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Treatment of cholangiocarcinoma in patients with primary sclerosing cholangitis: a comprehensive review

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ABSTRACT

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease, characterised by persistent biliary inflammation resulting in fibrosis and multifocal strictures of the biliary tree. The course of disease is highly variable, ranging from asymptomatic disease to the development of end-stage biliary cirrhosis and an increased risk of biliary tract cancer (BTC), particularly cholangiocarcinoma (CCA). PSC is the most important risk factor for CCA in younger people, with a reported lifetime prevalence ranging from 6% to 13%. Perihilar CCA (pCCA), involving the hepatic duct bifurcation, is the most common CCA amounting to approximately 50% of all cases, whereas intrahepatic CCA (iCCA), located within the hepatic parenchyma, represents less than 10%.

CCA is an aggressive tumour, and only a minority of patients are amenable to surgical resection with curative intent. Radical liver resection and liver transplantation are potentially curative therapeutic options in patients with PSC in the absence of metastatic or locally advanced disease. Liver transplantation with neoadjuvant chemoradiation could be considered in selected patients with unresectable pCCA and without pretreatment in patients with PSC with bile duct high-grade dysplasia. Recent reports demonstrating favourable outcomes in transplanted patients with small iCCA and patients with locally advanced disease following neoadjuvant therapy have challenged the previously described poor outcome in transplanted patients with iCCA.

Treatment for CCA is challenged by the inherent difficulties in enabling an early diagnosis and thereby preventing an otherwise dismal prognosis. This comprehensive review aims to describe therapeutic considerations and challenges in patients with PSC-CCA.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease, characterised by persistent biliary inflammation resulting in fibrosis and multifocal strictures of the biliary tree.[1–3] The course of disease is highly variable, ranging from asymptomatic disease to the development of end-stage biliary cirrhosis and an increased risk of biliary tract cancer (BTC), particularly cholangiocarcinoma (CCA).[4 5]

PSC can affect both sexes from early age until late adulthood but primarily affects men in their 30s–40s.[6 7] PSC is strongly associated with inflammatory bowel disease (IBD), and PSC-IBD represents one of the most well-described phenotypes with an increased incidence of colorectal dysplasia.[8] Small-duct PSC primarily affects the peripheral bile ducts and tends to be less symptomatic, whereas large-duct or classical PSC mainly involves the larger ducts and is prone to more cholestatic symptoms.[9] PSC with features of autoimmune hepatitis (AIH) usually affects younger patients.[10] A subset of patients with PSC have elevated serum IgG4 levels, representing a distinct clinical phenotype, which has been associated with a worse clinical outcome.[11] There is no medical therapy to prevent disease progression, even if ursodeoxycholic acid can improve biochemistry.[12] Instead, liver transplantation remains the only potentially curative treatment alternative for end-stage liver diseases.[5]

CCA is the most frequent cause of death in patients with PSC,[9 13 14] and the increased risk of CCA in patients with PSC has been reported hundred folds higher compared with the general population.[5 15] The risk of CCA is highest within the first year after PSC diagnosis, followed by an annual risk of 0.2%–1.5%,[4 9 16–18] suggesting either that CCA is unrelated to the duration of PSC or that the diagnosis of PSC has been delayed in these patients.[9 19] CCA in patients with PSC has been associated with concomitant IBD, especially ulcerative colitis as well as advanced age at PSC diagnosis, whereas patients with features of AIH and small-duct disease are at lower risk.[4 6 9 20]

Pathogenesis and classification

The pathogenesis of PSC has been associated with an interaction between a genetic predisposition and environmental factors, through multiple immune-mediated mechanisms, leading to a chronic injury to the cholangiocytes.[21–26] CCA pathogenesis in patients with PSC has been ascribed to the persistent

