients with *de novo* CCA[132]. It has been recently shown that the Enhanced Liver Fibrosis (ELF) score, a serum biomarker of fibrosis that has shown prognostic utility in PSC, is increased in patients with CCA compared with those without CCA[133]. In a retrospective study comparing patients with PSC alone, PSC and CCA, and CCA alone, ELF score was significantly higher in the presence of CCA, regardless of PSC. In the subgroup of patients affected by PSC, an ELF score ≥ 9.8 was found to be an independent predictor of CCA[134].

Imaging modalities including abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) are used to assess and characterise dominant strictures in PSC[135]. Appearances of CCA on imaging may be that of a mass lesion (in particular for IHCCA), hilar stricture (PHCCA) or distal bile duct stricture (DCCA), with or without biliary duct dilatation and/or extrahepatic metastases[33]. MRI and CT may potentially detect early features of CCA in PSC, although they are often unable to distinguish inflammatory, benign and malignant lesions[33]. US, CT, and MRI have all shown elevated specificity (all 100%) but low sensitivity (10%, 25%, and 32%, respectively), as well as, alone or even in combination with serum CA 19-9, suboptimal PPV for the diagnosis of CCA[136]. Also 18F-fluorodeoxyglucose positron emission tomography, which is useful in identifying lymph node involvement, presence of distant metastases, and postoperative disease recurrence[137], is often unable to definitively confirm the neoplastic nature of a dominant stricture, and histological confirmation is required in the majority of cases, with the exception of biliary strictures associated with a hilar mass, hypertrophy-atrophy complex and vascular encasement, which is a rather rare presentation[114].

Endoscopic retrograde cholangiopancreatography (ERCP) is complementary to non-invasive imaging modalities and recommended for the evaluation of suspected significant strictures identified at MRCP and endoscopic treatment in symptomatic patients who will likely benefit from the procedure[97]. ERCP allows to obtain histological and cytological samples required for the diagnosis of biliary dysplasia or CCA. CCA has highly desmoplastic, paucicellular nature, which limits the sensitivity of cytological and pathological diagnostic approaches[53]. Accordingly, brush cytology obtained with ERCP has a high specificity (95%-99%), but relatively low sensitivity (43%-67%)[138-140]. Similarly, histology obtained *via* fluoroscopy-guided intraductal biopsies at ERCP has poor outcomes, even when combined with brush cytology, as shown in a recent meta-analysis[140]. Endoscopic ultrasound with fine needle aspiration demonstrated a good diagnostic performance in establishing the diagnosis of CCA in patients with negative or unavailable brush cytology[140]. The addition of fluorescent in situ hybridisation (FISH) for detection CCA in PSC has an increased sensitivity (up to 68%), compared to ERCP and brush cytology, but significantly reduces the specificity (70%), and has therefore uncertain utility[141]. In a retrospective study of 102 patients with PSC, with an equivocal brush cytology, the combination of elevated CA 19-9 (≥ 129 U/mL) and polysomy on FISH was found to be predictive of biliary tract cancer at 2 years (HR 10.92; $P < 0.001$)[142]. Peroral cholangioscopy allows direct visualization of extrahepatic bile duct strictures and offers more defined views compared to fiberoptic cholangioscopy. It has been shown to have a higher diagnostic accuracy compared to ERCP with biopsy/brushing, but has not been evaluated specifically in PSC-associated CCA[97]. SpyGlass single-operator cholangioscopy has been prospectively evaluated in a relatively small Swedish PSC cohort[143], but its value in the diagnosis of indeterminate biliary strictures in PSC requires further evaluation. In this study of 47 PSC patients with a total of 64 biliary strictures, SpyGlass allowed targeted biopsies from otherwise inaccessible strictures. However, despite the high percentage of technical success (96%) and the adequacy of the samples obtained both with brushing cytology (98%) and mini-forceps biopsies (95%), the procedure showed high specificity (100%) but low sensitivity (33%)[143].

In summary, the diagnosis of CCA requires a combination of clinical, radiological and histological and/or biochemical markers[114]. While patients with a newly diagnosed PSC should be screened and regularly followed-up for CCA, in particular during the first two years, there is no validated approach for further routine follow-up. On the basis of test properties, availability and costs, 6-12 monthly assessment with a combination of serum CA 19-9 (cut-off 20 U/mL) and abdominal imaging with US or MRI has been proposed as sensible strategy for the screening/surveillance of CCA in PSC[33,45,135]. ERCP with biliary brush cytology and endobiliary biopsies (and FISH, if available) should be performed as part of the initial investigation for the diagnosis and staging of suspected PSC-associated CCA[97].

CHEMOPREVENTION

To date, there is no effective pharmacological agent recommended for the prevention of CCA. The role of ursodeoxycholic acid in preventing clinical outcomes in PSC has been evaluated in three randomised placebo-controlled trials, which all failed to prove significantly beneficial effects on OLT-free survival or development of CCA[144-147]. Furthermore, a recent meta-analysis of randomised clinical trials of pharmacological treatments in PSC, found no significant difference between any of the interventions and placebo in reducing the incidence proportion of CCA[37].

TREATMENT AND OUTCOMES

General considerations

PSC-associated CCA is not diagnosed until intended OLT or at autopsy, in up to 40% of patients[10]. Surgery is the only potentially curative treatment for all anatomical subtypes of CCA, either in the form or resection or OLT with or without neoadjuvant or adjuvant therapy, which is mainly offered in highly selected patients with early stage PHCCA[10,11,98,117,148]. Overall, the prognosis of CCA is dismal, with an overall survival of 12-16 mo, without surgical treatment[10,149], while long-term survival is rare with medical therapy alone, owing to the paucity of effective medical and locoregional therapies[12,150]. In the setting of PSC, historically and in the pre-transplant era, most patients succumbed to complications of cirrhosis, while most recently CCA appears to be the leading cause of deaths for the general PSC population (58%)[22,151], as well as for those on a transplant waiting list[22]. As such, it has been strongly recommended that PSC patients with suspected CCA should be promptly referred to the appropriate regional hepatopancreatobiliary (HPB) multidisciplinary cancer meeting or liver transplant centre for review[22].

Until the beginning of this century, particularly for PSC patients with CCA as opposed to those without, survival was poor regardless of OLT[152]. However, in the following decade, the results of surgical resection and OLT for CCA, recorded continuous improvement[116]. OLT has gained momentum in the treatment of malignant disease[153] and the current therapeutic approaches which combine principles of surgical oncology and transplant surgery outline the concept of "Transplant Oncology", which has the purpose of treating or even curing complex malignant disease in a multidisciplinary setting[154]. Particular considerations exist in the context of organ scarcity and in need of an ethical distribution of graft resources [11,153,154]. Many authors advocate that any potential indication for OLT should be associated with equal survival outcomes as all other accepted indications. Commonly, a 50% 5-year survival is considered acceptable and is currently the accepted threshold in most centres worldwide, for patients undergoing OLT for cancer[11].

CCA is a complex and aggressive disease and, particularly in the context of significant underlying disease as is PSC, warrants collaboration of specialists from different fields, including HPB and liver transplant surgeons, radiologists, hepatologists, medical oncologists, radiation oncologists, interventional radiologists, gastroenterologists, endoscopists and pathologists[150,155].

The notion of resectability of CCA in PSC

Despite resectional surgery offering a chance for cure in suitable patients with CCA, this is usually not possible in patients with PSC, particularly those with PHCCA or IHCCA[22]. While surgical exploration was generally advised in this setting a few decades ago in patients with favourable oncological features[8], this concept has been

largely abandoned in the recent years, for a number of reasons. Namely, PSC is commonly associated with complex biliary strictures, coexistent advanced parenchymal liver disease with extensive periductal fibrosis and hepatic dysfunction, while CCA in this setting has a predilection for skip cancer lesions, compounded by the biliary field defect which makes metachronous lesions a common manifestation[9,12,22,117,154-156]. PSC-associated CCA is not uncommonly multifocal[12,155,157]. A recent retrospective study found that among 49 patients with PSC-associated CCA and available preoperative liver biopsy, 92% had histological stage III-IV at the time of OLT or resection[158]. Additionally, as PSC is considered a premalignant condition, a high-risk of CCA recurrence remains in case of liver resection (LR) for PHCCA or IHCCA[14]. Furthermore, these tumours are also usually technically unresectable owing to the local extent[119]. Moreover, in some cases the presence of decompensated cirrhosis or significant portal hypertension is sufficiently prohibitive[11,159]. Most patients with IHCCA or PHCCA require major or extended LR, while the recommended future LR (FLR) is at least 25% of liver volume for patients with normal parenchyma, and 30%-40% on grounds of chronic liver disease and in the absence of portal hypertension[118,159]. Owing to the above, patients with PSC are usually poor candidates for LR even in the context of apparently early disease[12]. From a functional point of view, the underlying liver disease impedes the ability of postoperative regeneration, resulting in poor tolerance of extensive surgical resection and a high-risk of liver failure, while from a technical perspective the overall features may make the acquisition of clear surgical margins (R0) extremely difficult[157,159]. At present, for the majority of specialist centres, particularly in the transplant setting, PSC-associated PHCCA or IHCCA equals unresectable disease and is directly precluded from hepatic resection[5,9,12,14,22,149,160,161]. PSC-associated CCA was included in the original indications for neoadjuvant chemoradiotherapy and OLT, described by the Mayo Clinic[162], and has remained among the inclusion criteria of this protocol ever since[118]. Notably, the ongoing prospective, randomised, multicenter "TRANSPHILL" study which aims to compare OLT with neoadjuvant radiochemotherapy *vs* standard of care liver and bile duct resection for PHCCA, lists PSC among the exclusion criteria[163]. Even though LRs in the context of PSC are largely discouraged, some authors accept that for a subset of patients who may present with surgically resectable CCA in the absence of advanced hepatic fibrosis and candidacy for transplant, an attempt at surgical resection should be considered[4,150,154,156]. Furthermore, in 2008, a retrospective study from Birmingham in the UK (where CCA is still not an accepted indication for OLT[22]), reported good outcomes with 7 major LRs and 1 Local excision of the extrahepatic biliary tree, for PSC-associated CCA. The authors advocated that surgical treatment at an early stage offers good long-term outcomes, hence, early detection might increase the number of eligible patients before they develop end-stage liver disease and become unsuitable for resection. In their experience, early surgical treatment was the best means of increasing survival[87].

IHCCA

Resection

IHCCA has recorded an increasing incidence worldwide, but despite several advances and efforts to develop effective treatment strategies, its prognosis remains poor[159]. Its resectability varies from 18% to 70%, while postoperative 5-year survival is 20%-40%[159,164]. After diagnosis of IHCCA the median survival is 12-37.4 mo[164]. Among surgical candidates, at the time of intended resection, up to 27% are diagnosed with metastatic disease[164]. In general terms, R0 LR is the only established and widely accepted potentially curative treatment option for IHCCA, however, this materialises in less than 30% of cases due to a great proportion of advanced stage and irresectability at diagnosis[11,98,159]. Nevertheless, this is the mainstay of treatment and should be offered when feasible[153,159]. R0 resection has been reported to be associated with a median overall survival of 80 mo, in some series[150]. More than 70% of cases require major LR to achieve clear margins[118,159]. Pre-operative portal vein embolization (PVE) has appeared to be beneficial in suitable cases[118]. Lymphadenectomy with a minimum of 6 harvested nodes is increasingly advised as adequate, due to presence of microscopic involvement in more than 40% of cases[159]. However, on a background of cirrhosis, lymphadenectomy is associated with a complication rate of up to 71%, thus limiting its wider applicability[159]. Neoadjuvant systemic or locoregional therapies may be used in locally advanced IHCCA, with a

view to downstaging the disease to achieve eligibility for surgical management[159]. The probability of cure by means of LR has been estimated at 9.7%, while 95% certainty of cure can only be reached 9.5 years postoperatively[159]. Median disease-free survival following hepatectomy is about 26 mo, while recurrence will develop in 60%-65% of patients[11]. However, owing to considerations mentioned earlier, although LR may be curative, in the setting of PSC this is largely discouraged. As such, reported data regarding treatment of PSC-associated CCA with LR are extremely rare. A retrospective analysis from the Mayo Clinic over a 20-year period, reported 19 cases of PSC-associated IHCCA, 7 of which were treated with LR, and two of them received adjuvant chemotherapy. The remaining 12 patients were not surgical candidates because of advanced or metastatic disease, and 5 of them received palliative treatment. Three patients developed recurrence at a median of 4 mo post-diagnosis. The overall 5-year survival for all 19 patients was 12.1%[158]. In the experience of Birmingham with 8 resections for PSC-associated CCA, 3 patients had IHCCA and underwent right hepatectomy (n = 2) or left hepatectomy (n = 1). Six out of 8 resected patients were alive 5-years postoperatively, with a reported median survival of 52.8 mo[87]. In a retrospective study of 25 patients with PSC-associated CCA from the John Hopkins (US), only one patient was treated with left hepatectomy for IHCCA, without mortality[8]. In a US multicentre study of 26 patients with PSC-associated CCA, a single patient was treated with right hepatectomy and was alive 26 mo postoperatively [152]. For the very few reported cases, no operation-related morbidity and mortality have been described and survival data specifically for patients who underwent LR for IHCCA are extremely scarce. In the absence of alternative options, patients with PSC-associated IHCCA may be evaluated for potential LR if the liver disease is not too advanced[98]. This may be particularly applicable when a limited resection is required and under the understanding that hepatic resection remains, to date, the treatment of choice particularly for IHCCA smaller than 2 cm in non-cirrhotic livers[9].

