

Malignancy and Primary Sclerosing Cholangitis: Cholangiocarcinoma, Hepatocellular Carcinoma, and Gallbladder Carcinoma

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Technical Terms and Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AJCC	American Joint Committee on Cancer
BCLC	Barcelona Clinic Liver Cancer
CCA	Cholangiocarcinoma
CLIP	Cancer of the Liver Italian Program
CT	Computerized tomography
CTP	Child-Turcotte-Pugh
DDLT	Deceased donor liver transplantation
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasound
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
GBC	Gallbladder carcinoma
HCC	Hepatocellular carcinoma
LDLT	Living donor liver transplantation
MELD	Model for end-stage liver disease
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging

NCCN	National Comprehensive Cancer Network
OLT	Orthotopic liver transplantation
PDT	Photodynamic therapy
PIVKA II	Prothrombin induced by vitamin K absence II
PSC	Primary sclerosing cholangitis
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
TNM	Tumor, node, metastasis
UCSF	University of California, San Francisco
UNOS	United Network for Organ Sharing
US	Ultrasound
Y-90	Yttrium-90

Cholangiocarcinoma

Introduction

Cholangiocarcinoma (CCA) is a common and devastating malignancy associated with primary sclerosing cholangitis (PSC). Cholangiocarcinoma is classified into intrahepatic CCA and extrahepatic CCA. Intrahepatic cholangiocarcinomas are located within the hepatic parenchyma. The anatomic boundary between intrahepatic CCAs and extrahepatic CCAs are the second-order bile ducts. Extrahepatic CCA is further differentiated into perihilar tumors, also known as Klatskin tumors, and distal tumors. The cystic ducts serve

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as the anatomic boundary between perihilar and distal tumors. The location of CCA affects both the management and prognosis. The majority of CCAs associated with PSC are perihilar. Overall CCA has a poor prognosis in PSC.

Epidemiology

Individuals with PSC are at significantly higher risk for developing CCA. Bergquist et al. found that in a Swedish cohort, the incidence of hepatobiliary malignancy was 161 times higher in individuals with PSC compared to the general population [5]. The incidence of CCA in PSC reported in the literature varies widely but is most frequently reported to be in the range 7–14 % in population-based studies [5, 12, 38]. A higher incidence is reported in transplant studies with 10–36 % of incidental diagnoses of CCA at the time of transplant for PSC [1, 27, 34, 49, 52]. Up to 50 % of cases of cholangiocarcinoma are diagnosed within the first year of PSC diagnosis [10]. The exact reason is not known; however, we suspect that this may be due in part that the symptoms associated with malignancy prompt the diagnosis of PSC. After the first year, the annual incidence is 0.5–1.5 % [5, 15, 19, 29].

Pathogenesis

CCA arises from the bile duct epithelial cells (cholangiocytes) (Fig. 2.1) [16]. Chronic inflammation in the biliary tract, as is found in PSC, predisposes individuals to the development of CCA. Conversion from normal to malignant bile epithelium likely involves an accumulation of successive genetic mutations, similar to colorectal carcinoma. The oncogenesis in PSC, however, is not as well understood. The mechanism of chronic inflammation leading to somatic mutations is thought to be in part facilitated by inducible nitric oxide synthase (iNOS). Studies have found iNOS expression in PSC cholangiocytes, and formation of iNOS is thought to cause oxidative DNA damage and inactivation of the DNA repair process [35]. Mutations in several genes involved in cell

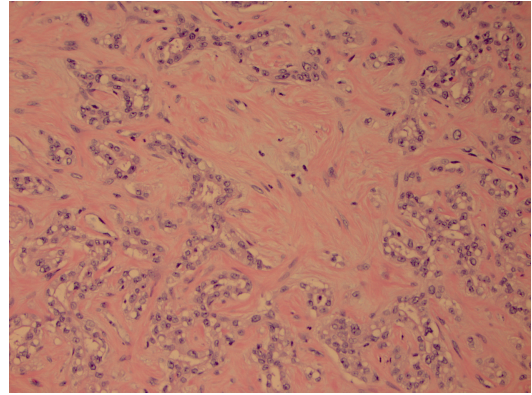


Fig. 2.1 Cholangiocarcinoma is represented by infiltrative glands with morphologic atypia with nuclear hyperchromasia and distinct nucleoli with surrounding desmoplastic tissue (200 \times ; Courtesy of Dr. Jeffery Kaplan)

growth and tumor suppression have been identified in the oncogenesis of PSC-associated CCA. Overexpression of the *p53* tumor suppressor gene has been identified in up to 93 % of PSC-associated CCA; other genes include *p16*, *EGFR*, and *Her2/neu* [64]. In addition polymorphisms in *NKG2D*, an activating receptor on the surface of T lymphocytes and natural killer cells, have been found to be associated with increased risk of cholangiocarcinoma in PSC [64]. Identifying additional molecular targets is an area of avid research in PSC-associated CCA with the ultimate goal of developing new targeted therapies.