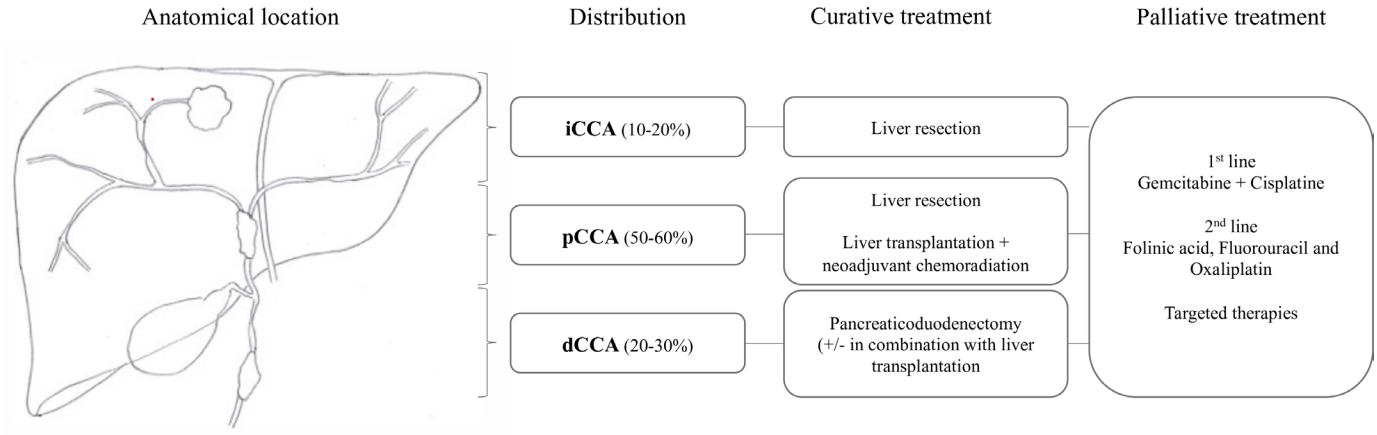

Figure 1 Anatomical location, distribution and treatment of intrahepatic, perihilar and distal cholangiocarcinoma in primary sclerosing cholangitis. dCCA, distal cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma.

inflammation in the cholangiocytes resulting in dysplastic transformation and ultimately carcinoma.[27–29] Similar to the distribution of CCA in the general population, PSC-CCA can occur in any part of the biliary tree but is most frequently observed in the hilar bifurcation, perihilar CCA (pCCA), followed by the distal common bile duct, distal CCA (dCCA), and an intrahepatic manifestation, intrahepatic CCA (iCCA) (figure 1).[19 30 31] pCCAs are further classified morphologically based on the primary growth pattern, ie, the intraductal, periductal and mass-forming subtypes. The periductal subtype, which is the most common subtype, has a characteristic longitudinal growth pattern that causes biliary strictures.[32] Genetic alterations associated with iCCA include isocitrate dehydrogenases 1 and 2 (IDH1/2), neuroblastoma RAS oncogene and fibroblast growth factor receptor 2 (FGFR2), whereas mutations in tumour protein p53 (TP53), Kirsten rat sarcoma viral (KRAS) ongogene, v-raf murine sarcoma viral oncogene homolg B1 (BRAF) and suppressor of transcriptor factor mothers against decapentaplegic 4 (SMAD4) are more prevalent in extrahepatic CCA.[33–35] Two molecular subgroups, assessed by genomic methodologies, have been described for iCCA: an inflammation class characterised by the activation of inflammatory signalling pathways and a proliferation class characterised by cellular signals involved in cell-cycle regulation.[36] The latter is associated with a worse outcome.[36] In addition, patients with PSC have an increased risk of gallbladder carcinoma through a malignant transformation of gallbladder polyps.[37 38]

Diagnosis

Identifying CCA in patients with PSC remains difficult, due to diagnostic limitations and the unspecific symptoms, which often present late and overlap with those of progressive benign disease.[39 40] Patients with pCCA and dCCA often present with tumour-mediated biliary obstruction, whereas the symptoms of iCCA are often unspecific.[41] Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) is the imaging modality of choice when PSC-CCA is suspected.[42] CCA in patients with PSC has been ascribed to the development of severe stricturing, ie, dominant/high-grade strictures.[43 44] However, dominant/high-grade strictures may present without symptoms and are present in approximately 50% of patients at the time of PSC diagnosis.[43–45] Another condition mimicking malignant biliary strictures is IgG4-related systemic disease, which is a systemic inflammatory syndrome characterised by infiltration of IgG4-positive plasma cells.[46] This systemic inflammatory condition, which responds favourably to glucocorticoids, may be difficult to differentiate from CCA when only the bile ducts are affected.[47]

Malignant strictures are difficult to identify, and tissue sampling is usually required, especially in the absence of a mass lesion.[16 41 48 49] Tissue sampling obtained by brush cytology and complementary fluorescence in situ hybridisation (FISH) via endoscopic retrograde cholangiopancreatography improves the diagnosing of a malignant stricture but is limited by poor sensitivity, approximately 70%.[50–52] Endoscopic ultrasound with fine-needle aspiration can be used for diagnosing dCCA but ought to be avoided if liver transplantation can be considered.[53] The number of CCA, incidentally detected in liver explants, ranging from 1% to 7%, further illustrates the difficulty in early detection of CCA.[18 54]