OLT

Even though OLT appeared to be a promising treatment offering a wider surgical margin and a chance for cure of the underlying liver disease, the initial experience with IHCCA showed very poor outcomes, which led to abandonment of this approach [11]. Until the late 2000s, the available published results demonstrated a 5-year actuarial survival between 10 and 18%[11]. As such, IHCCA is considered a formal contraindication for OLT in most centres worldwide[11,118]. In 2004, a retrospective multicenter study of 23 patients who underwent OLT for IHCCA reported an overall 5-year survival of 42%, while in 10 cases IHCCA was diagnosed incidentally in the explant[165]. Subsequently, a series of 10 patients who underwent OLT for known IHCCA showed a 5-year survival of 33%[166]. In 2011, Sapisochin *et al*[167] reported that in patients with a preoperative diagnosis of HCC who underwent OLT and were ultimately diagnosed with IHCCA or mixed hepato-CCA from the explant pathology, the 5-year survival was 47%. Despite encouragingly improved outcomes from these studies, the 5-year survival rates fell short of what is considered acceptable for OLT in the context of organ scarcity[153]. Moreover, many publications showed high rates of recurrence (60%-90%), which was the main cause of death[11]. Based on this, in 2014, the International Liver Cancer Association (ILCA) reported that OLT is not recommended for IHCCA[150]. In the same year, a Spanish consortium reported a series of 29 patients with IHCCA in explant pathology, in which patients with "very early" IHCCA (≤ 2cm) had a 5-year recurrence-free survival of 73%, while patients with either tumours >2cm or multifocal disease had a 40% 5-year overall survival [168]. To validate these promising results suggesting that patients with "very early" IHCCA should possibly be considered as a formal indication for OLT, in 2016, Sapisochin *et al*[167] conducted a multicentre international study. In a total of 48 patients with exclusively IHCCA on explant pathology, 15 patients with "very early" IHCCA were compared with 33 patients with advanced disease (single tumour > 2 cm or multifocal disease). The 5-year actuarial survival in the "very early" IHCCA group was 65% *vs* 45% in the advanced group. The 5-year cumulative risk of recurrence was 18% *vs* 61%, respectively[169]. These studies showed promising results for early IHCCA, comparable to those in OLT for HCC[159], suggesting it might become an accepted indication for OLT[11,153]. These studies only included patients who were not eligible for LR, and suggested that this potential treatment should only be reserved for this group of patients[153]. However, early IHCCA as an indication for OLT still remains highly controversial[11,117]. In 2018, the group from Houston Methodist and MD Anderson Cancer Center (US) published the first prospective series of patients with IHCCA undergoing OLT after neoadjuvant chemotherapy. Of 21 referred non-cirrhotic patients with locally advanced anatomically unresectable IHCCA, 12 were

accepted and 6 ultimately received OLT. Neoadjuvant chemotherapy consisted of first-line platinum-based regimen and gemcitabine until OLT. OLT was offered after a minimum of 6 mo of radiological response or stability. Adjuvant chemotherapy with capecitabine, gemcitabine, or both, was given in the presence of active disease on explant. The overall survival was 100%, 83.3% and 83.3% at 1, 3 and 5 years post-OLT, respectively. Recurrence-free survival was 50% at 1, 3, and 5 years[170]. These excellent results showed that in patients with liver-confined unresectable advanced IHCCA, who demonstrate a sustained response to neoadjuvant treatment, OLT may be a reasonable option within prospective protocols[118,159]. While this may prove to be a viable strategy in this setting and in early tumours in the context of chronic liver disease[159], more data from clinical trials are needed to fully elucidate its role and define the best tools for prognostication of the outcomes[118,153]. A predictive risk index of recurrence post-OLT for IHCCA highlights the importance of tumour biology over size[9]. Locoregional therapies and molecular profiling are expected to offer better prognostic assessment, patient selection and risk stratification[159]. A paradigm shift for OLT for IHCCA may ultimately become reality as has previously been observed for PHCCA[11,150,154]. In 2020, a consensus statement of an international group of multidisciplinary experts in CCA recommended that OLT is a potentially curative option for IHCCA, and acknowledging the promising reported overall survival, recommended it must be considered for patients with cirrhosis and IHCCA ≤ 2 cm[148]. Importantly, even though all the above considerations appear directly applicable for PSC-associated IHCCA, it has to be noted that there are no studies reporting OLT outcomes specifically for this subgroup of patients.

Incidental CCA in PSC explants

The reported outcomes of OLT with incidental CCA in the explants have been controversial. Moreover, studies reporting outcomes specifically in PSC explants are limited. Early studies reported favourable prognosis in PSC patients with small incidental CCA and negative margins, reaching even an 83% 5-year survival, which was comparable to that in PSC patients without CCA[3,8,171-173]. A better 2-year survival of 55% in case of incidental CCA in PSC patients compared to 29% in known PSC-associated CCA, was also reported[174]. Other studies reported a significant decrease in the post-OLT survival of PSC patients in the presence of CCA[175]. In 2000, the Cincinnati Transplant Tumor Registry identified 43 cases of incidental CCA predominantly in PSC explants, without superior survival to those with known CCA[176]. In 2005, a Canadian study reported 10 cases of incidental stage I or II CCA, 8 of which were in PSC explants. In PSC explants the incidence of incidental CCA was 3%. A 3-year survival of 30%, an 80% recurrence rate, a median time-to-recurrence of 26 mo and a median time-to-death of 30 mo were reported, concluding that although early survival appeared to be good, intermediate- and long-term survival were similar to that of historical OLTs with known CCA[177]. In the experience of Birmingham, there were 6% incidental CCA in PSC explants and the actuarial 5-year survival was 46% for this group of 13 patients[87]. Another UK study from Cambridge reported 9 cases of incidental CCA accounting for 0.7% of all explants. Seven of 9 cases were PSC-related. The overall 1-year survival was 100% and 3-year survival was 66.7%. The overall 3-year survival for all PSC OLTs over the same period was 79%[178]. In 2008, the United Network of Organ Sharing (UNOS) database identified 77 cases of incidental CCA, with a 5-year survival of 20% compared with 38% in OLT for known CCA[179]. Overall, incidental CCA is found in 3%-21% of PSC liver explants[15]. The 5-year survival generally ranges between 20%-46% and the recurrence rates are high, with an overall poor prognosis[155,178]. Understandably, as coordinated efforts in the context of multidisciplinary approaches have improved the outcomes of OLT for known CCA in the last two decades, the notion of good outcomes for incidental CCA in liver explants is following the opposite direction, even more since these outcomes have to be compared to those of transplanted PSC patients without malignancy. Considering the global organ donor shortage, and the evolving advances of transplant oncology, it is important that rigorous assessment is undertaken to maximise the diagnostic yield for CCA before transplantation, especially in PSC patients[178].

CCA discovered during OLT for PSC

Very little has been commented on with regards to CCA being discovered during intended OLT for PSC. A number of reports have apparently described detection of CCA *during OLT* in order to indicate incidental finding of CCA in liver explants, which complicates interpretation. Nevertheless, the prognosis of CCA discovered during OLT has been expected to be poor, in historical reports[3]. A study of Scandinavian PSC patients from 2004, suggested no difference in survival between patients with a

cancer diagnosis made during OLT and those with an incidental finding of CCA on explant pathology. Hence, it was suggested that when CCA is discovered intraoperatively, in the absence of extrahepatic spread, OLT should not be mandatorily abandoned[77,180]. Clearly, the intraoperative decision-making in such cases will be driven by the individual findings and the accepted guidelines and protocols, in the given national and local transplant setting.

PHCCA

Resection

As regards PHCCA, it is well documented that an R0 resection is the most important determinant of survival, but this surgical goal often proves to be elusive[9,154]. Radical resection is associated with a 5-year survival of 20%-45%[11,150] and a median overall survival of 30 mo in some series[150], but this is only achieved in 25%-40% of cases[118,153,154,181], owing to the frequent extensive hilar invasion and/or bilateral vascular or liver involvement[9,154]. Among those who undergo resection, 53%-79% present with recurrence, with 83% of recurrences developing within two years postoperatively[150]. In the absence of R0 resection, the 5-year survival rate drops to 0%[118].

A consensus meeting of expert panellists in 2014 recommended that the management of patients with PHCCA requires a coordinated, multidisciplinary approach to optimise the chances for both long survival and successful palliation[155]. Treatment of the disease is challenging and involves complex surgery in combination with neoadjuvant or adjuvant therapies, including external beam radiation and systemic chemotherapy[154]. In general terms, for suitable patients with resectable PHCCA, the ideal treatment option is surgical resection[118,155]. The main goal of surgery is to achieve an R0 resection with a complex procedure involving a major hepatectomy with caudate lobectomy and en-bloc biliary resection, a hepaticojejunostomy and lymphadenectomy. Vascular resection and reconstruction may also be undertaken, when necessary and feasible[118,155]. Pre-operative PVE may improve postoperative outcomes[118,155]. Preoperative biliary drainage of the FLR is highly recommended and should preferably be offered by means of percutaneous transhepatic access[118,155]. Unfortunately, only 20%-25% of patients are suitable candidates for curative resection. Neoplastic invasion of the vascular structures (portal vein and hepatic arteries) at the liver hilum is the main reason for unresectability[118]. Neoadjuvant therapy has shown effectiveness in downstaging unresectable PHCCA to allow for R0 resection in selected cases with locally advanced disease[150]. Studies of combined surgical resection for PHCCA (but not only in PSC patients) have described a 3-year survival of 40%-48% and 5-year survival which rarely exceeds 40%[11,116,153,154]. Owing to the complexity of surgical resection of PHCCA, it is recommended that these operations are undertaken by high-volume, experienced HPB centres[164], but even so, the 30-day mortality ranges between 5%-15% with the main cause of death being postoperative liver failure[118]. High preoperative bilirubin is a significant risk factor for postoperative morbidity and mortality with a cut-off value of 42 μmol/L (2.5 mg/dL) and 106 μmol/L (6.2 mg/dL) for morbidity and mortality, respectively[118].

Understandably, all previously discussed considerations concerning hepatic resection in PSC patients are more strongly applicable in relation to PHCCA, which always requires complex major hepatectomy, compounded by unfavourable physiological aspects. It is therefore not surprising that data from experience with LR for PSC-associated PHCCA are extremely limited, even more since, for this group of patients, OLT is clearly the standard-of-care. Hence, in this era of OLT, PSC-associated PHCCA is largely considered unresectable[117]. In the experience of Birmingham 5 patients with PSC-associated PHCCA were treated with right trisectionectomy (n = 3) and right hepatectomy (n = 1) combined with excision of the extrahepatic biliary tree and lymphadenectomy, while one patient with localised extrahepatic tumour underwent local excision without hepatectomy. Good survival was achieved, as previously mentioned[87]. In the experience of John Hopkins from 1999, among 9 patients with PHCCA who were surgical candidates, 3 underwent extrahepatic biliary duct excision and one underwent left hepatectomy and extrahepatic biliary duct excision. Microscopic residual tumour was present at the surgical margin in 3 out of a total of 5 patients who had biliary and/or LR. There was no operative mortality in these 5 patients, despite a reported complication rate of 71%. The median survival was 9 mo, while the actuarial 1-, 3- and 5-year survival was 40%, 20% and 0%, respectively. All patients died of recurrent cancer[8]. The Mayo Clinic treated two patients with

PSC-associated CCA, one of which with carcinoma in situ, with major hepatectomy, excision of the extrahepatic duct and gallbladder, and regional lymphadenectomy [182]. A retrospective multicentre study found 8 cases with early detected PSC-associated CCA, and one patient with localised disease underwent resection[183]. In a retrospective US multicentre study from 2018, comparing OLT *vs* resection for PHCCA, the two groups consisted of PSC patients in 61% and 2%, respectively. Three patients with PSC underwent major LR, in the form of CBD resection and either hemihepatectomy, extended hepatectomy or trisectionectomy[184].

OLT

As already mentioned, PSC-associated PHCCA is largely considered unresectable [117]. The role of OLT in the management of unresectable PHCCA including PSC-associated PHCCA has gone through different phases over time. The initial experience which did not include any adjunctive therapy was disappointing, with high rates of recurrence and poor survival, which deemed PHCCA a contraindication for OLT[3,152,171,172,180]. At the end of the previous century, published results showed a 5-year survival rate of 23% and cancer recurrence rate of 51%, with 84% occurring in the first two years. Survival after recurrence was less than one year, and patients with PSC-associated PHCCA did not benefit any advantage in survival[118]. In 2004, a Scandinavian study, reported 1-, 3- and 5-year survival rates following OLT for PSC-associated PHCCA of 65%, 35% and 35%, respectively[77]. Even though patient selection in these initial studies was ambiguous, the dismal results in the context of a worldwide donor organ shortage prevented PHCCA from becoming an established indication to OLT[9]. The turning point that significantly improved outcomes occurred in the early 2000s, when building on the observation that the Mayo Clinic achieved a 5-year survival of 22% for unresectable PHCCA treated with primary radiotherapy and chemosensitization alone, the University of Nebraska pioneered a strategy of neoadjuvant chemoradiotherapy prior to OLT. Subsequently, they published a study demonstrating significant improvements in survival using their protocol, while half of the enrolled patients had PSC-associated PHCCA[185]. This approach was embraced by the Mayo Clinic group, who established a neoadjuvant protocol for the treatment of confirmed unresectable PHCCA and PSC-associated PHCCA with a maximum tumour diameter of 3cm, including external beam radiation therapy together with intravenous fluorouracil (5-FU), followed by intraluminal brachytherapy with endoscopically placed iridium-192 beads, and maintenance chemotherapy with oral capecitabine until the time of transplantation. Additionally, prior to proceeding to OLT, a staging procedure is undertaken (currently in the form of hand-assisted laparoscopic staging[117]), to assess locoregional lymph nodes and rule out metastatic disease. The initially reported outcomes were very encouraging[12,162]. Further to the known response of CCA to high-dose radiotherapy, the rationale for the protocol included the oncological radicality of OLT, which is not limited by vascular involvement, the obviation of the hepatotoxicity of high-dose radiotherapy by OLT, the treatment of the underlying liver disease, such as PSC, without the limitations set by residual liver volume and function, and the potential of neoadjuvant therapy to prevent tumour dissemination during staging and transplantation. The protocol involves thorough selection of patients with unresectable de novo PHCCA or PSC-associated PHCCA without intrahepatic or extrahepatic metastases. Lymph node involvement is an absolute contraindication[117,186]. Diagnostic transperitoneal biopsy must be avoided as it typically excludes the patient from transplant consideration, due to the risk of tumour seeding[7,117,155,186]. As of 2004, the initial experience comprised 71 patients enrolled in the protocol, of which 38 ultimately underwent OLT (58% had PSC). Outcomes of OLT were 92%, 82%, and 82% at 1-, 3-, and 5-year survival, respectively. No difference was noted in survival between patients with and without PSC[182]. The excellent results of these protocol-driven approaches, the lack of effective alternative therapeutic options, and the natural history-related mortality prompted Gores *et al*[149] to propose, in 2006, a model of end-stage liver disease (MELD) score exception for patients with unresectable de novo PHCCA or PSC-associated PHCCA, to improve the allocation of liver grafts[149]. In 2009, as a result of the outcomes from the Mayo Clinic protocol, the UNOS/Organ Procurement and Transplantation Network offered the allocation of a MELD exception score for patients with PHCCA after completion of an approved neoadjuvant therapy protocol. Owing to lack of data, the MELD score was set to equal the standard assigned score for HCC, corresponding to an expected 10% increase in waitlist mortality every 3 mo. In 2012, a multicentre retrospective study of 12 Large volume US Centres, including patients with PHCCA who received neoadjuvant therapy followed by OLT (NCR-OLT) as per the Mayo Clinic protocol, showed a 65% 5-year disease-free

survival, a 11.5% dropout rate after 3.5 mo of therapy, and an intention-to-treat 5-year survival of 53%. Recurrence after OLT was 20% which compared very favourably against a known 53%-84% recurrence when OLT has not been combined with any neoadjuvant protocol. The study demonstrated that the therapeutic protocol was highly effective and validated the hypothesis that for selected patients with PHCCA it is appropriate to offer the proposed MELD exception score and therefore a faster access to OLT. Of note, patients with PSC-associated PHCCA were 52% of the dropout group, and 66.7% of ultimately eligible patients for OLT[187].