Risk Factors

There are several risk factors associated with an increased risk of CCA (both intrahepatic and extrahepatic) in the general population including parasitic infections [62] and biliary tract disorders. In PSC, specifically, several risk factors have also been linked to an increased risk of developing PSC. High alcohol consumption has been found to be associated with a higher risk of CCA. Chalasani et al. found alcohol consumption had an odds ratio of 2.95 (95 % CI 1.04–8.3) for developing CCA [17]. A case control study of 20 patients found smoking to be higher in PSC patients with CCA ($p < 0.0004$) [6]. However,

subsequent studies have failed to replicate this correlation [15, 17]. Predictors of developing CCA in individuals with PSC include degree of serum bilirubin elevation, variceal bleeding, Mayo score >4, the presence of chronic ulcerative colitis with colorectal cancer or dysplasia, and the duration of inflammatory bowel disease [10]. Interestingly, the duration of PSC has not been found to be associated with a higher risk of CCA in contrast to the higher risk of colonic dysplasia associated with duration of ulcerative colitis. None of these risk factors or predictors have proven to be clinically useful in targeting a population to screen for CCA, however.

Screening

Currently the American Association for the Study of Liver Disease does not have published guidelines for routine screening for CCA in patients with PSC due to lack of highly sensitive and cost-effective diagnostic testing. The American College of Gastroenterology recommends considering screening with ultrasound or MRI and serial CA 19-9 every 6–12 months [43]. While consensus guidelines have not yet been established, most providers do screen for CCA in patients with PSC with routine liver chemistries every 3–6 months and annual MRI/MRCP and CA 19-9. Based on the results of these studies as well as clinical information, those with suspicion for CCA often undergo ERCP to assess for a dominant stricture where biliary tract brushings for cytology and fluorescent in situ hybridization (FISH) are typically performed [63].

Diagnosis

Overview

Diagnosis of CCA can be challenging. A dominant stricture in a patient with PSC is a stenosis with a diameter of ≤ 1.5 mm in the common bile duct or ≤ 1 mm in the hepatic ducts [9]. It is often difficult to distinguish a benign dominant stricture from PSC from a malignant stricture; thus, one should have a high index of suspicion for

CCA when a patient develops evidence of biliary obstruction (jaundice, cholestasis, pruritus, cholangitis), unexplained weight loss, or abdominal pain. A multidisciplinary approach is often needed to diagnose CCA including laboratory studies, cross-sectional imaging, cholangioscopy, and pathology.

Imaging

A variety of imaging modalities are used in the diagnosis of CCA including ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI) with concurrent magnetic resonance cholangiopancreatography (MRCP) (see Chap. 13). The positive predictive value is nearly 100 % if a characteristic lesion is found on US, CT, or MRI (Table 2.1). Characteristic lesions, however, are not commonly seen, especially in early-stage CCA. The overall positive predictive value for US, CT, and MRI are 48 %, 38 %, and 40 %, respectively [19].

CA 19-9

The most commonly used laboratory test besides routine liver enzymes to detect CCA is CA 19-9. CA 19-9 is an antibody that binds to the tumor surface marker Sialyl-Lewis A. CA 19-9 is found to be elevated (normal typically up to 35 U/ml) in multiple other diseases and bile duct conditions including ascending cholangitis, hepatocellular carcinoma, alcoholic liver disease, primary biliary cirrhosis, chronic viral hepatitis, autoimmune hepatitis, and pancreatitis. Levy et al. found that in PSC, a CA 19-9 of ≥ 129 U/mL had a sensitiv-

Table 2.1 Characteristic appearance of cholangiocarcinoma on various imaging modalities

Imaging modality	Appearance of characteristic lesion
Ultrasound	Well-defined mass with echogenicity different from that of the liver
CT	Well-defined mass with hypoattenuating enhancement relative to the liver on portovenous phase and hyperattenuating on delayed phase imaging
MRI	Well-defined mass hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging

ity of 79 %, a specificity of 98 %, and a positive predictive value of 79 % for CCA [40]. A change in CA 19-9 of ≥ 63.2 U/mL had a sensitivity of 90 %, specificity of 98 %, and a positive predictive value of 42 %.

Biliary Brushing

Endoscopic retrograde cholangiopancreatography (ERCP) is often used in patients with PSC to further investigate and characterize biliary strictures and to manage biliary obstruction with balloon dilation and stenting. Tissue sampling of dominant strictures is often achieved through bile duct brushings for cytology. Routine biliary cytology alone has been found to be highly specific (95–100 %) but to have lower sensitivity (36–83 %) [42]. The broad range in sensitivity cited in literature is due to the definition of a positive cytology results. Studies that defined a positive finding as both high-grade and low-grade dysplasia had a higher sensitivity than those that only defined high-grade dysplasia as a positive result.