The search for biomarkers for early detection of CCA is ongoing. Carbohydrate antigen 19–9 (CA19-9), a carbohydrate secreted by cancer cells, is the most used biomarker for CCA.[55–57] Elevated CA19-9 levels, especially in the absence of bacterial cholangitis and in the presence of suspicious lesion, have been associated with CCA, but measurements of CA19-9 are of limited value in predicting CCA.[58 59] CA19-9 synthesis is also dependent on the enzymes fucosyltransferases 2 and 3, and genotyping of these enzymes has been shown to improve the diagnostic value of CA19-9 for detecting BTC in patients with PSC, with a sensitivity of almost 80%.[60 61]

Surveillance for early detection of CCA

The potential survival benefit of early CCA detection has called for surveillance in patients with PSC,[62] and retrospective studies from tertiary centres have reported a survival benefit and/or risk reduction of hepatobiliary cancer-related death, in patients exposed to regular surveillance.[13 63] Despite limited evidence, regular imaging is recommended.[3 49] However, in a recent prospective surveillance study, yearly MRI/MRCP was found ineffective in diagnosing CCA early enough to benefit survival in an unselected cohort of patients with PSC.[18] Instead, surveillance with MRI/MRCP may be recommended in patients at time of PSC diagnosis, in the event of new symptoms and more regularly in patients with advanced disease.[9]

TREATMENT OF pCCA

CCA is in general treated similarly in patients with de novo CCA and PSC-associated CCA, yet the underlying liver disease in patients with PSC can have implications on therapeutic alternatives. The following sections initially describe treatment in CCA in general followed by specific considerations in patients with PSC.

Liver resection

For pCCA in general, liver resection is a potentially curative treatment alternative, if radicality can be achieved with preserved liver function.[41] Estimation of future liver remnant (FLR) is used to avoid postoperative hepatic insufficiency, with a minimum FLR of 20% in patients with normal liver function and 40% in those with chronic liver disease.[64] Resection of pCCA is complex as it often requires extended resections and vascular reconstructions.[65 66] Even so, radicality is difficult to obtain, morbidity is high and long-term survival remains low with a reported 5-year survival ranging from 20% to 40%.[65–68] Patients with resected BTC are offered 6 months of adjuvant chemotherapy with capecitabine, according to current guidelines.[69 70]

Due to the underlying parenchymal liver disease and the propensity of skip cancer lesions, liver resection in PSC-pCCA is even more challenging, often resulting in narrow margins despite extended resection and the high morbidity and mortality that it entails.[66 71] Transient elastography can be used to estimate liver fibrosis and aid in determining whether major liver resection with adequate liver remnant is feasible in a patient with PSC-pCCA.[72]

In an era of transplantation oncology, in which PSC-associated pCCA has been considered unresectable, recent data on patients with PSC undergoing liver resection are understandably limited.[66 71] A North American multicentre study from 2018 reported a similar outcome in patients with resectable pCCA with and without PSC, with a 5-year overall survival (OS) and disease-free survival (DFS) of approximately 20%.[73] Lymph node involvement, vascular invasion, low tumour differentiation and higher age are associated with worse OS.[74]

The outcome following liver resection has been compared with that of chemoradiotherapy followed by liver transplantation in patients with de novo CCA and PSC-associated CCA, describing a superior outcome in patients treated with chemoradiotherapy and liver transplantation.[71 75] A recent multicentre study reported a 64% 5-year survival in the transplantation group compared with 18% in the resection group.[71] Compared with resected patients, transplanted patients were younger and more frequently had PSC.[71] Other clinicopathological differences between resected and transplanted patients, ie, resectability and lymph node status, are expected, as these factors are used to select patients for one surgical approach over the other but impact comparative evaluations between the two treatment approaches.[71 75] There is currently an ongoing randomised intention-to-treat multicentre trial of CCA without PSC in France comparing neoadjuvant chemoradiation followed by liver transplantation with liver resection (NCT02232932).