In 2012, an updated study of the Mayo Clinic outcomes reported that pretreatment pathological confirmation of PHCCA specifically in PSC patients was associated with significantly worse 5-year survival after start of therapy and worse 5-year survival after transplantation (50% *vs* 80% and 66% *vs* 92%, respectively), compared to absence of pathological confirmation. This was not evident in the de novo PHCCA. Additionally, pretreatment pathological confirmation in PSC patients was associated with a considerably higher risk of falling out at staging. The difference in the PSC patients was not attributable to recurrent cancer. Absence of pretreatment pathological confirmation was not accompanied by reduced detection of residual CCA in the explants or lower recurrence rate after OLT. It was hypothesised that, possibly, attributes of the primary tumour lending it to biopsy/brushing, are negated by neoadjuvant therapy providing that metastases have not developed. In this regard, it was concluded that, despite a desirable pretreatment pathological confirmation, this should not be a requirement for enrolment to treatment. PSC patients showed a trend towards higher but not statistically significant survival compared to the de novo PHCCA patients, both after the start of neoadjuvant therapy and after OLT. It was commented that the recent results of the Mayo Clinic showed higher survival for PSC-associated PHCCA, in contrast with the results of earlier studies showing that underlying PSC is not an independent prognostic factor. It was suggested that the presence or absence of PSC is of paramount importance, with the main consideration for PSC patients being whether or not they have cancer and should therefore undergo neoadjuvant therapy prior to OLT. The reported results were excellent, especially under the understanding that no effective alternative therapy exists. The efficacy of NCR-OLT had already become apparent[186].

In 2020, the Mayo Clinic group published their experience with 376 patients enrolled in the CCA transplant protocol between 1993-2019. After 14% dropout due to disease progression, 237 have received OLT[117]. Upon being listed for NCR-OLT, patients are listed on the UNOS and assigned MELD exception points. The goal for NCR-OLT for unresectable PHCCA is to obtain R0 margins and complete histological response (i.e., no residual tumour on explant). The Mayo Clinic group noted that PSC-associated PHCCA comprises a distinct patient population[117]. At staging operation for PSC-associated PHCCA, 14% of the patients staged positive, in contrast with 27% in de novo PHCCA, hence resulting in lower rates of dropout. Remarkably, they found that long-term survival after OLT is better in PSC-associated PHCCA (74% 5-year survival and 67% 10-year survival) compared with de novo PHCCA (58% and 47%, respectively). This was in accordance with a significantly lower recurrence rate in PSC patients (22% *vs* 45%), but also likely due to PSC patients having less advanced disease at the time of enrolment, as a result of routine screening in that patient population. When controlled for risk factors, the risk of disease recurrence for PSC and non-PSC patients was found to be similar[117]. Even in the absence of direct evidence to support this concept, it has been assumed that one of the reasons for the significantly better outcomes in PSC patients could be a higher responsiveness to radiation therapy for PHCCA occurring in the setting of PSC[117,188]. The study concluded that NCR-OLT is the only curative treatment for patients with PHCCA who meet the specific criteria of the protocol and leads to much higher long-term survival than either treatment alone[117]. The same transplant unit published their experience with living donor liver transplantation (LDLT) under the same protocol in 2020[188]. They described how a low division of the recipient CBD with frozen section to assess the margin is warranted, especially in PSC patients, followed by Roux-en-Y choledochojejunostomy for biliary reconstruction. Forty-nine patients (66.2%) received LDLT for PSC-associated PHCCA and had 1-, 3-, 5-, and 10-year survival of 89.8%, 75.9%, 75.9%, and 73.2%, respectively, which was better than in de novo PHCCA. Residual tumour was found in 32.7% of PSC explants which was significantly less frequent than in de novo PHCCA. When no residual tumour was found, the survival was similar, with PSC patients surviving 93.9%, 90.3%, 90.3%, and 90.3% at 1, 3, 5, and 10 years, respectively. In the presence of residual tumour, outcomes were similarly inferior, with PSC patients surviving 81.3%, 45.1%, 45.1%, and 36.1% at 1, 3, 5, and 10 years, respectively. PSC patients experienced recurrence in 12.2% of cases[188]. A recent

retrospective comparative study on the outcomes of NCR-OLT for PHCCA treated between 2010-2017 as per the Mayo Clinic protocol showed that well-experienced centres (≥ 6 OLTs) had significantly better post-OLT outcomes in terms of survival, mortality, and recurrence-related mortality compared to non-experienced centres. In patients with PSC, the well-experienced centres showed significantly better patient survival (P = 0.048)[161].

A recent meta-regression and meta-analysis showed that in unresectable PHCCA, NCR-OLT confers long-term survival in highly selected patients who are able to complete the protocol, while PSC patients appear to have the most favourable outcomes[189]. Acceptable survival rates are only achieved if a neoadjuvant regime is completed. At 5 years there was a positive correlation between a diagnosis of PSC and enhanced survival which was not apparent for 3-year survival. The number of available studies was not sufficient to assess whether the proportion of patients with PSC affected recurrence of CCA[189].

The gradual accumulation of favourable data made OLT for PHCCA a promising option[153,184]. In the last two decades, owing to a strict selection process and a neoadjuvant chemoradiation protocol, OLT for patients with non-resectable PHCCA demonstrated excellent outcomes and this strategy has been adopted worldwide as an accepted indication for OLT, in selected transplant centres with both a transplant and surgical oncology expertise. In this setting, survival after OLT is comparable to the results of OLT for other indications[11,153]. For PSC-associated PHCCA, current data are overwhelmingly in favour of NCR-OLT as the optimal treatment strategy, which offers superior outcomes compared with de novo PHCCA[9,161]. For this group of often young patients with early-stage disease, the Mayo Clinic protocol appears to be most applicable, and represents the sole therapeutic option[9]. At present, NCR-OLT is considered the standard of care for the management of unresectable PHCCA, in several experienced centres[117,155,184]. Further advancements in OLT and postoperative patient care compounded by novel chemotherapeutics and biological drugs may further improve the outcomes[181].

Of course, general considerations regarding outcomes of OLT in PSC patients are applicable to the group of patients with PSC-associated PHCCA. Notably, CCA can occur at any stage of PSC including after OLT, which, however, does not preclude successful re-transplantation, when feasible[4,7,80,190].

DCCA

Resection

Standard treatment with curative intent for resectable DCCA involves a classic Whipple's pancreatoduodenectomy or variations of the procedure. Postoperative 5-year survival ranges between 27%-37%[164]. There are no ample reports on outcomes of isolated pancreatoduodenectomy specifically in PSC patients, as common aspects are standard. PSC patients with resectable DCCA should be treated aggressively, while long-term outcomes will depend on the histological stage, and particularly the lymph node status[191]. However, one point to be kept in mind is that, as this is a major procedure, in patients with PSC, assessment for eligibility will need to include evaluation of the stage of their liver disease[98]. Early experience from the Mayo Clinic identified a single patient eligible for surgery among 30 cases of PSC-associated CCA. This 32-year-old woman with DCCA and negative lymph nodes underwent potentially curative pancreatoduodenectomy and was alive and disease-free 26 mo postoperatively[2]. The King's College Hospital in London reported on two PSC patients, a 49-year-old woman and a 50-year-old man, who were treated with Whipple's procedure having been diagnosed with DCCA from the distal bile duct margin following previous OLT for PSC. Interval from OLT was 2 mo for both cases. The first patient had an uneventful recovery and died after 5 years and 7 months post-Whipple's, from an unrelated cause, without evidence of recurrent cancer. The second patient's Whipple's was complicated by pneumonia. He died with peritoneal recurrence 5 months post-Whipple's. Of note, the same team treated another 2 PSC patients with Whipple's, for pancreatic adenocarcinoma, one at the same time with OLT and one sequentially, without mortality, and with low morbidity in the form of a wound infection. The authors concluded that pancreatoduodenectomy after OLT can be performed safely in specialist centres with expertise in both OLT and major pancreatic surgery[191]. When a patient with PSC who requires OLT is diagnosed with DCCA or other distal pancreatobiliary tumours, curative resection is possible only by combining OLT with pancreatoduodenectomy. This is a major undertaking, especially

in the context of immunosuppression, although good long-term results have been published in small case series and reports[183,191]. Some reports have recommended a staged approach to reduce perioperative morbidity[191].

More recently, the Mayo Clinic published their experience with 79 patients diagnosed with PSC-associated cancers. Three patients were diagnosed with DCCA exclusively, and only one who was surgical candidate was treated with OLT and pancreatoduodenectomy. This type of combined operation was performed in 5 cases of this cohort[158].

Combined OLT-pancreatoduodenectomy (Whipple's procedure)

In the context of OLT for CCA, a combined OLT-Whipple's is justified to achieve a R0 resection, and this is particularly applicable for PSC-associated CCA. The Mayo Clinic protocol includes this indication in the presence of microscopic involvement of the CBD[182]. In 2008 a retrospective study presented results from the application of en bloc total hepatectomy-pancreatoduodenectomy and OLT (OLT-Whipple's) following neoadjuvant radiotherapy in a standardised fashion, to achieve complete eradication of early-stage PSC-associated PHCCA. All 6 patients had PHCCA, while in 2 cases this was involving the distal CBD, and in 3 there was atypia in the distal CBD. One patient died 55 mo postoperatively without recurrence and the remaining 5 were well without recurrence 5.7 to 10.1 years postoperatively. All patients recovered well[183]. A further case series reported results from 4 patients with early-stage PSC-associated PHCCA who were treated with OLT-Whipple's combined with perioperative chemoradiotherapy. Three patients had a staged procedure and one patient had en block combined procedure. One patient died with metastatic disease following a 3-year recurrence-free survival, and 3 patients remained recurrence-free after 23, 19, and 11 mo, respectively[192]. The authors of these studies advocated that OLT combined with en block pancreatoduodenectomy can be a reasonable approach in patients with PHCCA on a background of dysplastic biliary epithelium, in order to prevent development of CCA post-OLT in the native distal CBD, particularly as CCA in PSC may be a diffuse disease, arising from multifocal areas of dysplasia. They highlighted that this approach is most appropriate in early stage PHCCA, as the outcomes in patients with higher stage disease have not been equally good[183,192]. This preemptively aggressive approach has not been widely adopted. While it is commonly agreed that a combined procedure in the presence of DCCA is rational, it has been argued that in the setting of PHCCA without any malignant of premalignant changes in the distal CBD, it may be overly aggressive[119].

In the early experience of the Mayo Clinic, 5 of 22 (23%) patients undergoing OLT for PSC-associated PHCCA, were found to have unsuspected tumour involvement of the CBD margin. Four were treated with pancreatoduodenectomy at the time of OLT. Three patients were alive and disease-free 24 to 72 mo postoperatively, one patient died of late hepatic artery thrombosis without recurrence, and one patient was not amenable to pancreatoduodenectomy, due to technical reasons but was alive and recurrence-free 8 mo postoperatively. The authors concluded that in up to 23% of patients with PSC-associated PHCCA, pancreatoduodenectomy may be necessary at the time of OLT to achieve complete eradication when there is microscopic involvement of the CBD[182]. A recent study from the Mayo Clinic reporting results of LDLT for PHCCA identified 4 patients (5.4%) who underwent excision of intrapancreatic bile duct and 5 patients (6.8%) who required pancreatoduodenectomy for positive distal CBD margins[188].

Adjuvant therapies

Treatment with radiation and/or chemotherapy following surgical management of CCA, including in patients with PSC, was reported to be ineffective in preventing recurrence, in early reports[171,176]. The prospect of adjuvant therapies for patients with incidental CCA in liver explants has been an intriguing issue[177]. In further retrospective studies, chemoradiation appeared to reduce local recurrence, which prompted an expert consensus panel in 2015 to recommend that it should be offered to patients with resected PHCCA and high-risk histological features (i.e. positive margins or lymph nodes), who appeared to have the greatest benefit[155,164]. In 2017, the BILCAP study involving 447 patients with resected either CCA of any location or gallbladder cancer, showed significant difference in overall survival in patients treated with adjuvant capecitabine *vs* the no drug control group (53 mo *vs* 36 mo)[193]. In IHCCA, even though the role of adjuvant therapies is still under debate, it has been recommended that adjuvant chemotherapy is offered after surgical resection with curative intent, particularly to patients with high-risk features (positive margins or lymph nodes, multifocal disease, large lesions)[148,159]. It needs to be noted that the

applicability of any recommendations in the transplant setting is unclear, and probably difficult to extrapolate, as studies assessing the effectiveness of adjuvant therapy after OLT for PHCCA or IHCCA are very limited. Hence, this remains to be explored in future research protocols[153,159]. In 2011, the University of California, Los Angeles, in a retrospective study of patients treated for IHCCA and PHCCA, including PSC patients, published results of a subgroup of 38 patients who were treated with OLT combined or not with adjuvant ± neoadjuvant therapy. Chemotherapeutic agents used for adjuvant and neoadjuvant protocols involved a combination of a fluorouracil- or capecitabine-based regimen with oxaliplatin, leucovorin calcium, and gemcitabine hydrochloride. Patients who received OLT combined with both neoadjuvant and adjuvant therapies had significantly less CCA recurrence compared to those who received OLT and adjuvant therapy and those who received OLT only (28% *vs* 40% *vs* 50%, respectively), and significantly better 5-year survival (47% *vs* 33% *vs* 20%, respectively)[194]. In the prospective study of the group from Houston Methodist and MD Anderson Cancer Center from 2018, of 6 patients with IHCCA who underwent NCR-OLT, all patients received adjuvant chemotherapy with capecitabine, gemcitabine, or both, commenced 4-6 wk post-OLT with a duration of a minimum of 4-6 mo, on grounds of active disease on explant. The overall survival was 100% at 1 year, and 83.3% at 3 and 5 years post-OLT, and recurrence-free survival was 50% at 1, 3, and 5 years[170]. The aggressive nature of CCA commonly warrants a multimodal approach to reduce the risk of recurrence following resection or OLT. However, in PSC patients, the toxicity of systemic and liver-directed therapies has to be balanced with the functional hepatic reserve, in order to minimise potential morbidity that may preclude definitive therapy[150].