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) can be used in addition to cytology to increase sensitivity for malignancy. Fluorescence in situ hybridization uses fluorescently labeled DNA probes to detect chromosomal aneuploidy (losses or gains of chromosomes). Abnormalities are characterized as trisomy, tetrasomy, and polysomy of chromosomes 3 and/or 7. Trisomy refers to ≥ 10 cells with three copies of chromosome 3 and 7, tetrasomy refers to ≥ 10 cells with four copies of all probes, and polysomy refers to ≥ 5 cells with ≥ 3 signals in two or more of the four probes [3]. Trisomy and tetrasomy of chromosomes 3 and 7 have low specificity for PSC as these findings are frequently found in biliary tree inflammation without malignancy. In contrast, polysomy has a specificity of 88 % for CCA [3]. It is difficult to interpret positive FISH polysomy in the setting of negative cytology. Patients with positive polysomy on serial brushings are significantly more likely to be diagnosed with cholangiocarcinoma than those with subsequent nonpolysomy results [4]. The presence of both polysomy and CA 19-9 ≥ 129 U/mL was a

significant predictor for developing CCA (hazard ratio of 20.4 (95 % CI 7.94–52.63)) for polysomy and CA 19-9 ≥ 129 U/mL versus nonpolysomy and CA 19-9 < 129 U/mL [4]. If a patient with PSC is found to have negative cytology and polysomy, they should be followed up closely with repeat ERCP and biliary brushings for cytology and FISH especially if there is a non-resolving dominant stricture and/or elevated CA 19-9. Compared with other prognostic features, multifocal (multiple areas of the biliary tree) polysomy carries the highest risk for cholangiocarcinoma compared to unifocal polysomy HR 82.4 (95 % CI 24.5–277.3) vs. 13.27 (95 % CI 3.32–53.1), respectively, on univariate analysis [24]. Multifocality remains a stronger predictor of CCA even when adjusting for CA 19-9, cytology, and prior abnormal FISH. Patients with unifocal polysomy with suspicious cytology remain at increased risk. If serial polysomy is detected in a malignant appearing stricture, even in the setting of negative cytology, liver transplantation should be considered. Figure 2.2 summarizes the approach to managing a dominant stricture in patients with PSC.

Cholangioscopy with Biopsy

Cholangioscopy allows for direct visualization of the biliary tree and theoretically improves sampling as it allows for directed bile duct biopsies. Visual characteristics suspicious for malignancy are exophytic lesions, ulcerations, papillary mucosal projections, dilated tortuous vessels, and raised lesions [20, 60]. A meta-analysis showed that cholangioscopy with targeted biopsies of dominant strictures was able to detect CCA with a sensitivity and specificity of 66.2 % and 97 %, respectively [37].

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) of a biliary stricture has also been used for additional tissue sampling in the setting of indeterminate biliary brushings and FISH. However, this method carries a risk of tract seeding and peritoneal metastasis and should be avoided, especially in patients potentially eligible for liver transplantation. In one study, 83 % of individuals who underwent a transperitoneal or trans-

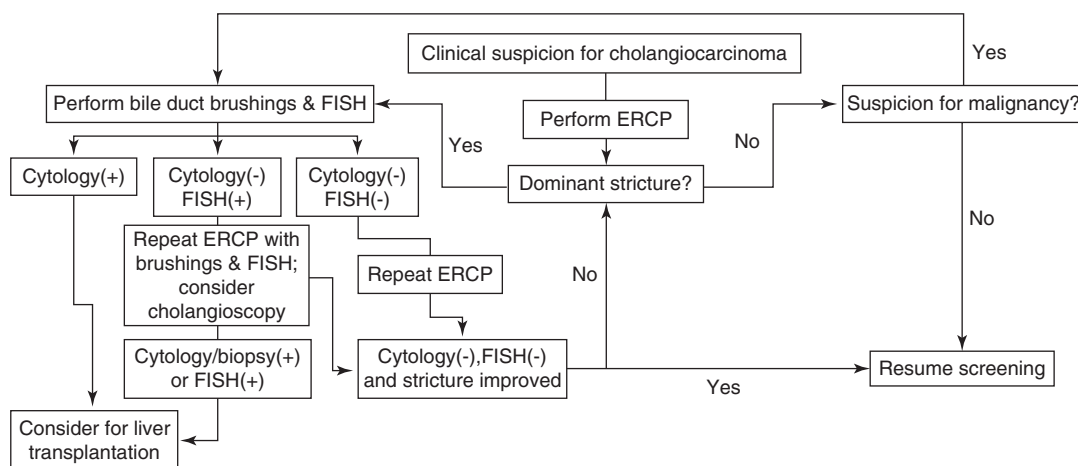


Fig. 2.2 Evaluation of the primary sclerosing cholangitis patient with clinical suspicion for cholangiocarcinoma. A dominant stricture in a patient with PSC is a stenosis with a diameter of ≤ 1.5 mm in the common bile duct or ≤ 1 mm in the hepatic ducts. Positive cytology and biopsy refers to

that which is diagnostic for cholangiocarcinoma, and positive fluorescence in situ hybridization (FISH) refers to the presence of polysomy (ERCP endoscopic retrograde cholangiopancreatography)

luminal biopsy of biliary strictures had peritoneal metastasis compared to 8% peritoneal metastasis in those who did not undergo biopsy [32]. EUS with FNA may be useful to sample lymph nodes to evaluate for metastatic disease in those being considered for liver transplantation and is often done prior to exploratory laparotomy.

Management

The mainstay of treatment for CCA is surgery. The only potential curative therapies include either liver resection or liver transplant. Patients with PSC are often not candidates for surgical resection due to the presence of diffuse bile duct disease and/or the presence of advanced hepatic fibrosis or cirrhosis. Patients with distal common bile duct tumors may be amenable to surgical resection if advanced liver disease is not present.