Liver transplantation

Liver transplantation has over the last decades emerged as a potentially curative treatment alternative for pCCA in patients with PSC and de novo CCA. The following section describes the paradigm shift of treating pCCA with liver transplantation, especially with regard to PSC-CCA. The initial experience of treating pCCA with liver transplantation was marked by high recurrence rates and poor survival.[76 77] In 1993, the Mayo Clinic developed a protocol to treat patients with unresectable, de novo early-stage pCCA or early-stage pCCA arising in PSC, with liver transplantation following chemoradiation therapy.[78 79]

The Mayo protocol

Patients eligible for treatment according to the Mayo protocol are selected according to the following criteria: a malignant-appearing stricture on cholangiography and one of the following—(1) brush cytology or tissue biopsy positive or strongly suspicious for CCA, (2) levels of CA19–9 >100 U/mL in the absence of acute bacterial cholangitis or (3) polysomy by FISH or a mass-forming lesion <3 cm in radial diameter.[78] Patients with extrahepatic disease, prior radiation to the abdomen, percutaneous transhepatic tumour biopsy and conditions precluding liver transplantation are not eligible for the treatment.[78] The favourable outcome following treatment according to the Mayo protocol has partly been ascribed to a strict adherence to the selection criteria and the highly selected group of patients that it entails.

Treatment according to the Mayo protocol includes external bean radiotherapy (EBRT) with a target dose of 4500 cGy delivered over 3 weeks alongside an infusion of 5-FU or followed by intraluminal brachytherapy using Iridium-192 seeds.[78] Patients are treated with oral capecitabine until liver transplantation.[78] On completion of chemoradiation therapy, a surgical staging is performed, with varying time intervals from the transplantation.[78]

The surgical staging involves exploration of the abdominal cavity and examination of regional hepatic lymph nodes.[78] At liver transplantation, arterial jump grafts are recommended due to the risk of irradiated native vessels.[78] The portal vein and bile duct are divided as close to the pancreas as possible, and frozen section of the distal bile duct is checked for tumour infiltration. In the event of tumour infiltration in the distal bile duct, pancreaticoduodenectomy is considered to enable radicality.[78] In this highly selected group of patients, a 5-year survival of 82% was reported.[78]

In 2012, the Mayo Clinic reported a worse 5-year survival in PSC-patients with pretreatment pathological confirmation compared with PSC-patients lacking pathological confirmation.[80] The 5-year survival in patients with PSC-associated CCA with pathological confirmation was 66% compared with 92% in PSC-associated CCA without pathological confirmation.[80] As pathological confirmation was not associated with survival in patients with de novo pCCA and pathological confirmation neither had an impact on the detection of residual pCCA in the explants nor recurrence, the authors concluded that although desirable, pretreatment pathological confirmation should not be a requirement.[80] When combining patients with pretreatment pathological confirmation of pCCA, explant pathological confirmation and recurrence, 5% of treated patients did not have a confirmed pCCA, which has been one objection to the Mayo protocol.[81] The favourable results in patients treated according to the Mayo protocol have partly been ascribed to a stringent patient selection.[81] Even so, with the lack of pathological confirmation, there is a risk of treating patients without malignancy.

Versions of the Mayo protocol with varying selection criteria and pretransplantation chemoradiation have since then been applied in several well-experienced centres.[71 82 83] Following confirming reports of favourable outcome in patients with pCCA treated with chemoradiation and liver transplantation, from other North American centres, the highly selected group of patients with pCCA eligible for the treatment was granted model for end-stage liver disease (MELD) score exception points and thereby faster access to liver transplantation.[81]

Treatment outcome

A recent meta-regression and meta-analysis showed that chemoradiation therapy and liver transplantation enable long-term survival in the highly selected group of patients eligible for the treatment, out of whom patients with PSC appear to have the most favourable outcome.[82] In 2020, long-term data on patients treated according to the Mayo protocol showed a superior long-term survival in PSC-associated pCCA compared with de novo pCCA, 5-year survival 74% vs 58% and 10-year survival 67% vs 47%.[84] In addition, patients with PSC were less likely to drop out due to disease progression and less likely to suffer from recurrence, 14% vs 26% and 22% vs 45%, respectively.[84]

In the Mayo Clinic experience, 30% of transplants performed for pCCA were living donor liver transplantations (LDLTs), with results comparable with those of deceased donor liver transplantations.[85] A majority of recipients (66%) were patients with PSC.[85] In LDLT, a greater frequency of vascular complications was observed, which could be ascribed to an effect of radiation therapy, yet its occurrence did not appear to adversely affect long-term outcome.[85]