Palliative treatments in unresectable cases/non-surgical candidates/metastatic disease

For patients with unresectable disease who are not surgical candidates or patients with metastatic disease, palliative options can be considered, including chemotherapy, stenting and targeted radiation[164]. Chemotherapy remains the main palliative treatment and may improve the quality of life, but only offers a modest improvement in overall survival[10,22]. The median survival for unresectable PSC-associated CCA is 5-12 mo after diagnosis with or without chemotherapy[7,11,150]. Patients with PSC-associated CCA may require meticulous optimization of biliary drainage and photodynamic therapy in the palliative setting. These modalities can offer symptom control and potentially improve survival[14,155,195]. For patients with advanced, locally recurrent, and metastatic PHCCA or patients with unresectable IHCCA the standard of care is first-line chemotherapy with combined gemcitabine and cisplatin, with a median survival rate of less than one year[13,118,148,150,155]. FOLFOX (folinic acid, fluorouracil and oxaliplatin) can be utilised as second-line chemotherapy[148]. Chemoradiation with or without intraluminal brachytherapy can also be utilised in locally advanced, unresectable PHCCA, and has produced modest results with median survival ranging from 10.7-14.6 mo[155]. In unresectable DCCA, palliative biliary drainage and systemic chemotherapy confer a median survival of 12 mo[157].

Various locoregional therapeutic modalities can be used in the palliative setting of CCA, such as radiofrequency ablation, microwave ablation and irreversible electroporation, photodynamic therapy, hepatic artery-based therapies such as selective internal radiotherapy, hepatic artery infusion and transarterial chemoembolization (TACE), stereotactic body radiotherapy and proton beam therapy, but data on their efficacy are limited and no relevant guidelines exist[150,195], while, specifically in the PSC setting, outcomes are largely unknown. TACE has shown some survival benefit in unresectable CCA, with overall 1-year survival of 52% after TACE independent of chemotherapy[164]. However, its response rates in unresectable IHCCA are around 20%, which is lower than with intra-arterial chemotherapy and selective internal radiotherapy. This may be a reflection of the hypovascular nature of IHCCA featuring extensive fibrosis and predominantly non-arterial blood supply[159]. Studies on stereotactic body radiotherapy in the management of unresectable CCA have been limited. The largest so far retrospective multicentre study of 64 patients with 82 lesions (IHCCA and PHCCA) demonstrated a median overall survival of 15 mo, with 2-year and 3-year overall survival rates of 32% and 21%, respectively. Higher doses achieved a significantly improved overall survival and local control, while tolerance was excellent[196]. A previous retrospective series of 34 patients with 42 lesions, reported a local control rate of 79%, and a median overall survival of 17 mo with median progression-free survival of 10 mo[197].

FUTURE PERSPECTIVES

Advances achieved over the last decades in the surgical management of CCA, with particular reference to the use of neoadjuvant therapy and OLT, imply that introduction of novel biomarkers for early detection could further improve the outcomes[7,10]. Continued efforts to standardise best practices, broaden the present treatment options and tailor treatment choices, warrant a coordinated multidisciplinary approach, as well as input from translational research[155]. Moreover, given that CCA is a rare disease, the collaboration of international consortia is required to collate large-scale data[118]. As regards the role of OLT, it has been suggested that a minimum expected dataset should be established for all future studies, to improve the quality of data and allow adequate interpretation of outcomes[189]. For IHCCA, future prospective studies should explore the role of adjuvant and neoadjuvant therapies combined with OLT in the context of standardised selection criteria, which may change the management of this entity, should previous favourable results be confirmed[11]. Moreover, further prospective studies in patients with CCA are expected to further outline which patients may benefit most from OLT[9].

Detailed evaluation of genetic and epigenetic determinants is expected to outline useful insights and provide guidance in prioritising targetable molecules and pathways for the prevention, diagnosis and treatment of PSC-associated CCA[6]. It has been suggested that significant differences may exist between patients with de novo PHCCA and those with PSC-associated PHCCA, who have an aberrant DNA methylation profile and may be noted to have oncogenic mutations prior to clinical manifestations[198]. Non-surgical management of PSC-associated cancers remains a therapeutic conundrum, partly because of their genetic heterogeneity and rapid development of therapeutic resistance with genetic evolution of the tumour. The genetic aberrations of PSC-associated CCA, as well as the clinical implications of such differences with de novo CCA, have yet to be elucidated[119,198]. Molecular profiling of CCA tissue is highly recommended, as it could lead to effective, personalised treatment options[148]. Potentially actionable events such as mutations, which are present in nearly 40% of patients with biliary cancers, may become candidates for targeted therapy[119,159]. Chemotherapy directed at the aberrant pathway has shown evidence of disease regression in recent reports[119]. Furthermore, novel drugs, such as checkpoint inhibitors and molecular-targeted molecules, either alone or combined with locoregional therapies, may provide future options for adjuvant and neoadjuvant treatments. Several ongoing trials are exploring the efficacy and safety of promising targeted therapies, particularly those combining different molecules[118,159]. Equally, the efficacy of locoregional therapies remains to be clarified through future clinical trials[195]. Moreover, in the last years the interest in immunotherapy has grown, as CCA is a malignancy with rich neoplastic stroma[118].

CONCLUSION

CCA is the most common malignancy in PSC and represents the leading cause of mortality in these patients. The incidence appears to be increasing worldwide and, as PSC, follows a South-to-North and East-to-West gradient.

CCA often occurs within the first year of PSC diagnosis, but may present later over the course of the disease, with clinical features overlapping with those of PSC itself. Surgery is the only potentially curative treatment for all anatomical subtypes. Without surgical treatment, the prognosis is dismal. Unfortunately, PSC-associated CCA is frequently diagnosed late, when no surgical options are available. Therefore, vigilant surveillance is fundamental to detect early cancers potentially amenable to curative treatment. LR in usually unsuitable for PSC patients, but may be reserved for a limited number of patients with early stage liver disease, in the absence of effective alternative options. A chance of cure exists only in the presence of radical resection with clear margins, which is feasible in a minority of patients. OLT for IHCCA remains controversial and currently contraindicated, but its role remains to be further explored, particularly as recent results with early tumours ≤ 2 cm are promising. Hence it may play a more prominent role in the future, in PSC patients. For incidentally discovered CCA in PSC liver explants, recurrence rates are commonly high, with an overall unfavourable prognosis. Remarkable progress has been made in the treatment of PHCCA over the last decades, after the implementation of a protocol of neoadjuvant chemoradiation followed by OLT, in suitable patients within specific criteria. Excellent outcomes prompted the conversion of PHCCA into an accepted indication for OLT in

several selected experienced transplant centres. Patients with PSC-associated PHCCA have the most favourable outcomes with high long-term survival rates and low recurrence rates. Suitable patients with PSC-associated DCCA may benefit long-term survival from aggressive radical resection with pancreatoduodenectomy, depending on histological features. A combined OLT and pancreatoduodenectomy may be suitable in patients with PSC-associated PHCCA when there is involvement of the distal CBD, with good outcomes in experienced centres. In the palliative setting, patients may benefit from chemotherapy and biliary stenting, but the prognosis remains poor. Future prospective studies are expected to further outline which patients with PSC-associated CCA may benefit most from OLT. Molecular profiling of PSC-associated CCA may guide the introduction of targeted therapies.

REFERENCES

1 **Taniai M**, Higuchi H, Burgart LJ, Gores GJ. p16INK4a promoter mutations are frequent in primary sclerosing cholangitis (PSC) and PSC-associated cholangiocarcinoma. *Gastroenterology* 2002; **123**: 1090-1098 [PMID: 12360471 DOI: 10.1053/gast.2002.36021]

2 **Rosen CB**, Nagorney DM. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Semin Liver Dis* 1991; **11**: 26-30 [PMID: 1646485 DOI: 10.1055/s-2008-1040419]

3 **van Leeuwen DJ**, Reeders JW. Primary sclerosing cholangitis and cholangiocarcinoma as a diagnostic and therapeutic dilemma. *Ann Oncol* 1999; **10** Suppl 4: 89-93 [PMID: 10436794]

4 **Fung BM**, Lindor KD, Tabibian JH. Cancer risk in primary sclerosing cholangitis: Epidemiology, prevention, and surveillance strategies. *World J Gastroenterol* 2019; **25**: 659-671 [PMID: 30783370 DOI: 10.3748/wjg.v25.i6.659]

5 **Chapman MH**, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. *Eur J Gastroenterol Hepatol* 2012; **24**: 1051-1058 [PMID: 22653260 DOI: 10.1097/MEG.0b013e3283554bbf]

6 **Chung BK**, Karlsen TH, Folseraas T. Cholangiocytes in the pathogenesis of primary sclerosing cholangitis and development of cholangiocarcinoma. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 1390-1400 [PMID: 28844951 DOI: 10.1016/j.bbadis.2017.08.020]

7 **Song J**, Li Y, Bowlus CL, Yang G, Leung PSC, Gershwin ME. Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis (PSC): a Comprehensive Review. *Clin Rev Allergy Immunol* 2020; **58**: 134-149 [PMID: 31463807 DOI: 10.1007/s12016-019-08764-7]

8 **Ahrendt SA**, Pitt HA, Nakeeb A, Klein AS, Lillemoe KD, Kalloo AN, Cameron JL. Diagnosis and management of cholangiocarcinoma in primary sclerosing cholangitis. *J Gastrointest Surg* 1999; **3**: 357-367; discussion 367-368 [PMID: 10482687 DOI: 10.1016/s1091-255x(99)80051-1]

9 **Hand F**, Hoti E. Contemporary role of liver transplantation for the treatment of cholangiocarcinoma. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 475-481 [PMID: 32401554 DOI: 10.1080/17474124.2020.1765771]

10 **Vedeld HM**, Folseraas T, Lind GE. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis - The promise of DNA methylation and molecular biomarkers. *JHEP Rep* 2020; **2**: 100143 [PMID: 32939446 DOI: 10.1016/j.jhepr.2020.100143]

11 **Sapisochín G**, Fernández de Sevilla E, Echeverri J, Charco R. Liver transplantation for cholangiocarcinoma: Current status and new insights. *World J Hepatol* 2015; **7**: 2396-2403 [PMID: 26464755 DOI: 10.4254/wjh.v7.i22.2396]

12 **Heimbach JK**, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB, Gores GJ. Transplantation for hilar cholangiocarcinoma. *Liver Transpl* 2004; **10**: S65-S68 [PMID: 15382214 DOI: 10.1002/Lt.20266]

13 **Tabibian JH**, Ali AH, Lindor KD. Primary Sclerosing Cholangitis, Part 2: Cancer Risk, Prevention, and Surveillance. *Gastroenterol Hepatol (N Y)* 2018; **14**: 427-432 [PMID: 30166959]

14 **Lazaridis KN**, Gores GJ. Primary sclerosing cholangitis and cholangiocarcinoma. *Semin Liver Dis* 2006; **26**: 42-51 [PMID: 16496232 DOI: 10.1055/s-2006-933562]

15 **Taghavi SA**, Eshraghian A, Niknam R, Sivandzadeh GR, Bagheri Lankarani K. Diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Expert Rev Gastroenterol Hepatol* 2018; **12**: 575-584 [PMID: 29781738 DOI: 10.1080/17474124.2018.1473761]

16 **Hirschfield GM**, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet* 2013; **382**: 1587-1599 [PMID: 23810223 DOI: 10.1016/S0140-6736(13)60096-3]

17 **Chapman RW**, Arborgh BA, Rhodes JM, Summerfield JA, Dick R, Scheuer PJ, Sherlock S. Primary sclerosing cholangitis: a review of its clinical features, cholangiography, and hepatic histology. *Gut* 1980; **21**: 870-877 [PMID: 7439807 DOI: 10.1136/gut.21.10.870]

18 **Lazaridis KN**, LaRusso NF. Primary Sclerosing Cholangitis. *N Engl J Med* 2016; **375**: 2501-2502 [PMID: 28002707 DOI: 10.1056/NEJMc1613273]

19 **Tischendorf JJ**, Hecker H, Krüger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: A single center study. *Am J Gastroenterol* 2007; **102**: 107-114 [PMID: 17037993 DOI: 10.1111/j.1572-0241.2006.00872.x]

20 **Maggs JR**, Chapman RW. An update on primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2008; **24**: 377-383 [PMID: 18408468 DOI: 10.1097/MOG.0b013e3282f9e239]

21 **Freeman E**, Majeed A, Kemp W, Roberts SK. Long-term outcomes of primary sclerosing cholangitis: an Australian non-transplant tertiary hospital perspective. *Intern Med J* 2019; **49**: 323-327 [PMID: 30043518 DOI: 10.1111/imj.14041]

22 **Chapman MH**, Thorburn D, Hirschfield GM, Webster GGJ, Rushbrook SM, Alexander G, Collier J, Dyson JK, Jones DE, Patanwala I, Thain C, Walmsley M, Pereira SP. British Society of Gastroenterology and UK-PSC guidelines for the diagnosis and management of primary sclerosing cholangitis. *Gut* 2019; **68**: 1356-1378 [PMID: 31154395 DOI: 10.1136/gutjnl-2018-317993]