Surgical Resection

Surgical resection is an option for localized lesions with otherwise normal hepatic parenchyma. Contraindications to surgical resection of hilar CCA include bilateral tumor extension involving the left and right secondary biliary radicles, unilobar involvement with encasement of

contralateral portal vein or hepatic artery, bilateral vascular involvement, distant metastases, underlying liver disease (advanced fibrosis or cirrhosis), future liver remnant $<25\text{--}30\%$ with no or poor response to portal vein occlusion, and severe comorbidities [33, 55]. Due to the diffuse nature of PSC and risk for advanced hepatic fibrosis, PSC patients with CCA are often not candidates for resection.

Liver Transplantation

Most patients with PSC and the diagnosis of hilar CCA will need to be considered for liver transplantation (LT) as means for a definitive cure. Liver transplantation is not generally considered a treatment for intrahepatic or distal bile duct tumors. The management of the latter is a Whipple procedure which in a patient with severe end-stage liver disease may require concurrent liver transplantation. Historically, LT for CCA has been associated with very poor outcomes. In 2000, The Mayo Clinic developed a protocol for both patient selection and treatment of patients with CCA undergoing LT [23]. Patients fulfilling the so-called Mayo criteria showed superior outcomes with LT compared to historical controls. One study found a median survival of 3.3 years after LT prior to the publication of the Mayo results in

May 2000 compared to a median survival of 7.8 years for LTs done after May 2000 [58].

The Mayo protocol employs neoadjuvant therapy followed by LT as a definitive therapy for patients with hilar CCA. The criteria include patients with biliary duct obstruction and cytologically proven CCA or a mass lesion seen on cross-sectional imaging with biliary obstruction (Table 2.2). The protocol utilizes external and intraductal radiation therapy followed by chemotherapy (capecitabine) until the patient undergoes LT. All patients undergo exploratory surgery prior to LT to exclude extrahepatic disease, either after completing radiation or just prior to transplant. Using this protocol, Rea et al. found that LT with neoadjuvant chemoradiation had signifi-

cantly improved 5-year survival when compared to conventional resection (82 % vs. 21 %) and had fewer recurrences (12 % versus 27 %) [56]. Overall survival of patients with PSC is approximately 70 % at 5 years. This approach has been externally validated at centers outside Mayo having nearly identical outcomes (65 % 5-year survival) [21]. Currently the United Network for Organ Sharing allows model for end-stage liver disease (MELD) exception points for patients meeting the criteria outlined in the Mayo protocol.

Contributing to the excellent outcomes of this protocol are the strict selection criteria. Predictors of pre-LT dropout include CA 19-9 ≥ 500 U/mL, mass lesion ≥ 3 cm, malignant brushing or biopsy, and biological lab MELD score ≥ 20 . Predictors of post-LT recurrence include elevated CA 19-9, portal vein encasement, and residual tumor on explant [22]. Finally, it is important to note that this protocol does not require the diagnosis of CCA but includes the presence of polysomy alone or elevation in CA 19-9 > 100 with a concurrent malignant appearing dominant stricture. It is possible that excellent outcomes with this protocol are further explained by the fact that patients simply did not have cancer. This is supported by the external validation of this protocol at 12 large volume transplant centers which found that patients without residual CCA on explant did better and had a significantly lower chance of recurrence than those with residual tumor tissue on explant [22]. It is impossible to determine whether these individuals never had CCA to begin with or that their CCA was effectively treated with neoadjuvant chemoradiation.

Palliative Therapies

For patients with unresectable cancers and those who are ineligible for LT, there are a variety of palliative therapies. Multiple locoregional therapies, including transarterial chemoembolization (TACE), radiofrequency ablation (RFA), and transarterial hepatic yttrium-90 (Y-90) can be utilized for debulking and biliary decompression. Systemic chemotherapy with gemcitabine and cisplatin are used in those with unresectable or metastatic disease. Biliary stenting (endoscopic

Table 2.2 Criteria for managing cholangiocarcinoma with liver transplantation

<i>Eligible candidates for evaluation:</i>
1. Unresectable hilar cholangiocarcinoma or cholangiocarcinoma in setting of primary sclerosing cholangitis
2. No clinical evidence of metastases
<i>Diagnosis:</i>
1. Intraluminal brush cytology or biopsy positive for cholangiocarcinoma
2. In case of negative cytology, malignant appearing stricture with at least one of the following:
(a) CA 19-9 > 100 ng/ml
(b) Biliary polysomy by FISH
<i>Exclusion criteria:</i>
Medical and psychosocial conditions that preclude transplantation
Prior abdominal radiation preventing further radiation or other malignancy within 5 years
Prior attempted resection with violation of tumor plane or attempt at transperitoneal biopsy of tumor
The presence of mass lesion > 3 cm radial margin (longitudinal margin not a contraindication). Vascular encasement, the presence of poorly defined hilar enhancement, and length of hilar stricture not considered exclusion criteria
Intrahepatic metastases
Evidence of extrahepatic disease – includes regional lymph node involvement
Intrahepatic cholangiocarcinoma (tumor originating from second branch (segmental branch) or the proximal branch of bile duct – further classified into hilar type and peripheral type) or gallbladder involvement

and percutaneous) is utilized for palliation of obstructive jaundice. Photodynamic therapy (PDT) has recently emerged as an endoscopic palliative treatment modality. Kahaleh et al. found that ERCP with PDT decreased mortality in patients with unresectable cholangiocarcinoma compared to ERCP alone (56% vs. 82% at 12 months, respectively) [36].

Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of hepatocytes. It most commonly develops in the setting of cirrhosis, though can occur without cirrhosis in patients with chronic hepatitis B virus infection and hemochromatosis. In the setting of PSC, HCC is almost always seen in the setting of cirrhosis. Hepatocellular carcinoma is a leading cause of cancer in the world, largely contributed to chronic hepatitis B virus infection. Each year HCC is diagnosed in more than half a million people worldwide and 20,000 people in the United States [28].

Epidemiology

There is limited data on the incidence of HCC in PSC, but studies suggest that the cumulative incidence is lower than what is described for other etiologies of cirrhosis. One review of 134 patients with PSC undergoing LT found a prevalence of 2% [31]. In another study with 119 patients with cirrhosis secondary to PSC, none were diagnosed with HCC over a median follow-up of 7 years [69].

Pathogenesis

Not a lot is known about the specific mechanism of HCC development in PSC, but the pathogenesis is likely similar to other etiologies of cirrhosis. Chronic inflammation in PSC leads to hepatocyte necrosis and regeneration. The repetitive necrosis and regeneration leads to the devel-

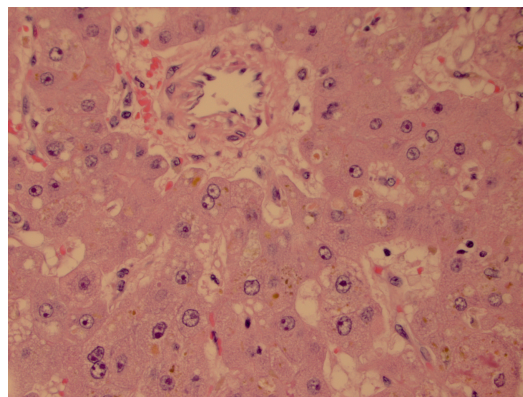


Fig. 2.3 Hepatocellular carcinoma resembles normal hepatocytes with more than 2–3 cell-thick hepatocellular plates or cords, nuclear atypia as evident by enlarged nuclei (high N/C ratio) with prominent nucleoli, and the absence of portal tracks. Bile production is pathognomonic for hepatocyte differentiation and aids in differentiating metastatic neoplasms and intrahepatic cholangiocarcinomas (400 \times ; Courtesy of Dr. Jeffery Kaplan)

opment of benign hyperplastic nodules. Genomic instability and mutations in key oncogenes and tumor suppression genes then lead to the development of dysplastic polyps and ultimately HCC (Fig. 2.3). The exact oncogenesis of HCC is not as well understood as that of other malignant processes; however, several key events have been identified. Important genetic events include inactivation of tumor suppressor *p53*, mutations in β -catenin, overexpression of ErbB receptor family members, and overexpression of the MET receptor [26]. *p53*, in particular, plays a critical role in destabilizing the HCC genome [30]. Specific genomic alterations that have been shown to frequently be present in HCC include chromosomal gains in 1q, 6p, 8q, 11q, and 17q and chromosomal losses in 1p, 4q, 8p, 13q, and 17p [26]. Future studies in this area include utilizing genomic characteristics to help stage and predict recurrence as well as developing targeted therapies.

Risk Factors

The most significant risk factor for PSC-associated HCC is cirrhosis. The stage of cirrho-

sis and activity of liver disease influences the risk of HCC. Child-Pugh class B/C cirrhosis carries at three- to eightfold increased risk of HCC compared to Child-Pugh class A [28]. One should have a high suspicion for HCC in patients with previously compensated cirrhosis who develop decompensated disease with ascites, jaundice, variceal bleeding, or encephalopathy. Ongoing inflammation in the liver also increases the risk of HCC as evidenced by an increased risk of HCC observed in patients with persistently elevated ALT levels compared to those with normal levels [28]. Additional independent risk factors associated with HCC in cirrhotic patients are age >55 and male sex, which each carry a two- to fourfold increased risk [25, 28].

Screening

Despite the lower risk of HCC in PSC compared to other etiologies of cirrhosis, screening for HCC is important to perform in all patients who have cirrhosis or advanced fibrosis regardless of the etiology of liver disease. Screening tests fall into two categories, serological and radiological. Alpha-fetoprotein (AFP) has been the most extensively studied. Alpha-fetoprotein can be elevated in both chronic liver disease and HCC; however, an AFP >500 ng/mL (normal is 10–20 ng/mL) is considered diagnostic for HCC [8]. While previously recommended as a screening test for HCC, given its low sensitivity of only about 60%, AASLD no longer recommends utilizing AFP to screen patients for HCC. Other serological tests such as prothrombin induced by vitamin K absence II (PIVKA II), descarboxyprothrombin, and AFP-L3 have not performed significantly better. Guidelines by AASLD currently recommend screening with ultrasonography (US) every 6 months [13]. Nodules detected on US that are >1 cm in diameter should be further evaluated with contrasted computed tomography (CT) or magnetic resonance imaging (MRI). Nodules <1 cm should be followed with US every 3 months. If no growth is detected over 2 years, regular surveillance can be resumed. As a screening test, US has been

reported to have sensitivity between 65 and 80% and specificity >90% [11]. While US is the recommended imaging modality for HCC screening in cirrhosis, CT and MRI should be considered in patients with PSC given concurrent need for CCA screening for which US is not adequate.