The reported 5-year patient survival following liver transplantation in patients with PSC amounts to 80%, yet transplanted patients have an increased risk of rejection, and PSC recurs in 15%–25% of transplanted patients.[86 87] The increased risk of recurrence and thereby retransplantation stresses the importance of adequately diagnosing dysplasia and malignancy.[88]

Palliative therapy

The majority of patients with pCCA are neither eligible for curative surgery with liver resection nor liver transplantation at the time of diagnosis.[89–91] pCCA is considered unresectable in the event of bilateral involvement of the second-order bile ducts, bilateral or contralateral hepatic artery or portal vein encasement, intrahepatic or extrahepatic metastases and distant lymph node metastases.[71] In addition, patients eligible for chemoradiation and liver transplantation according to the Mayo criteria are limited, 5% according to a recent European study.[92] In addition, reports on dropout during the pretransplantation treatment due to disease progression, therapy intolerance and death vary from 10% to 60%.[81 84]

The prognosis of unresectable pCCA is poor, both in patients with PSC-associated CCA and de novo PSC, with a median survival of less than a year with combined gemcitabine and cisplatin, as first-line chemotherapy, and FOLFOX (folinic acid, fluorouracil and oxaliplatin), as second-line chemotherapy.[19 93–95] Approximately 20% of patients are not eligible for active palliative treatment and receive best supportive care.[41]

TARGETED THERAPIES

Durvalumab is a monoclonal antibody that binds to the programmed death ligand 1 (PD-L1) and induces apoptosis by inhibiting T cell effector functions.[96] Prolonged survival in patients with advanced BTC has been reported in patients treated with durvalumab in combination with gemcitabine and cisplatin.[97] Mutations in the genes for IDH1/2 result in excess production of an important oncometabolite. In patients with iCCA, a clinical benefit was reported following treatment with the IDH1 inhibitor, ivosidenib.[98] Clonal FGFR2 gene fusion in CCA leads to the activation of multiple signalling networks that promote tumour progression.[33] There is currently an ongoing phase III trial to treat participants with FGFR2-mutated iCCA with infigratinib, which selectively inhibits FGFR2 (NCT03773302).

TREATMENT OF iCCA

Liver resection

For iCCA in general, liver resection is the recommended curative treatment if radicality with preserved liver function by adequate liver remnant can be achieved, with a 5-year survival of approximately 30%–40%.[99 100] Portal vein occlusion, hepatic liver vein occlusion and two-stage liver resections including associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are surgical strategies for optimising the FLR volume and enabling radical resections.[101] In addition to the major liver resections, lymphadenectomy is often performed to improve prognosis.[49 100] Minimally invasive liver surgery can be considered in selected patients.[102] The risk of recurrence following liver resection is approximately 60%–70% and is associated with vascular invasion, aggressive biological features, narrow surgical margin and lymph node metastases.[100 103] Most recurrences occur in the liver.[103] Similar to resected patients with pCCA, resected patients with iCCA are offered adjuvant capecitabine to improve OS and DFS.[70] Neoadjuvant chemotherapy is not routinely offered to patients with upfront resectable iCCA but has been shown to enable resection in selected patients with advanced iCCA.[49 104]

The number of patients with PSC in studies on iCCA is small. Over a 20-year period, out of 830 patients with PSC, 19 patients developed iCCA. Seven patients were resected, and the remaining 12 patients had advanced and/or disseminated disease. The 5-year OS for all 19 patients was 12%.[63]

Liver transplantation

Due to poor survival, iCCA was for a long time regarded as a contraindication for liver transplantation.[105] This was challenged when a survival benefit was reported in transplanted patients, in whom iCCA <2 cm were incidentally found in the native liver.[54] A later study demonstrated a favourable outcome in patients, in whom an iCCA <5 cm and >2 cm were found incidentally.[106] The study compared the outcome in transplanted patients and resected patients with a 5-year DFS of 67% vs 36% in resected patients.[106]

Liver transplantation following neoadjuvant therapy for locally advanced iCCA has also been evaluated with promising results in a prospective case series of 12 patients.[107] Patients with non-cirrhotic, locally advanced iCCA without extrahepatic disease or vascular involvement were treated with liver transplantation following gemcitabine-based chemotherapy.[107] Patients were listed for liver transplantation after a minimum of 6 months of radiological response or stability.[107] The 5-year OS was 83%, and the 5-year DFS was 50%.[107] Out of 21 patients that were evaluated for enrolment, 9 patients were considered ineligible due to extrahepatic disease, and 2 patients were downstaged to resectable disease.[107] Out of the 12 patients that were listed for liver transplantation, 6 patients were transplanted, 3 patients were waiting for liver transplantation at the end of the study, 2 patients did not receive a transplant due to adhesion severity and 1 patient was at the time for exploration found with resectable disease and instead underwent partial hepatectomy.[107]