23 **Boonstra K**, Weersma RK, van Erpecum KJ, Rauws EA, Spanier BW, Poen AC, van Nieuwkerk KM, Drenth JP, Witteman BJ, Tuynman HA, Naber AH, Kingma PJ, van Buuren HR, van Hoek B, Vleggaar FP, van Geloven N, Beuers U, Ponsioen CY; EpiPSCPBC Study Group. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013; **58**: 2045-2055 [PMID: 23775876 DOI: 10.1002/hep.26565]

24 **Tanaka A**, Takikawa H. Geoepidemiology of primary sclerosing cholangitis: a critical review. *J Autoimmun* 2013; **46**: 35-40 [PMID: 23932346 DOI: 10.1016/j.jaut.2013.07.005]

25 **Lindkvist B**, Benito de Valle M, Gullberg B, Björnsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. *Hepatology* 2010; **52**: 571-577 [PMID: 20683956 DOI: 10.1002/hep.23678]

26 **Boberg KM**, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H. Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. *Scand J Gastroenterol* 1998; **33**: 99-103 [PMID: 9489916 DOI: 10.1080/00365529850166284]

27 **Bambha K**, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, Loftus EV Jr, Yawn BP, Dickson ER, Melton LJ 3rd. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology* 2003; **125**: 1364-1369 [PMID: 14598252]

28 **Kaplan GG**, Laupland KB, Butzner D, Urbanski SJ, Lee SS. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. *Am J Gastroenterol* 2007; **102**: 1042-1049 [PMID: 17313496 DOI: 10.1111/j.1572-0241.2007.01103.x]

29 **Molodecky NA**, Kareemi H, Parab R, Barkema HW, Quan H, Myers RP, Kaplan GG. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. *Hepatology* 2011; **53**: 1590-1599 [PMID: 21351115 DOI: 10.1002/hep.24247]

30 **Escorsell A**, Parés A, Rodés J, Solís-Herruzo JA, Miras M, de la Morena E. Epidemiology of primary sclerosing cholangitis in Spain. Spanish Association for the Study of the Liver. *J Hepatol* 1994; **21**: 787-791 [PMID: 7890895 DOI: 10.1016/s0168-8278(94)80240-8]

31 **Kingham JG**, Kochar N, Gravenor MB. Incidence, clinical patterns, and outcomes of primary sclerosing cholangitis in South Wales, United Kingdom. *Gastroenterology* 2004; **126**: 1929-1930 [PMID: 15188211 DOI: 10.1053/j.gastro.2004.04.052]

32 **Weismüller TJ**, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Holm K, Gotthardt D, Färkkilä MA, Marschall HU, Thorburn D, Weersma RK, Fevery J, Mueller T, Chazouillères O, Schulze K, Lazaridis KN, Almer S, Pereira SP, Levy C, Mason A, Naess S, Bowlus CL, Floreani A, Halilbasic E, Yimam KK, Milkiewicz P, Beuers U, Huynh DK, Pares A, Manser CN, Dalekos GN, Eksteen B, Invernizzi P, Berg CP, Kirchner GI, Sarrazin C, Zimmer V, Fabris L, Braun F, Marzioni M, Juran BD, Said K, Rupp C, Jokelainen K, Benito de Valle M, Saffioti F, Cheung A, Trauner M, Schramm C, Chapman RW, Karlsen TH, Schrumpf E, Strassburg CP, Manns MP, Lindor KD, Hirschfield GM, Hansen BE, Boberg KM; International PSC Study Group. Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis. *Gastroenterology* 2017; **152**: 1975-1984.e8 [PMID: 28274849 DOI: 10.1053/j.gastro.2017.02.038]

33 **Karlsen TH**, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. *J Hepatol* 2017; **67**: 1298-1323 [PMID: 28802875 DOI: 10.1016/j.jhep.2017.07.022]

34 **Björnsson E**. Small-duct primary sclerosing cholangitis. *Curr Gastroenterol Rep* 2009; **11**: 37-41 [PMID: 19166657 DOI: 10.1007/s11894-009-0006-6]

35 **Björnsson E**, Olsson R, Bergquist A, Lindgren S, Braden B, Chapman RW, Boberg KM, Angulo P. The natural history of small-duct primary sclerosing cholangitis. *Gastroenterology* 2008; **134**: 975-980 [PMID: 18395078 DOI: 10.1053/j.gastro.2008.01.042]

36 **Björnsson E**, Boberg KM, Cullen S, Fleming K, Clausen OP, Fausa O, Schrumpf E, Chapman RW. Patients with small duct primary sclerosing cholangitis have a favourable long term prognosis. *Gut* 2002; **51**: 731-735 [PMID: 12377815 DOI: 10.1136/gut.51.5.731]

37 **Saffioti F**, Gurusamy KS, Hawkins N, Toon CD, Tsochatzis E, Davidson BR, Thorburn D. Pharmacological interventions for primary sclerosing cholangitis: an attempted network meta-analysis. *Cochrane Database Syst Rev* 2017; **3**: CD011343 [PMID: 28417463 DOI: 10.1002/14651858.CD011343.pub2]

38 **Ponsioen CY**, Vrouenraets SM, Prawirodirdjo W, Rajaram R, Rauws EA, Mulder CJ, Reitsma JB, Heisterkamp SH, Tytgat GN. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut* 2002; **51**: 562-566 [PMID: 12235081 DOI: 10.1136/gut.51.4.562]

39 **Broomé U**, Olsson R, Lööf L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzén

H, Wallerstedt S, Lindberg G. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996; **38**: 610-615 [PMID: 8707097 DOI: 10.1136/gut.38.4.610]

40 **Kotlyar DS**, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. *Am J Gastroenterol* 2006; **101**: 1370-1378 [PMID: 16771963 DOI: 10.1111/j.1572-0241.2006.00586.x]

41 **Ravikumar R**, Tsochatzis E, Jose S, Allison M, Athale A, Creamer F, Gunson B, Iyer V, Madanur M, Manas D, Monaco A, Mirza D, Owen N, Roberts K, Sen G, Srinivasan P, Wigmore S, Fusai G, Fernando B, Burroughs A. Risk factors for recurrent primary sclerosing cholangitis after liver transplantation. *J Hepatol* 2015; **63**: 1139-1146 [PMID: 26186988 DOI: 10.1016/j.jhep.2015.07.005]

42 **Burak K**, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2004; **99**: 523-526 [PMID: 15056096 DOI: 10.1111/j.1572-0241.2004.04067.x]

43 **Fevery J**, Henckaerts L, Van Oirbeek R, Vermeire S, Rutgeerts P, Nevens F, Van Steenbergen W. Malignancies and mortality in 200 patients with primary sclerosering cholangitis: a long-term single-centre study. *Liver Int* 2012; **32**: 214-222 [PMID: 21745316 DOI: 10.1111/j.1478-3231.2011.02575.x]

44 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; **51**: 237-267 [PMID: 19501929 DOI: 10.1016/j.jhep.2009.04.009]

45 **Bowlus CL**, Lim JK, Lindor KD. AGA Clinical Practice Update on Surveillance for Hepatobiliary Cancers in Patients With Primary Sclerosing Cholangitis: Expert Review. *Clin Gastroenterol Hepatol* 2019; **17**: 2416-2422 [PMID: 31306801 DOI: 10.1016/j.cgh.2019.07.011]

46 **Ngu JH**, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. *Hepatology* 2012; **55**: 522-529 [PMID: 21994151 DOI: 10.1002/hep.24743]

47 **Saffioti F**, Roccarina D, Marshall A, Pinzani M, Thorburn D. Risk factors for hepatocellular carcinoma in a large cohort of patients affected by primary sclerosing cholangitis. *J Hepatol* 2018; **68**: S223 [DOI: 10.1016/S0168-8278(18)30661-5]

48 **Card TR**, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. *J Hepatol* 2008; **48**: 939-944 [PMID: 18433916 DOI: 10.1016/j.jhep.2008.02.017]

49 **Okolicsanyi L**, Fabris L, Viaggi S, Carulli N, Podda M, Ricci G. Primary sclerosing cholangitis: clinical presentation, natural history and prognostic variables: an Italian multicentre study. The Italian PSC Study Group. *Eur J Gastroenterol Hepatol* 1996; **8**: 685-691 [PMID: 8853259]

50 **Ukai M**, Ajimura S, Akikawa H, Alburger DE, Banu A, Chrien RE, Franklin GB, Franz J, Hashimoto O, Hayakawa T, Hotchi H, Imai K, Kishimoto T, May M, Millener DJ, Minami S, Miura Y, Miyoshi T, Mizunuma K, Nagae T, Nakamura SN, Nakazawa K, Okayasu Y, Pile P, Quinn BP, Rusek A, Sato Y, Sutter R, Takahashi H, Tang L, Tamura H, Tanida K, Yuan L, Zhou SH; [E930('01) Collaboration]. Hypernuclear fine structure in (16)(Lambda)O and the LambdaN tensor interaction. *Phys Rev Lett* 2004; **93**: 232501 [PMID: 15601150 DOI: 10.1103/PhysRevLett.93.232501]

51 **Ataseven H**, Parlak E, Yüksel I, Başar O, Ertuğrul I, Saşmaz N, Sahin B. Primary sclerosing cholangitis in Turkish patients: characteristic features and prognosis. *Hepatobiliary Pancreat Dis Int* 2009; **8**: 312-315 [PMID: 19502174]

52 **Shaib YH**, Davila JA, McGlynn K, El-Serag HB. Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase? *J Hepatol* 2004; **40**: 472-477 [PMID: 15123362 DOI: 10.1016/j.jhep.2003.11.030]

53 **Rizvi S**, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol* 2018; **15**: 95-111 [PMID: 28994423 DOI: 10.1038/nrclinonc.2017.157]

54 **Farley DR**, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin Proc* 1995; **70**: 425-429 [PMID: 7537346 DOI: 10.4065/70.5.425]

55 **Bergquist A**, Ekbom A, Olsson R, Kornfeldt D, Lööf L, Danielsson A, Hultcrantz R, Lindgren S, Prytz H, Sandberg-Gertzén H, Almer S, Granath F, Broomé U. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. *J Hepatol* 2002; **36**: 321-327 [PMID: 11867174 DOI: 10.1016/s0168-8278(01)00288-4]

56 **Boberg KM**, Bergquist A, Mitchell S, Pares A, Rosina F, Broomé U, Chapman R, Fausa O, Egeland T, Rocca G, Schrumpf E. Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation. *Scand J Gastroenterol* 2002; **37**: 1205-1211 [PMID: 12408527 DOI: 10.1080/003655202760373434]

57 **Bridgewater J**, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014; **60**: 1268-1289 [PMID: 24681130 DOI: 10.1016/j.jhep.2014.01.021]

58 **Liang H**, Manne S, Shick J, Lissoos T, Dolin P. Incidence, prevalence, and natural history of primary sclerosing cholangitis in the United Kingdom. *Medicine (Baltimore)* 2017; **96**: e7116 [PMID: 28614231 DOI: 10.1097/MD.0000000000007116]

59 **Bergquist A**, von Seth E. Epidemiology of cholangiocarcinoma. *Best Pract Res Clin Gastroenterol* 2015; **29**: 221-232 [PMID: 25966423 DOI: 10.1016/j.bpg.2015.02.003]

60 **Sripa B**, Pairojkul C. Cholangiocarcinoma: lessons from Thailand. *Curr Opin Gastroenterol* 2008; **24**: 349-356 [PMID: 18408464 DOI: 10.1097/MOG.0b013e3282fbf9b3]

61 **Valle JW**, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet* 2021; **397**: 428-444 [PMID: 33516341 DOI: 10.1016/S0140-6736(21)00153-7]

62 **Sripa B**, Kaewkes S, Sithithaworn P, Mairiang E, Laha T, Smout M, Pairojkul C, Bhudhisawasdi V, Tesana S, Thinkamrop B, Bethony JM, Loukas A, Brindley PJ. Liver fluke induces cholangiocarcinoma. *PLoS Med* 2007; **4**: e201 [PMID: 17622191 DOI: 10.1371/journal.pmed.0040201]

63 **Saha SK**, Zhu AX, Fuchs CS, Brooks GA. Forty-Year Trends in Cholangiocarcinoma Incidence in the U.S.: Intrahepatic Disease on the Rise. *Oncologist* 2016; **21**: 594-599 [PMID: 27000463 DOI: 10.1634/theoncologist.2015-0446]

64 **Taylor-Robinson SD**, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, Khan SA, Elliott P, Thomas HC. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1998. *Gut* 2001; **48**: 816-820 [PMID: 11358902 DOI: 10.1136/gut.48.6.816]

65 **Khan SA**, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. *J Hepatol* 2002; **37**: 806-813 [PMID: 12445422 DOI: 10.1016/s0168-8278(02)00297-0]

66 **Patel T**. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001; **33**: 1353-1357 [PMID: 11391522 DOI: 10.1053/jhep.2001.25087]

67 **West J**, Wood H, Logan RF, Quinn M, Aithal GP. Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971-2001. *Br J Cancer* 2006; **94**: 1751-1758 [PMID: 16736026 DOI: 10.1038/sj.bjc.6603127]

68 **Global Burden of Disease Cancer Collaboration**; Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrook R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwebel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park EK, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD 3rd, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijnse J, Petzold M, Shrime MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pourmalek F, Lotufo PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas-Rueda D, Westerman R, Sepanlou SG, Nolte S, Patten S, Weichenthal S, Abera SF, Fereshtehnejad SM, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov VV, Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshrati B, Williams HC, Shibuya K, Dandona R, Murthy K, Cowie B, Amare AT, Antonio CA, Castañeda-Orjuela C, van Gool CH, Violante F, Oh IH, Deribe K, Soreide K, Knibbs L, Kereselidze M, Green M, Cardenas R, Roy N, Tillmann T, Li Y, Krueger H, Monasta L, Dey S, Sheikhbahaei S, Hafezi-Nejad N, Kumar GA, Sreeramareddy CT, Dandona L, Wang H, Vollset SE, Mokdad A, Salomon JA, Lozano R, Vos T, Forouzanfar M, Lopez A, Murray C, Naghavi M. The Global Burden of Cancer 2013. *JAMA Oncol* 2015; **1**: 505-527 [PMID: 26181261 DOI: 10.1001/jamaoncol.2015.0735]

69 **Takakura WR**, Tabibian JH, Bowlus CL. The evolution of natural history of primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2017; **33**: 71-77 [PMID: 28030370 DOI: 10.1097/MOG.0000000000000333]