Diagnosis

Imaging

Diagnosis of HCC is primarily radiographic. The diagnosis of HCC on cross-sectional imaging requires CT or MRI with three phases: arterial, venous, and delayed. Hepatocellular carcinomas are typically supplied by the hepatic arterial system and not the portal venous system; therefore, characteristic lesions are hyperintense compared to the background liver parenchyma in the arterial phase and hypointense in the venous phase. Another diagnostic feature of HCC is pseudocapsulation. The presence of these characteristic findings is considered diagnostic of HCC and does not require liver biopsy. Rarely, HCCs can be hypovascular, and such characteristic findings are not present. In such cases biopsy may need to be pursued.

Biopsy

Percutaneous biopsy of liver nodules suspicious for HCC should only be performed in lesions that were nondiagnostic with cross-sectional imaging. Biopsy carries the risk of bleeding and malignant seeding of the biopsy tract. A meta-analysis found the incidence of needle tract tumor seeding to be 2.7% [62]. When biopsy is performed, per AASLD guidelines, lesions should be evaluated by expert pathologists. Staining for tumor markers including CD34, CK7, glypican 3, Hsp60, and glutamine synthetase can help characterize lesions that are not clearly HCC on biopsy. If biopsy is negative, lesions should be followed every 3–6 months until they disappear, enlarge, or display diagnostic characteristics of HCC. If the lesions enlarge but imaging remains atypical, repeat biopsy should be pursued.

Staging

There is no universal staging system for HCC. The four most commonly used are the Barcelona Clinic Liver Cancer (BCLC) staging system; the tumor, node, metastasis (TNM) staging system; the Okuda system; and the Cancer of the Liver Italian Program (CLIP) score. The BCLC staging system has four stages based on the extent of primary lesion, degree of invasion, symptoms, and performance status [46]. The American Joint Committee on Cancer (AJCC) TNM staging system is based on the number and size of primary tumors, the presence of regional lymph node metastasis, the distance metastasis, and the fibrosis score [2]. The Okuda staging system classifies individuals into three stages based on the presence of four criteria: tumor size >50 % of the area of the liver, the presence of ascites, albumin <3 mg/dL, and bilirubin >3 mg/dL [52]. The CLIP is a prognostic scoring system based on tumor morphology, AFP levels, the presence or absence of portal vein thrombosis, and the severity of cirrhosis. A score from 0 to 6 is calculated based on subscores from variables. For scores 0, 1, 2, 3, and 4–6, median survival was 36, 22, 9, 7, and 3 months, respectively [47]. Regardless of which stage of disease is utilized, in clinical practice the main determinate of management is whether a patient is a candidate for surgical resection or OLT.

Management

The management of HCC depends largely on the size and number of tumors, the presence of macrovascular invasion, and the presence of cirrhosis and portal hypertension.

Surgical Resection

Resection is the treatment of choice for solitary HCCs in individuals without cirrhosis or those with compensated cirrhosis (Child-Pugh class A). Patient with multifocal HCC and/or Child-Pugh class B/C, evidence of portal hypertension (transhepatic pressure gradient >10 mmHg or platelets <100,000/ μ L and splenomegaly), or elevated bilirubin are at high risk for surgical

resection and require consideration for LT. Patients with PSC who develop HCC are not likely to be surgical candidates due to chronic biliary disease, and therefore management is focused on LT and locoregional therapy.

Liver Transplantation and the Milan Criteria

Liver transplantation is the mainstay of treatment for HCC in PSC as it is the only potentially curative therapy. Mazzaferro et al. demonstrated that LT in patients with a single tumor ≤ 5 cm or 2–3 separate lesions, all ≤ 3 cm with no evidence of macrovascular invasion or extrahepatic disease resulted in a 5-year survival of 75 %, similar to the survival rate of non-HCC patients undergoing OLT [50]. This so-called Milan criteria are the most widely used criteria for determining eligibility for LT. Patients fulfilling these criteria are eligible for automatic MELD exception points as long as the tumor remains within Milan criteria. Depending on when a patient may be transplanted which currently depends on regional donor availability and whether living donor liver transplantation is considered, locoregional therapy with TACE or RFA is often performed to keep patients within the Milan criteria while awaiting LT. Table 2.3 summarizes the diagnostic criteria of HCC eligible for standard MELD exceptions on the transplant list. Currently patients fulfilling the Milan criteria are granted a MELD exception of 28 points 6 months after the initial upgrade request. Once to 28 points, a MELD score equivalent to a 10 % mortality risk is added every 3 months to a maximum of 34 points (i.e., initially 28, then 29, then 31, then 33, and finally 34). The 6-month delay in receiving MELD exception points was recently included in the allocation of livers for HCC to allow time to assess tumor biology at transplant centers that do transplants at low MELD scores (<25). The cap of 34 points was so patients with HCC do not participate in regional sharing of donor livers which is the case for MELD scores ≥ 35 (see Chap. 15).