There are currently ongoing prospective clinical trials to evaluate liver transplantation in iCCA. One North American and Spanish-based prospective clinical trial evaluates liver transplantation for small iCCA in patients who are not amenable to liver resection due to underlying liver disease (NCT02878473), and part of the same network is also investigating liver transplantation for locally advanced iCCA (NCT04195503) following neoadjuvant chemotherapy. In addition, a Norwegian trial is studying the outcome of liver transplantation in unresectable iCCA following neoadjuvant chemotherapy (NCT0455621).

Palliative therapy

Due to the lack of data specifically on PSC-associated iCCA, these patients are treated as patients with de novo iCCA. iCCA, which has the poorest prognosis of the CCA, often presents at a late stage, in both patients with PSC and in control cohorts without PSC, and less than 30% of patients are amenable to curative surgical resection.[41 108] iCCA primarily metastasises to the lungs, distant lymph nodes and bone, whereas pCCA and dCCA more often disseminate to the liver and peritoneum.[41]

Patients with unresectable iCCA are offered palliative chemotherapy, like pCCA, with combined gemcitabine and cisplatin as first-line chemotherapy and FOLFOX as second-line chemotherapy.[94 95] Patients with PSC are less likely to receive active palliative therapy, which might be ascribed to late diagnosis, rapid deterioration and underlying liver dysfunction.[19]

Patients with locally advanced, unresectable disease, limited to the liver locoregional therapies (LRTs), have been evaluated. Transarterial chemoembolisation (TACE), EBRT, hepatic artery infusion (HAI) and transarterial radioembolisation (TARE) have reported an OS ranging from 13 to 21 months, but as of yet, LRT is not considered a standard therapy for unresectable iCCA.[109 110] In addition, patients are treated with targeted therapies as described in the section about palliative therapy for pCCA.

TREATMENT OF dCCA

Pancreaticoduodenectomy

Pancreaticoduodenectomy is the potentially curative surgical treatment for dCCA in general, with a reported 5-year survival of 22%.[111] Resected patients are offered adjuvant capecitabine.[70] In the event of dCCA and simultaneous pCCA, pancreaticoduodenectomy could be considered simultaneous or sequential to liver transplantation.[75 112] The reported higher frequency of pancreatic cancer in patients with PSC in epidemiological studies might partly in fact be dCCA.[13 113]

Palliative therapy

As for unresectable iCCA and pCCA, the recommended palliative chemotherapy includes combined gemcitabine

and cisplatin as first-line chemotherapy and FOLFOX as second-line chemotherapy.[94 95] Data on the specifics of unresectable dCCA in patients with PSC are limited. In addition, patients are treated with targeted therapies as described in the section about palliative therapy for pCCA.

DISCUSSION

Treatment for PSC-pCCA has evolved over the last decades with a favourable outcome for a selected group of patients at well-experienced centres, yet the most pressing issue is the detection of pCCA early enough to enable curative therapy. Even though diagnostics are improving with, for instance, the addition of FISH and improved radiological criteria for identifying malignant strictures, most patients are diagnosed at a late stage and not amenable to curative treatment. Until more advanced surveillance strategies or early diagnostic tests have emerged and have been implemented, a low threshold for suspicion ought to be recommended, especially in patients with the highest cancer risk. For instance, high-quality MRI/MRCP is of highest value at the time of PSC diagnosis to rule out concomitant CCA and should be used in the event of new symptoms and regularly in patients with advanced disease.

The paradigm shift to treat CCA with liver transplantation, which has already occurred for pCCA, is potentially ahead for iCCA but is highly dependent on the characterisation of eligible patient groups and the evaluation of neoadjuvant chemotherapy.

Organ resources are scarce, and a potentially increasing allocation of organs to patients with CCA is not uncontroversial. The scarcity of organ resources requires a strict and optimal patient selection to enable survival benefit for patients with CCA without compromising the outcome of other patients on the waiting list for liver transplantation. However, patients with PSC might be a group of patients eligible for LDLT, which could increase the organ pool with potentially improved neoadjuvant chemoradiation therapy, and could even widen the indication for treatment.

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