70 **Ehlken H**, Zenouzi R, Schramm C. Risk of cholangiocarcinoma in patients with primary sclerosing cholangitis: diagnosis and surveillance. *Curr Opin Gastroenterol* 2017; **33**: 78-84 [PMID: 28146445 DOI: 10.1097/MOG.0000000000000335]

71 **Blechacz B**. Cholangiocarcinoma: Current Knowledge and New Developments. *Gut Liver* 2017; **11**: 13-26 [PMID: 27928095 DOI: 10.5009/gnl15568]

72 **Bonato G**, Cristoferi L, Strazzabosco M, Fabris L. Malignancies in Primary Sclerosing Cholangitis--A Continuing Threat. *Dig Dis* 2015; **33** Suppl 2: 140-148 [PMID: 26641079 DOI: 10.1159/000440826]

73 **Horsley-Silva JL**, Rodriguez EA, Franco DL, Lindor KD. An update on cancer risk and surveillance in primary sclerosing cholangitis. *Liver Int* 2017; **37**: 1103-1109 [PMID: 28028930 DOI: 10.1111/Liv.13354]

74 **Claessen MM**, Vleggaar FP, Tytgat KM, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. *J Hepatol* 2009; **50**: 158-164 [PMID: 19012991 DOI: 10.1016/j.jhep.2008.08.013]

75 **Farrant JM**, Hayllar KM, Wilkinson ML, Karani J, Portmann BC, Westaby D, Williams R. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991; **100**: 1710-1717 [PMID: 1850376 DOI: 10.1016/0016-5085(91)90673-9]

76 **Gatto M**, Alvaro D. Cholangiocarcinoma: risk factors and clinical presentation. *Eur Rev Med Pharmacol Sci* 2010; **14**: 363-367 [PMID: 20496549]

77 **Brandsaeter B**, Isoniemi H, Broomé U, Olausson M, Bäckman L, Hansen B, Schrumpf E, Oksanen A, Ericzon BG, Höckerstedt K, Mäkisalo H, Kirkegaard P, Friman S, Bjøro K. Liver transplantation for primary sclerosing cholangitis; predictors and consequences of hepatobiliary malignancy. *J Hepatol* 2004; **40**: 815-822 [PMID: 15094230 DOI: 10.1016/j.jhep.2004.01.002]

78 **Geramizadeh B**, Ghavvas R, Kazemi K, Shamsaeefar A, Nikeghbalian S, Malekhosseini SA. Cholangiocarcinoma Secondary to Primary Sclerosing Cholangitis in Explanted Livers: A Single-

Center Study in the South of Iran. *Hepat Mon* 2015; **15**: e33626 [PMID: 26977169 DOI: 10.5812/hepatmon.33626]

79 **Rademacher S**, Seehofer D, Eurich D, Schoening W, Neuhaus R, Oellinger R, Denecke T, Pascher A, Schott E, Sinn M, Neuhaus P, Pratschke J. The 28-year incidence of de novo malignancies after liver transplantation: A single-center analysis of risk factors and mortality in 1616 patients. *Liver Transpl* 2017; **23**: 1404-1414 [PMID: 28590598 DOI: 10.1002/Lt.24795]

80 **Mouchli MA**, Singh S, Loftus EV Jr, Boardman L, Talwalkar J, Rosen CB, Heimbach JK, Wiesner RH, Hasan B, Poterucha JJ, Kymberly WD. Risk Factors and Outcomes of De Novo Cancers (Excluding Nonmelanoma Skin Cancer) After Liver Transplantation for Primary Sclerosing Cholangitis. *Transplantation* 2017; **101**: 1859-1866 [PMID: 28272287 DOI: 10.1097/TP.0000000000001725]

81 **Khorsandi SE**, Salvans S, Zen Y, Agarwal K, Jassem W, Heaton N. Cholangiocarcinoma complicating recurrent primary sclerosing cholangitis after liver transplantation. *Transpl Int* 2011; **24**: e93-e96 [PMID: 21884553 DOI: 10.1111/j.1432-2277.2011.01324.x]

82 **Landaverde C**, Ng V, Sato A, Tabibian J, Durazo F, Busuttil R. De-novo cholangiocarcinoma in native common bile duct remnant following OLT for primary sclerosing cholangitis. *Ann Hepatol* 2009; **8**: 379-383 [PMID: 20009140]

83 **Graziadei IW**, Wiesner RH, Batts KP, Marotta PJ, LaRusso NF, Porayko MK, Hay JE, Gores GJ, Charlton MR, Ludwig J, Poterucha JJ, Steers JL, Krom RA. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology* 1999; **29**: 1050-1056 [PMID: 10094945 DOI: 10.1002/hep.510290427]

84 **Lerut J**, Demetris AJ, Stieber AC, Marsh JW, Gordon RD, Esquivel CO, Iwatsuki S, Starzl TE. Intrahepatic bile duct strictures after human orthotopic liver transplantation. Recurrence of primary sclerosing cholangitis or unusual presentation of allograft rejection? *Transpl Int* 1988; **1**: 127-130 [PMID: 3075471]

85 **Cardinale V**, Semeraro R, Torrice A, Gatto M, Napoli C, Bragazzi MC, Gentile R, Alvaro D. Intra-hepatic and extra-hepatic cholangiocarcinoma: New insight into epidemiology and risk factors. *World J Gastrointest Oncol* 2010; **2**: 407-416 [PMID: 21160904 DOI: 10.4251/wjgo.v2.i11.407]

86 **Fevery J**, Verslype C, Lai G, Aerts R, Van Steenbergen W. Incidence, diagnosis, and therapy of cholangiocarcinoma in patients with primary sclerosing cholangitis. *Dig Dis Sci* 2007; **52**: 3123-3135 [PMID: 17431781 DOI: 10.1007/s10620-006-9681-4]

87 **Morris-Stiff G**, Bhati C, Olliff S, Hübscher S, Gunson B, Mayer D, Mirza D, Buckels J, Bramhall SR. Cholangiocarcinoma complicating primary sclerosing cholangitis: a 24-year experience. *Dig Surg* 2008; **25**: 126-132 [PMID: 18446034 DOI: 10.1159/000128169]

88 **de Valle MB**, Björnsson E, Lindkvist B. Mortality and cancer risk related to primary sclerosing cholangitis in a Swedish population-based cohort. *Liver Int* 2012; **32**: 441-448 [PMID: 22098097 DOI: 10.1111/j.1478-3231.2011.02614.x]

89 **Deneau MR**, El-Matary W, Valentino PL, Abdou R, Alqoaer K, Amin M, Amir AZ, Auth M, Bazerbachi F, Broderick A, Chan A, Cotter J, Doan S, El-Youssef M, Ferrari F, Furuya KN, Gottrand M, Gottrand F, Gupta N, Homan M, Kamath BM, Kim KM, Kolho KL, Konidari A, Koot B, Iorio R, Ledder O, Mack C, Martinez M, Miloh T, Mohan P, O'Cathain N, Papadopoulou A, Ricciuto A, Saubermann L, Sathya P, Shteyer E, Smolka V, Tanaka A, Varier R, Venkat V, Vitola B, Vos MB, Woynarowski M, Yap J, Jensen MK. The natural history of primary sclerosing cholangitis in 781 children: A multicenter, international collaboration. *Hepatology* 2017; **66**: 518-527 [PMID: 28390159 DOI: 10.1002/hep.29204]

90 **Deneau M**, Jensen MK, Holmen J, Williams MS, Book LS, Guthery SL. Primary sclerosing cholangitis, autoimmune hepatitis, and overlap in Utah children: epidemiology and natural history. *Hepatology* 2013; **58**: 1392-1400 [PMID: 23686586 DOI: 10.1002/hep.26454]

91 **Liu K**, Wang R, Kariyawasam V, Wells M, Strasser SI, McCaughan G, Corte C, Leong RW. Epidemiology and outcomes of primary sclerosing cholangitis with and without inflammatory bowel disease in an Australian cohort. *Liver Int* 2017; **37**: 442-448 [PMID: 27891750 DOI: 10.1111/Liv.13328]

92 **Tanaka A**, Takamori Y, Toda G, Ohnishi S, Takikawa H. Outcome and prognostic factors of 391 Japanese patients with primary sclerosing cholangitis. *Liver Int* 2008; **28**: 983-989 [PMID: 18397233 DOI: 10.1111/j.1478-3231.2008.01726.x]

93 **Broomé U**, Glaumann H, Lindstöm E, Lööf L, Almer S, Prytz H, Sandberg-Gertzén H, Lindgren S, Fork FT, Järnerot G, Olsson R. Natural history and outcome in 32 Swedish patients with small duct primary sclerosing cholangitis (PSC). *J Hepatol* 2002; **36**: 586-589 [PMID: 11983440 DOI: 10.1016/s0168-8278(02)00036-3]

94 **Singal AK**, Stanca CM, Clark V, Dixon L, Levy C, Odin JA, Fiel MI, Friedman SL, Bach N. Natural history of small duct primary sclerosing cholangitis: a case series with review of the literature. *Hepatol Int* 2011; **5**: 808-813 [PMID: 21484124 DOI: 10.1007/s12072-011-9260-4]

95 **Sinakos E**, Saenger AK, Keach J, Kim WR, Lindor KD. Many patients with primary sclerosing cholangitis and increased serum levels of carbohydrate antigen 19-9 do not have cholangiocarcinoma. *Clin Gastroenterol Hepatol* 2011; **9**: 434-9.e1 [PMID: 21334457 DOI: 10.1016/j.cgh.2011.02.007]

96 **European Society of Gastrointestinal Endoscopy**; European Association for the Study of the Liver. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline.

J Hepatol 2017; **66**: 1265-1281 [PMID: 28427764 DOI: 10.1016/j.jhep.2017.02.013]

97 **Aabakken L**, Karlsen TH, Albert J, Arvanitakis M, Chazouilleres O, Dumonceau JM, Färkkilä M, Fickert P, Hirschfield GM, Laghi A, Marzioni M, Fernandez M, Pereira SP, Pohl J, Poley JW, Ponsioen CY, Schramm C, Swahn F, Tringali A, Hassan C. Role of endoscopy in primary sclerosing cholangitis: European Society of Gastrointestinal Endoscopy (ESGE) and European Association for the Study of the Liver (EASL) Clinical Guideline. *Endoscopy* 2017; **49**: 588-608 [PMID: 28420030 DOI: 10.1055/s-0043-107029]

98 **Ehlken H**, Schramm C. How Should Cancer Surveillance in Primary Sclerosing Cholangitis Be Performed? *Viszeralmedizin* 2015; **31**: 173-177 [PMID: 26468311 DOI: 10.1159/000431350]

99 **Rudolph G**, Gotthardt D, Klöters-Plachky P, Kulaksiz H, Rost D, Stiehl A. Influence of dominant bile duct stenoses and biliary infections on outcome in primary sclerosing cholangitis. *J Hepatol* 2009; **51**: 149-155 [PMID: 19410324 DOI: 10.1016/j.jhep.2009.01.023]

100 **Gulamhusein AF**, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN. Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD. *Am J Gastroenterol* 2016; **111**: 705-711 [PMID: 27002801 DOI: 10.1038/ajg.2016.55]

101 **Tischendorf JJ**, Meier PN, Strassburg CP, Klempnauer J, Hecker H, Manns MP, Krüger M. Characterization and clinical course of hepatobiliary carcinoma in patients with primary sclerosing cholangitis. *Scand J Gastroenterol* 2006; **41**: 1227-1234 [PMID: 16990210 DOI: 10.1080/00365520600633495]

102 **Ngu JH**, Gearry RB, Wright AJ, Stedman CA. Inflammatory bowel disease is associated with poor outcomes of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2011; **9**: 1092-7; quiz e135 [PMID: 21893134 DOI: 10.1016/j.cgh.2011.08.027]

103 **Franceschet I**, Cazzagon N, Del Ross T, D'Incà R, Buja A, Floreani A. Primary sclerosing cholangitis associated with inflammatory bowel disease: an observational study in a Southern Europe population focusing on new therapeutic options. *Eur J Gastroenterol Hepatol* 2016; **28**: 508-513 [PMID: 26872110 DOI: 10.1097/MEG.0000000000000596]

104 **Aoki CA**, Bowlus CL, Gershwin ME. The immunobiology of primary sclerosing cholangitis. *Autoimmun Rev* 2005; **4**: 137-143 [PMID: 15823499 DOI: 10.1016/j.autrev.2004.09.003]

105 **Timmer MR**, Beuers U, Fockens P, Ponsioen CY, Rauws EA, Wang KK, Krishnadath KK. Genetic and epigenetic abnormalities in primary sclerosing cholangitis-associated cholangiocarcinoma. *Inflamm Bowel Dis* 2013; **19**: 1789-1797 [PMID: 23615529 DOI: 10.1097/MIB.0b013e318281f49a]

106 **Ørntoft NW**, Munk OL, Frisch K, Ott P, Keiding S, Sørensen M. Hepatobiliary transport kinetics of the conjugated bile acid tracer ^{11}C-CSar quantified in healthy humans and patients by positron emission tomography. *J Hepatol* 2017; **67**: 321-327 [PMID: 28249726 DOI: 10.1016/j.jhep.2017.02.023]

107 **Beuers U**, Hohenester S, de Buy Wenniger LJ, Kremer AE, Jansen PL, Elferink RP. The biliary HCO(3)(-) umbrella: a unifying hypothesis on pathogenetic and therapeutic aspects of fibrosing cholangiopathies. *Hepatology* 2010; **52**: 1489-1496 [PMID: 20721884 DOI: 10.1002/hep.23810]

108 **Ehlken H**, Schramm C. Primary sclerosing cholangitis and cholangiocarcinoma: pathogenesis and modes of diagnostics. *Dig Dis* 2013; **31**: 118-125 [PMID: 23797133 DOI: 10.1159/000347206]

109 **Han C**, Leng J, Demetris AJ, Wu T. Cyclooxygenase-2 promotes human cholangiocarcinoma growth: evidence for cyclooxygenase-2-independent mechanism in celecoxib-mediated induction of p21waf1/cip1 and p27kip1 and cell cycle arrest. *Cancer Res* 2004; **64**: 1369-1376 [PMID: 14973068 DOI: 10.1158/0008-5472.can-03-1086]

110 **Jones H**, Alpini G, Francis H. Bile acid signaling and biliary functions. *Acta Pharm Sin B* 2015; **5**: 123-128 [PMID: 26579437 DOI: 10.1016/j.apsb.2015.01.009]