Expanded Criteria

There have been several studies that have looked at expanding the criteria for transplanting HCC

Table 2.3 Organ procurement and transplantation network diagnosis, classification and reporting of hepatocellular carcinoma, and eligibility for MELD exceptions

<i>OPTN Class 5B nodules</i>
T2 lesion(s)
1 lesion ≥ 2 cm and ≤ 5 cm
2–3 lesions ≥ 1 cm and ≤ 3 cm
And
Increased contrast enhancement on late arterial imaging
And
One of the following:
1. Washout on portal venous/delayed phases
2. Late capsule or pseudocapsule enhancement
3. Growth by $>50\%$ on CT or MRI <6 months apart
4. Biopsy
<i>OPTN Class 5A nodules</i>
Single nodule, ≥ 1 cm and <2 cm (T1 lesion) with increased contrast enhancement on late arterial images
And
Both of the following:
1. Washout during portal venous/delayed phases
2. Peripheral rim enhancement on delayed phase
Or
Biopsy
<i>Eligible for automatic MELD exception</i>
Two 5A lesions
One 5A and one 5B
One 5B (≤ 5 cm)
Two 5B (both <3 cm)
<i>Not eligible for automatic MELD exception</i>
One 5A lesion

beyond the Milan criteria. The University of California, San Francisco (UCSF), has demonstrated equivalent outcome compared to Milan criteria by expanding criteria to a single tumor ≤ 6.5 cm, maximum of three total tumors with none >4.5 cm, and cumulative tumor size <8 cm [66]. The 5-year survival of these so-called UCSF criteria was 72.4% similar to that of the Milan criteria, suggesting the Milan criteria may be too strict [67]. AASLD guidelines, however, state there is inadequate evidence to support LT outside of the Milan criteria [13]. UCSF has also shown good outcomes with transplant for patients outside Milan criteria who are downstaged to within the Milan criteria with locoregional therapy and remain within Milan criteria for a mini-

mum of 3 months. Results of this protocol showed similar outcomes to the Milan criteria with 5-year posttransplant survival of 77.8% in the downstaging group versus 81% in the Milan group ($p=0.69$) [67]. Patients fulfilling either of these expanded criteria do not receive automatic MELD exception points as is the case with those fulfilling Milan criteria, but rather must appeal to the regional review board on a case-by-case basis.

Living Donor Transplantation

Given the long wait times for deceased donor liver transplantation (DDLT) in many areas of the United States and the associated risk of HCC progression to point of exceeding criteria for LT, many transplant centers offer the option of living donor liver transplantation (LDLT). In one retrospective study of LDLT versus DDLT, overall 5-year survival was similar in the two cohorts: 73% in the LDLT cohort and 71% in the DDLT cohort [7]. Dropout rates were significantly lower in the LDLT cohort (0% versus 18%), and waiting time to LT was significantly shorter (2.6 versus 7.9 months) [7]. Given the potential risk to a living donor, LDLTs in general should only be performed in candidates who meet standard criteria for LT.

Non-curative Treatment

The goals of therapy for patients who are not candidates for surgical resection or LT are aimed at both extending life expectancy and symptomatic management.

Locoregional Therapy

The main goal of locoregional therapy is to reduce tumor burden and extend survival. Overall there are no consensus guidelines, and choice of modality is often based on institutional preferences. Transarterial chemoembolization is the most commonly employed locoregional therapy. This therapy utilizes HCC's dependence on the arterial blood supply by inducing acute arterial obstruction leading to ischemic tumor necrosis in addition to the local effects of chemotherapy administration. It is contraindicated in patients

with portal vein tumor thrombus as well as those with Child-Pugh class C cirrhosis due to increased risk of liver failure and death. Survival is improved compared to conservative management. In a randomized control trial, TACE was found to have a 2-year survival of 63 % compared to 27 % in the conservative management group [46]. An issue specific to patients with PSC is TACE cannot be done after in the setting of biliary obstruction or after sphincterotomy due to biliary infectious complications and liver abscess.

Radiofrequency ablation utilizes a needle electrode to deliver high-frequency alternating current from the tip of the electrode to the surrounding tissues which results in increased temperature and subsequent necrosis [51]. It is most often selected for tumors ≤ 5 cm in diameter as the rate for complete necrosis decreases with larger lesions [45].

Radioembolization using intra-arterial injection of yttrium-90 is another regional therapy utilized to induce tumor necrosis as well as provide local radiotherapy. However, similar to TACE, radioembolization also cannot be used in the setting of prior sphincterotomy and biliary obstruction. Percutaneous ethanol injection is also utilized: 95 % ethanol is injected directly into tumor to induce necrosis and tissue ischemia.

Systemic Chemotherapy

Overall systemic chemotherapy is of limited utility in HCC as it is a relatively chemotherapy-refractory tumor, and patients often do not tolerate chemotherapy due to underlying liver dysfunction associated with HCC. Newer molecularly targeted agents have shown some promise for unresectable, metastatic HCC. The agent with the most data is sorafenib which is a multi-kinase inhibitor which inhibits tumor angiogenesis through the vascular endothelial growth factor receptor and platelet-derived growth factor receptor as well as directly inhibiting tumor cell proliferation and survival [44]. The SHARP trial, which compared sorafenib to placebo, showed a significant difference in overall survival (10.7 versus 7.9 months; $p < 0.05$) in patients who were CTP-A and not candidates for surgical resection [48].