111 **Fleming KA**, Boberg KM, Glaumann H, Bergquist A, Smith D, Clausen OP. Biliary dysplasia as a marker of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2001; **34**: 360-365 [PMID: 11322195 DOI: 10.1016/s0168-8278(00)00034-9]

112 **Rizvi S**, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology* 2013; **145**: 1215-1229 [PMID: 24140396 DOI: 10.1053/j.gastro.2013.10.013]

113 **Labib PL**, Goodchild G, Pereira SP. Molecular Pathogenesis of Cholangiocarcinoma. *BMC Cancer* 2019; **19**: 185 [PMID: 30819129 DOI: 10.1186/s12885-019-5391-0]

114 **Banales JM**, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, Lind GE, Folseraas T, Forbes SJ, Fouassier L, Geier A, Calvisi DF, Mertens JC, Trauner M, Benedetti A, Maroni L, Vaquero J, Macias RI, Raggi C, Perugorria MJ, Gaudio E, Boberg KM, Marin JJ, Alvaro D. Expert consensus document: Cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). *Nat Rev Gastroenterol Hepatol* 2016; **13**: 261-280 [PMID: 27095655 DOI: 10.1038/nrgastro.2016.51]

115 **de Groen PC**. Cholangiocarcinoma in primary sclerosing cholangitis: who is at risk and how do we screen? *Hepatology* 2000; **31**: 247-248 [PMID: 10613754 DOI: 10.1002/hep.510310137]

116 **Jesudian AB**, Jacobson IM. Screening and diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis. *Rev Gastroenterol Disord* 2009; **9**: E41-E47 [PMID: 19668124]

117 **Azad AI**, Rosen CB, Taner T, Heimbach JK, Gores GJ. Selected Patients with Unresectable Perihilar Cholangiocarcinoma (pCCA) Derive Long-Term Benefit from Liver Transplantation. *Cancers (Basel)* 2020; **12** [PMID: 33121179 DOI: 10.3390/cancers12113157]

118 **Gringeri E**, Gambato M, Sapisochin G, Ivanics T, Lynch EN, Mescoli C, Burra P, Cillo U, Russo FP. Cholangiocarcinoma as an Indication for Liver Transplantation in the Era of Transplant

Oncology. *J Clin Med* 2020; **9** [PMID: 32380750 DOI: 10.3390/jcm9051353]

119 **Rizvi S**, Eaton JE, Gores GJ. Primary Sclerosing Cholangitis as a Premalignant Biliary Tract Disease: Surveillance and Management. *Clin Gastroenterol Hepatol* 2015; **13**: 2152-2165 [PMID: 26051390 DOI: 10.1016/j.cgh.2015.05.035]

120 **Fung BM**, Tabibian JH. Cholangiocarcinoma in patients with primary sclerosing cholangitis. *Curr Opin Gastroenterol* 2020; **36**: 77-84 [PMID: 31850928 DOI: 10.1097/MOG.0000000000000616]

121 **Abu-Wasel B**, Keough V, Renfrew PD, Molinari M. Biliary stent therapy for dominant strictures in patients affected by primary sclerosing cholangitis. *Pathobiology* 2013; **80**: 182-193 [PMID: 23652282 DOI: 10.1159/000347057]

122 **Hilscher M**, Enders FB, Carey EJ, Lindor KD, Tabibian JH. Alkaline phosphatase normalization is a biomarker of improved survival in primary sclerosing cholangitis. *Ann Hepatol* 2016; **15**: 246-253 [PMID: 26845602 DOI: 10.5604/16652681.1193721]

123 **Al Mamari S**, Djordjevic J, Halliday JS, Chapman RW. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2013; **58**: 329-334 [PMID: 23085647 DOI: 10.1016/j.jhep.2012.10.013]

124 **Rupp C**, Rössler A, Halibasic E, Sauer P, Weiss KH, Friedrich K, Wannhoff A, Stiehl A, Stremmel W, Trauner M, Gotthardt DN. Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Aliment Pharmacol Ther* 2014; **40**: 1292-1301 [PMID: 25316001 DOI: 10.1111/apt.12979]

125 **Levy C**, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. *Dig Dis Sci* 2005; **50**: 1734-1740 [PMID: 16133981 DOI: 10.1007/s10620-005-2927-8]

126 **Liu W**, Liu Q, Wang W, Wang P, Chen J, Hong T, Zhang N, Li B, Qu Q, He X. Differential diagnostic roles of the serum CA19-9, total bilirubin (TBIL) and the ratio of CA19-9 to TBIL for benign and malignant. *J Cancer* 2018; **9**: 1804-1812 [PMID: 29805707 DOI: 10.7150/jca.25093]

127 **Jendrek ST**, Gotthardt D, Nitzsche T, Widmann L, Korf T, Michaels MA, Weiss KH, Liaskou E, Vesterhus M, Karlsen TH, Mindorf S, Schemmer P, Bär F, Teegen B, Schröder T, Ehlers M, Hammers CM, Komorowski L, Lehnert H, Fellermann K, Derer S, Hov JR, Sina C. Anti-GP2 IgA autoantibodies are associated with poor survival and cholangiocarcinoma in primary sclerosing cholangitis. *Gut* 2017; **66**: 137-144 [PMID: 27406039 DOI: 10.1136/gutjnl-2016-311739]

128 **Cuenco J**, Wehnert N, Blyuss O, Kazarian A, Whitwell HJ, Menon U, Dawnay A, Manns MP, Pereira SP, Timms JF. Identification of a serum biomarker panel for the differential diagnosis of cholangiocarcinoma and primary sclerosing cholangitis. *Oncotarget* 2018; **9**: 17430-17442 [PMID: 29707118 DOI: 10.18632/oncotarget.24732]

129 **Arbelaiz A**, Azkargorta M, Krawczyk M, Santos-Laso A, Lapitz A, Perugorria MJ, Erice O, Gonzalez E, Jimenez-Agüero R, Lacasta A, Ibarra C, Sanchez-Campos A, Jimeno JP, Lammert F, Milkiewicz P, Marzioni M, Macias RIR, Marin JJG, Patel T, Gores GJ, Martinez I, Elortza F, Falcon-Perez JM, Bujanda L, Banales JM. Serum extracellular vesicles contain protein biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* 2017; **66**: 1125-1143 [PMID: 28555885 DOI: 10.1002/hep.29291]

130 **Banales JM**, Iñarrairaegui M, Arbelaiz A, Milkiewicz P, Muntané J, Muñoz-Bellvis L, La Casta A, Gonzalez LM, Arretxe E, Alonso C, Martínez-Arranz I, Lapitz A, Santos-Laso A, Avila MA, Martínez-Chantar ML, Bujanda L, Marin JJG, Sangro B, Macias RIR. Serum Metabolites as Diagnostic Biomarkers for Cholangiocarcinoma, Hepatocellular Carcinoma, and Primary Sclerosing Cholangitis. *Hepatology* 2019; **70**: 547-562 [PMID: 30325540 DOI: 10.1002/hep.30319]

131 **Olaizola P**, Lee-Law PY, Arbelaiz A, Lapitz A, Perugorria MJ, Bujanda L, Banales JM. MicroRNAs and extracellular vesicles in cholangiopathies. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 1293-1307 [PMID: 28711597 DOI: 10.1016/j.bbadis.2017.06.026]

132 **Wannhoff A**, Gotthardt DN. Recent developments in the research on biomarkers of cholangiocarcinoma in primary sclerosing cholangitis. *Clin Res Hepatol Gastroenterol* 2019; **43**: 236-243 [PMID: 30266579 DOI: 10.1016/j.clinre.2018.08.013]

133 **Vesterhus M**, Hov JR, Holm A, Schrumpf E, Nygård S, Godang K, Andersen IM, Naess S, Thorburn D, Saffioti F, Vatn M, Gilja OH, Lund-Johansen F, Syversveen T, Brabrand K, Parés A, Ponsioen CY, Pinzani M, Färkkilä M, Moum B, Ueland T, Røsjø H, Rosenberg W, Boberg KM, Karlsen TH. Enhanced liver fibrosis score predicts transplant-free survival in primary sclerosing cholangitis. *Hepatology* 2015; **62**: 188-197 [PMID: 25833813 DOI: 10.1002/hep.27825]

134 **Saffioti F**, Roccarina D, Vesterhus M, Hov JR, Rosenberg W, Pinzani M, Pereira SP, Boberg KM, Thorburn D. Cholangiocarcinoma is associated with a raised enhanced liver fibrosis score independent of primary sclerosing cholangitis. *Eur J Clin Invest* 2019; **49**: e13088 [PMID: 30762236 DOI: 10.1111/eci.13088]

135 **Lindor KD**, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG Clinical Guideline: Primary Sclerosing Cholangitis. *Am J Gastroenterol* 2015; **110**: 646-659; quiz 660 [PMID: 25869391 DOI: 10.1038/ajg.2015.112]

136 **Charatcharoenwitthaya P**, Enders FB, Halling KC, Lindor KD. Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis. *Hepatology* 2008; **48**: 1106-1117 [PMID: 18785620 DOI: 10.1002/hep.22441]

137 **Lamarca A**, Barriuso J, Chander A, McNamara MG, Hubner RA, ÓReilly D, Manoharan P, Valle JW. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) for patients with biliary

tract cancer: Systematic review and meta-analysis. *J Hepatol* 2019; **71**: 115-129 [PMID: 30797051 DOI: 10.1016/j.jhep.2019.01.038]

138 **Kuzu UB**, Ödemiş B, Suna N, Yıldız H, Parlak E, Dişibeyaz S, Torun S, Akpınar MY, Coşkun O, Turhan N, Yüksel M, Kayaçetin E. The Detection of Cholangiocarcinoma in Primary Sclerosing Cholangitis Patients: Single Center Experience. *J Gastrointest Cancer* 2016; **47**: 8-14 [PMID: 26537791 DOI: 10.1007/s12029-015-9777-1]

139 **Trikudanathan G**, Navaneethan U, Njei B, Vargo JJ, Parsi MA. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 783-789 [PMID: 24140129 DOI: 10.1016/j.gie.2013.09.015]

140 **Navaneethan U**, Njei B, Lourdusamy V, Konjeti R, Vargo JJ, Parsi MA. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2015; **81**: 168-176 [PMID: 25440678 DOI: 10.1016/j.gie.2014.09.017]

141 **Navaneethan U**, Njei B, Venkatesh PG, Vargo JJ, Parsi MA. Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 943-950.e3 [PMID: 24360654 DOI: 10.1016/j.gie.2013.11.001]

142 **Barr Fritcher EG**, Voss JS, Jenkins SM, Lingineni RK, Clayton AC, Roberts LR, Halling KC, Talwalkar JA, Gores GJ, Kipp BR. Primary sclerosing cholangitis with equivocal cytology: fluorescence in situ hybridization and serum CA 19-9 predict risk of malignancy. *Cancer Cytopathol* 2013; **121**: 708-717 [PMID: 23839915 DOI: 10.1002/cncy.21331]

143 **Arnelo U**, von Seth E, Bergquist A. Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis. *Endoscopy* 2015; **47**: 696-702 [PMID: 25826274 DOI: 10.1055/s-0034-1391845]

144 **Vesterhus M**, Karlsen TH. Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities. *J Gastroenterol* 2020; **55**: 588-614 [PMID: 32222826 DOI: 10.1007/s00535-020-01681-z]

145 **Olsson R**, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsøy-Kristiansen M, Matre J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzén H, Ung KA, Eriksson A, Lööf L, Prytz H, Marschall HU, Broomé U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology* 2005; **129**: 1464-1472 [PMID: 16285948 DOI: 10.1053/j.gastro.2005.08.017]

146 **Lindor KD**, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009; **50**: 808-814 [PMID: 19585548 DOI: 10.1002/hep.23082]

147 **Lindor KD**. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *N Engl J Med* 1997; **336**: 691-695 [PMID: 9041099 DOI: 10.1056/NEJM199703063361003]

148 **Banales JM**, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gaudio E, Alvaro D, Gradilone SA, Strazzabosco M, Marzioni M, Coulouarn C, Fouassier L, Raggi C, Invernizzi P, Mertens JC, Moncsek A, Rizvi S, Heimbach J, Koerkamp BG, Bruix J, Forner A, Bridgewater J, Valle JW, Gores GJ. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 557-588 [PMID: 32606456 DOI: 10.1038/s41575-020-0310-z]

149 **Gores GJ**, Gish RG, Sudan D, Rosen CB; MELD Exception Study Group. Model for end-stage liver disease (MELD) exception for cholangiocarcinoma or biliary dysplasia. *Liver Transpl* 2006; **12**: S95-S97 [PMID: 17123289 DOI: 10.1002/Lt.20965]

150 **Panayotova GG**, Paterno F, Guarrera JV, Lunsford KE. Liver Transplantation for Cholangiocarcinoma: Insights into the Prognosis and the Evolving Indications. *Curr Oncol Rep* 2020; **22**: 49 [PMID: 32297105 DOI: 10.1007/s11912-020-00910-1]

151 **Guerrero Bermúdez C**, Vélez Marín M, Restrepo Gutiérrez JC. Cholangiocarcinoma in patients with primary sclerosing cholangitis. *Revista Colombiana de Gastroenterologia* 2018; **33**: 285-291 [DOI: 10.22516/25007440.188]

152 **Chalasani N**, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, McCashland TM, Reddy KR, Zervos X, Anbari MA, Hoen H. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. *Hepatology* 2000; **31**: 7-11 [PMID: 10613720 DOI: 10.1002/hep.510310103]

153 **Goldaracena N**, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. *Liver Transpl* 2018; **24**: 294-303 [PMID: 29024405 DOI: 10.1002/Lt.24955]

154 **Moris D**, Kostakis ID, Machairas N, Prodromidou A, Tsilimigras DI, Ravindra KV, Sudan DL, Knechtle SJ, Barbas AS. Comparison between liver transplantation and resection for hilar cholangiocarcinoma: A systematic review and meta-analysis. *PLoS One* 2019; **14**: e0220527 [PMID: 31365594 DOI: 10.1371/journal.pone.0220527]

155 **Mansour JC**, Aloia TA, Crane CH, Heimbach JK, Nagino M, Vauthey JN. Hilar cholangiocarcinoma: expert consensus statement. *HPB (Oxford)* 2015; **17**: 691-699 [PMID:

26172136 DOI: 10.1111/hpb.12450]
156 **Tabibian JH**, Bowlus CL. Primary sclerosing cholangitis: A review and update. *Liver Res* 2017; **1**: 221-230 [PMID: 29977644 DOI: 10.1016/j.livres.2017.12.002]
157 **Qureshi K**, Jesudoss R, Al-Osaimi AM. The treatment of cholangiocarcinoma: a hepatologist's perspective. *Curr Gastroenterol Rep* 2014; **16**: 412 [PMID: 25183579 DOI: 10.1007/s11894-014-0412-2]
158 **Ali AH**, Tabibian JH, Nasser-Ghodsi N, Lennon RJ, DeLeon T, Borad MJ, Hilscher M, Silveira MG, Carey EJ, Lindor KD. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. *Hepatology* 2018; **67**: 2338-2351 [PMID: 29244227 DOI: 10.1002/hep.29730]
159 **Mazzaferro V**, Gorgen A, Roayaie S, Droz Dit Busset M, Sapisochin G. Liver resection and transplantation for intrahepatic cholangiocarcinoma. *J Hepatol* 2020; **72**: 364-377 [PMID: 31954498 DOI: 10.1016/j.jhep.2019.11.020]
160 **Rosen CB**, Heimbach JK, Gores GJ. Surgery for cholangiocarcinoma: the role of liver transplantation. *HPB (Oxford)* 2008; **10**: 186-189 [PMID: 18773052 DOI: 10.1080/13651820801992542]
161 **Kitajima T**, Hibi T, Moonka D, Sapisochin G, Abouljoud MS, Nagai S. Center Experience Affects Liver Transplant Outcomes in Patients with Hilar Cholangiocarcinoma. *Ann Surg Oncol* 2020; **27**: 5209-5221 [PMID: 32495286 DOI: 10.1245/s10434-020-08682-5]
162 **De Vreede I**, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. *Liver Transpl* 2000; **6**: 309-316 [PMID: 10827231 DOI: 10.1053/Lv.2000.6143]
163 **Vimbert E**. Randomized prospective multicentric study: radiochemotherapy and liver transplantation vs liver resection to treat respectable hilar cholangiocarcinoma. [cited 28 March 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT02232932?term=TRANSPHIL&rank=1
164 **Doherty B**, Nambudiri VE, Palmer WC. Update on the Diagnosis and Treatment of Cholangiocarcinoma. *Curr Gastroenterol Rep* 2017; **19**: 2 [PMID: 28110453 DOI: 10.1007/s11894-017-0542-4]
165 **Robles R**, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, Calleja J, Valdivieso A, Valdecasas JC, López P, Gómez M, de Vicente E, Loinaz C, Santoyo J, Fleitas M, Bernardos A, Lladó L, Ramírez P, Bueno FS, Jaurrieta E, Parrilla P. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004; **239**: 265-271 [PMID: 14745336 DOI: 10.1097/01.sla.0000108702.45715.81]
166 **Sotiropoulos GC**, Kaiser GM, Lang H, Molmenti EP, Beckebaum S, Fouzas I, Sgourakis G, Radtke A, Bockhorn M, Nadalin S, Treckmann J, Niebel W, Baba HA, Broelsch CE, Paul A. Liver transplantation as a primary indication for intrahepatic cholangiocarcinoma: a single-center experience. *Transplant Proc* 2008; **40**: 3194-3195 [PMID: 19010231 DOI: 10.1016/j.transproceed.2008.08.053]
167 **Sapisochin G**, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. *Liver Transpl* 2011; **17**: 934-942 [PMID: 21438129 DOI: 10.1002/Lt.22307]
168 **Sapisochin G**, Rodríguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, Castroagudín JF, Varo E, López-Andujar R, Palacios F, Sanchez Antolín G, Perez B, Guiberteau A, Blanco G, González-Diéguez ML, Rodriguez M, Varona MA, Barrera MA, Fundora Y, Ferron JA, Ramos E, Fabregat J, Ciria R, Rufian S, Otero A, Vazquez MA, Pons JA, Parrilla P, Zozaya G, Herrero JI, Charco R, Bruix J. "Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? *Am J Transplant* 2014; **14**: 660-667 [PMID: 24410861 DOI: 10.1111/ajt.12591]
169 **Sapisochin G**, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, Vibert E, Cherqui D, Grant DR, Hernandez-Alejandro R, Dale CH, Cucchetti A, Pinna A, Hwang S, Lee SG, Agopian VG, Busuttil RW, Rizvi S, Heimbach JK, Montenovo M, Reyes J, Cesaretti M, Soubrane O, Reichman T, Seal J, Kim PT, Klintmalm G, Sposito C, Mazzaferro V, Dutkowski P, Clavien PA, Toso C, Majno P, Kneteman N, Saunders C, Bruix J; iCCA International Consortium. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment. *Hepatology* 2016; **64**: 1178-1188 [PMID: 27481548 DOI: 10.1002/hep.28744]
170 **Lunsford KE**, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, Mobley CM, Saharia A, Victor DW, Nguyen DT, Graviss EA, Kaseb AO, McFadden RS, Aloia TA, Conrad C, Li XC, Monsour HP, Gaber AO, Vauthey JN, Ghobrial RM; Methodist-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. *Lancet Gastroenterol Hepatol* 2018; **3**: 337-348 [PMID: 29548617 DOI: 10.1016/S2468-1253(18)30045-1]
171 **Stieber AC**, Marino IR, Iwatsuki S, Starzl TE. Cholangiocarcinoma in sclerosing cholangitis. The role of liver transplantation. *Int Surg* 1989; **74**: 1-3 [PMID: 2540107]
172 **Devlin J**, O'Grady J. Indications for referral and assessment in adult liver transplantation: a clinical guideline. British Society of Gastroenterology. *Gut* 1999; **45** Suppl 6: VI1-VI22 [PMID: 10561164]
173 **Goss JA**, Shackleton CR, Farmer DG, Arnaout WS, Seu P, Markowitz JS, Martin P, Stribling RJ,

Goldstein LI, Busuttil RW. Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. *Ann Surg* 1997; **225**: 472-481; discussion 481-483 [PMID: 9193175 DOI: 10.1097/00000658-199705000-00004]

174 **Abu-Elmagd KM**, Malinchoc M, Dickson ER, Fung JJ, Murtaugh PA, Langworthy AL, Demetris AJ, Krom RA, Van Thiel DH, Starzl TE. Efficacy of hepatic transplantation in patients with primary sclerosing cholangitis. *Surg Gynecol Obstet* 1993; **177**: 335-344 [PMID: 8211575]

175 **Furmanczyk PS**, Grieco VS, Agoff SN. Biliary brush cytology and the detection of cholangiocarcinoma in primary sclerosing cholangitis: evaluation of specific cytomorphologic features and CA19-9 Levels. *Am J Clin Pathol* 2005; **124**: 355-360 [PMID: 16191503 DOI: 10.1309/J030-JYPW-KQTH-CLNJ]

176 **Meyer CG**, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation* 2000; **69**: 1633-1637 [PMID: 10836374 DOI: 10.1097/00007890-200004270-00019]

177 **Ghali P**, Marotta PJ, Yoshida EM, Bain VG, Marleau D, Peltekian K, Metrakos P, Deschênes M. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience. *Liver Transpl* 2005; **11**: 1412-1416 [PMID: 16237695 DOI: 10.1002/Lt.20512]

178 **Ali JM**, Bonomo L, Brais R, Griffiths WJ, Lomas DJ, Huguet EL, Praseedom RK, Jamieson NV, Jah A. Outcomes and diagnostic challenges posed by incidental cholangiocarcinoma after liver transplantation. *Transplantation* 2011; **91**: 1392-1397 [PMID: 21516065 DOI: 10.1097/TP.0b013e31821aba57]

179 **Becker NS**, Rodriguez JA, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. *J Gastrointest Surg* 2008; **12**: 117-122 [PMID: 17963015 DOI: 10.1007/s11605-007-0335-4]

180 **Chazouillères O**. Primary sclerosing cholangitis and biliary malignancy: a glimmer of hope? *J Hepatol* 2004; **40**: 857-859 [PMID: 15094236 DOI: 10.1016/j.jhep.2004.02.018]

181 **Resch T**, Esser H, Cardini B, Schaefer B, Zoller H, Schneeberger S. Liver transplantation for hilar cholangiocarcinoma (h-CCA): is it the right time? *Transl Gastroenterol Hepatol* 2018; **3**: 38 [PMID: 30148223 DOI: 10.21037/tgh.2018.06.06]

182 **Rea DJ**, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **242**: 451-458; discussion 458-461 [PMID: 16135931 DOI: 10.1097/01.sla.0000179678.13285.fa]

183 **Wu Y**, Johlin FC, Rayhill SC, Jensen CS, Xie J, Cohen MB, Mitros FA. Long-term, tumor-free survival after radiotherapy combining hepatectomy-Whipple en bloc and orthotopic liver transplantation for early-stage hilar cholangiocarcinoma. *Liver Transpl* 2008; **14**: 279-286 [PMID: 18306329 DOI: 10.1002/Lt.21287]

184 **Ethun CG**, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD, Salem A, Pawlik TM, Poultsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. *Ann Surg* 2018; **267**: 797-805 [PMID: 29064885 DOI: 10.1097/SLA.0000000000002574]

185 **Sudan D**, DeRoover A, Chinnakotla S, Fox I, Shaw B Jr, McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002; **2**: 774-779 [PMID: 12243499 DOI: 10.1034/j.1600-6143.2002.20812.x]

186 **Rosen CB**, Darwish Murad S, Heimbach JK, Nyberg SL, Nagorney DM, Gores GJ. Neoadjuvant therapy and liver transplantation for hilar cholangiocarcinoma: is pretreatment pathological confirmation of diagnosis necessary? *J Am Coll Surg* 2012; **215**: 31-38; discussion 38-40 [PMID: 22621893 DOI: 10.1016/j.jamcollsurg.2012.03.014]

187 **Darwish Murad S**, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; **143**: 88-98.e3; quiz e14 [PMID: 22504095 DOI: 10.1053/j.gastro.2012.04.008]

188 **Tan EK**, Rosen CB, Heimbach JK, Gores GJ, Zamora-Valdes D, Taner T. Living Donor Liver Transplantation for Perihilar Cholangiocarcinoma: Outcomes and Complications. *J Am Coll Surg* 2020; **231**: 98-110 [PMID: 32035181 DOI: 10.1016/j.jamcollsurg.2019.12.037]

189 **Cambridge WA**, Fairfield C, Powell JJ, Harrison EM, Søreide K, Wigmore SJ, Guest RV. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. *Ann Surg* 2021; **273**: 240-250 [PMID: 32097164 DOI: 10.1097/SLA.0000000000003801]

190 **Heneghan MA**, Tuttle-Newhall JE, Suhocki PV, Muir AJ, Morse M, Bornstein JD, Sylvestre PB, Collins B, Kuo PC, Rockey DC. De-novo cholangiocarcinoma in the setting of recurrent primary sclerosing cholangitis following liver transplant. *Am J Transplant* 2003; **3**: 634-638 [PMID: 12752322 DOI: 10.1034/j.1600-6143.2003.00110.x]

191 **Sutcliffe RP**, Lam W, O'Sullivan A, Prachalias A, Rela M, Heaton N. Pancreaticoduodenectomy after liver transplantation in patients with primary sclerosing cholangitis complicated by distal pancreatobiliary malignancy. *World J Surg* 2010; **34**: 2128-2132 [PMID: 20499064 DOI:

10.1007/s00268-010-0624-z]

192 **Nikeghbalian S**, Shamsaeefar A, Eshraghian A, Mansoorian MR, Kazemi K, Geramizadeh B, Malek-Hosseini SA. Liver transplantation and whipple surgery combined with chemoradiotherapy for treatment of hilar cholangiocarcinoma in patients with primary sclerosing cholangitis. *Liver Transpl* 2015; **21**: 696-699 [PMID: 25690752 DOI: 10.1002/Lt.24095]

193 **Primrose JN**, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Finch-Jones M, Wasan H, Ross P, Wall L, Wadsley J, Evans JTR, Stocken D, Praseedom R, Ma YT, Davidson B, Neoptolemos JP, Iveson T, Raftery J, Zhu S, Cunningham D, Garden OJ, Stubbs C, Valle JW, Bridgewater J; BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019; **20**: 663-673 [PMID: 30922733 DOI: 10.1016/S1470-2045(18)30915-X]

194 **Hong JC**, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, Finn R, Durazo FA, Saab S, Tong MJ, Hiatt JR, Busuttil RW. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. *Arch Surg* 2011; **146**: 683-689 [PMID: 21690444 DOI: 10.1001/archsurg.2011.116]

195 **Labib PL**, Davidson BR, Sharma RA, Pereira SP. Locoregional therapies in cholangiocarcinoma. *Hepat Oncol* 2017; **4**: 99-109 [PMID: 29367874 DOI: 10.2217/hep-2017-0014]

196 **Brunner TB**, Blanck O, Lewitzki V, Abbasi-Senger N, Momm F, Riesterer O, Duma MN, Wachter S, Baus W, Gerum S, Guckenberger M, Gkika E. Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. *Radiother Oncol* 2019; **132**: 42-47 [PMID: 30825968 DOI: 10.1016/j.radonc.2018.11.015]

197 **Mahadevan A**, Dagoglu N, Mancias J, Raven K, Khwaja K, Tseng JF, Ng K, Enzinger P, Miksad R, Bullock A, Evenson A. Stereotactic Body Radiotherapy (SBRT) for Intrahepatic and Hilar Cholangiocarcinoma. *J Cancer* 2015; **6**: 1099-1104 [PMID: 26516357 DOI: 10.7150/jca.13032]

198 **Vugts JJA**, Gaspersz MP, Roos E, Franken LC, Olthof PB, Coelen RJS, van Vugt JLA, Labeur TA, Brouwer L, Besselink MGH, IJzermans JNM, Darwish Murad S, van Gulik TM, de Jonge J, Polak WG, Busch ORC, Erdmann JL, Groot Koerkamp B, Buettner S. Eligibility for Liver Transplantation in Patients with Perihilar Cholangiocarcinoma. *Ann Surg Oncol* 2021; **28**: 1483-1492 [PMID: 32901308 DOI: 10.1245/s10434-020-09001-8]

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