Gallbladder Carcinoma

Introduction

Gallbladder carcinoma (GBC) is an adenocarcinoma arising from the epithelial lining of the gallbladder. Just as chronic inflammation in the biliary tract leads to an increased risk of CCA, patients with PSC are also at an increased risk for gallbladder dysplasia and carcinoma due to chronic inflammation and stasis within the gallbladder.

Epidemiology

In the general population, GBC is a relatively rare disease. Patients with PSC, however, have greater than a tenfold increased risk of GBC compared to the general population. The prevalence of gallbladder carcinoma in patients with PSC is reported to be 3.5–7 % compared to 0.35 % in the general population [14, 57].

Risk Factors

Risk factors for GBC in general are chronic infection with salmonella and gallbladder stones. While there is an increased risk of gallbladder stones in PSC alone, PSC appears to be an independent risk factor for GBC.

Pathogenesis

Not much is known about the pathogenesis of PSC-associated GBC, but the underlying mechanism is likely related to chronic inflammation. The gallbladder epithelium is continuous with the extrahepatic bile duct system, and 25 % of individuals with PSC have been found to have cholecystitis, the majority of which is not associated with gallbladder stones [57]. It has been proposed that there is a metaplasia-dysplasia-carcinoma sequence in PSC-associated GBC [41]. Gallbladder dysplasia, carcinoma in situ, and invasive carcinoma have been shown to have high rates of *p53* mutation; in contrast gallbladder adenomas tend to

lack *p53* mutations and have *K-ras* mutations, which are less likely to be found in GBC [41].

Screening

The AASLD recommends annual screening for gallbladder polyps with ultrasound [18]. Whether CT and MRI/MRCP typically used to screen for CCA is adequate to screen for GBC is unclear. In the general population, gallbladder polyps <1 cm are often nonmalignant and can be followed with serial imaging. In PSC, however, even small polyps detected on US are often malignant, and therefore all PSC patients with gallbladder polyps should be considered for cholecystectomy [39].

Diagnosis

The diagnosis of GBC is a histologic one. Most diagnoses of GBC in the general population are detected incidentally during cholecystectomy. Laboratory analysis is of limited utility especially in PSC where patients will have aberrations in serum bilirubin, alkaline phosphatase, and CA 19-9 due to their chronic biliary disease. Suspicious US findings include a mass occupying or replacing the gallbladder lumen, focal or diffuse asymmetric wall thickening, and gallbladder polyps [65]. MRI/MRCP is utilized to further differentiate between benign gallbladder lesions and malignant ones and is also useful in the preoperative staging of GBC [59, 68].

Treatment

Surgical Management

As with CCA and HCC, surgical management is the only potentially curative treatment. Therapy for GBC is largely based on TNM staging. Cholecystectomy alone is sufficient for early tumors which are confined to the mucosa (Tis) or lamina propria (T1a). A radical cholecystectomy with resection of the liver bed is recommended for T1b and T2 lesions [70]. T3 and T4 lesions often involve significant invasion of adjacent

organs and surgical resection carries substantial morbidity and mortality. This is especially true in PSC given preexisting hepatic disease. Due to the relative rarity of GBC, there are no large randomized trials to evaluate the role of adjuvant radiation and chemotherapy. 5-Fluorouracil (5-FU)-based chemotherapy regimens are often combined with radiation as adjuvant therapy in $\geq T2$ disease.

Advanced Stage

For unresectable T3 and T4 lesions, debulking and palliative therapies are similar to those utilized in CCA. For locoregionally advanced and unresectable lesions, external beam radiation with concurrent 5-FU-based chemotherapy is used to attempt to decrease tumor size. For distal metastases, the National Comprehensive Cancer Network (NCCN) recommends gemcitabine and/or a platinum or fluoropyrimidine-based regimen [54]. Percutaneous or endoscopic stenting is also utilized to relieve obstructive jaundice.

Prognosis

The overall prognosis of GBC is poor and declines rapidly with more advanced stages. The 5-year survival of stages I, II, III, and IV in the general population was 54 %, 32 %, 9–10 %, and 2–3 %, respectively [53].

Conclusion

Individuals with PSC are at increased risk for hepatobiliary malignancies which is a significant cause of morbidity and mortality. Surgical resection or liver transplantation in highly selected cases is usually the only curative therapy. Resection is amenable typically in early-stage carcinomas, necessitating early diagnosis in a surveillance program for cholangiocarcinoma, hepatocellular carcinoma, and gallbladder carcinoma. Cholangiocarcinoma is the most common hepatobiliary malignancy associated with PSC and is a common reason for liver transplantation in such patients. Diagnosis of CCA in PSC is challenging due to the difficulty distinguishing benign from

malignant biliary strictures. PSC-associated HCC is rare and only arises in cirrhosis. Diagnosis and management is similar to HCC associated with other etiologies of cirrhosis. Gallbladder carcinoma is the less common and less researched hepatobiliary carcinoma associated with PSC; however, it is associated with significant mortality as it is often detected in later stages. More research in the diagnosis and targeted therapies could significantly improve the mortality of PSC-associated hepatobiliary malignancies.

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