Cholangiocarcinoma
Diagnosis and Management

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KEYWORDS

• Cholangiocarcinoma • Diagnosis • Management • Transplant • Resection
• Chemotherapy • ERCP

KEY POINTS

- Cholangiocarcinoma is relatively rare but highly lethal so requires a high index of suspicion in order to detect disease at an early stage.
- Diagnosis requires a combination of imaging with magnetic resonance cholangiopancreatography, laboratory testing, and endoscopic retrograde cholangiopancreatography.
- Primary sclerosing cholangitis is a strong risk factor, and patients should be enrolled in surveillance programs with imaging and laboratory testing.
- Surgical resection and transplantation are potentially curative; unfortunately, high recurrence rates persist with 5-year survival rates of 50% to 70%.
- Systemic chemotherapy, locoregional therapy, and radiation provide marginal benefit but should be offered to patients without surgical resection options.

INTRODUCTION

Cholangiocarcinoma (CCA) is a biliary tract epithelial malignancy and the second most common primary hepatic cancer. Defined as a cancer with cholangiocyte origin, CCA is otherwise quite heterogeneous in location, histology, and clinical course, providing diagnostic and management challenges even for experts. Despite recent advances, CCA still has a high mortality with poor prognosis, especially in advanced disease.

In this review, CCA is considered a distinct entity from primary gallbladder or ampulla of Vater cancer. Although the localization can be challenging, CCA is subdivided by anatomic location within the biliary tract. Tumors proximal to the main intrahepatic ducts are termed intrahepatic cholangiocarcinoma (iCCA), extrahepatic tumors (eCCA) proximal to the cystic duct are perihilar cholangiocarcinoma (pCCA),

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and distal to the cystic duct are distal cholangiocarcinoma (dCCA) (Fig. 1).[1] Frequency of occurrence by the various subtypes differs by risk factors. Location impacts surgical options and outcomes and treatment choice in unresectable disease. pCCA is the most common subtype, accounting for approximately 50% to 60% of cases, with dCCA another 25% of cases, and iCCA 20% of cases.[2] CCA can be further subdivided by histologic subtype, but almost all are sclerosing-type carcinomas.[2]

The incidence of iCCA appears to be increasing, whereas that of eCCA is decreasing.[3] Some of this is likely due to improved diagnostic techniques and more accurate classification; for example, 1 study found that many hepatic lesions previously described as Cancer of Unknown Primary were likely in fact CCA.[4] However, increased burden of chronic viral hepatitis and nonalcoholic fatty liver disease likely accounts for some of the documented increase in iCCA.[5] There are several known risk factors helpful to understand when considering a diagnosis of CCA. Some of these risk factors are unlikely to be encountered in a western setting, such as the endemic liver fluke of Northern Thailand, which increases risk by up to 100-fold,[6] or the inherited choledochal cystic Caroli disease (lifetime CCA risk 10%–30%).[7] More common risk factors with lower disease hazard include obesity, viral hepatitis, and cholelithiasis, especially for iCCA. Likewise, advanced liver disease and cirrhosis appear to be independent risk factors.[8] Alcohol appears to have a moderate (odds ratio 2.4)[9] increase in risk of CCA, whereas the contribution of tobacco use is controversial. Primary sclerosing cholangitis (PSC) is a well-established risk factor and is discussed further elsewhere.

DIAGNOSIS

There are 3 distinct but interrelated circumstances that should prompt consideration for CCA: a patient with asymptomatic cholestatic elevation of liver enzymes, a patient with symptoms or imaging findings concerning for hepatobiliary malignancy (Fig. 2), or a patient with known ulcerative colitis (UC) or PSC (Fig. 3).

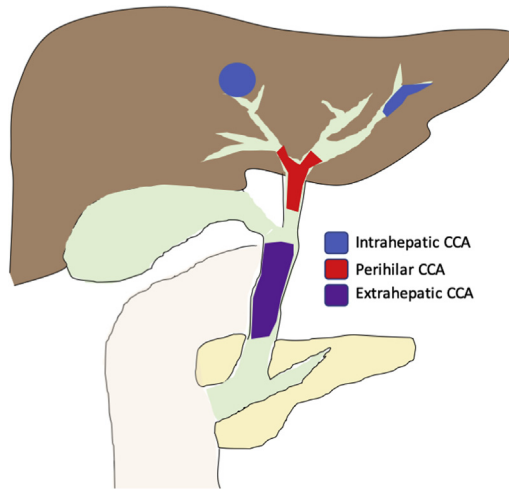

Fig. 1. CCA is subdivided by anatomic location, which affects management and prognosis. dCCA is distal to the cystic duct, pCCA is from proximal to the cystic duct to the hilum and main hepatic ducts, whereas CCA involving the small proximal ducts within the liver is intrahepatic.

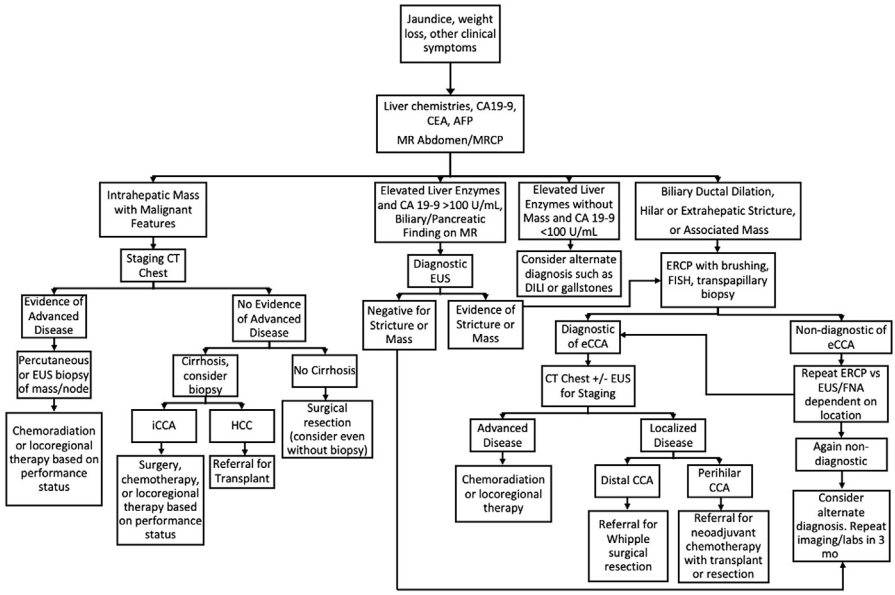

Fig. 2. Diagnosis and management of suspected CCA in patients without PSC. AFP, alpha feto protein; DILI, drug induced liver injury.

Elevated Liver Panel

The typical laboratory pattern for CCA is a cholestatic liver injury, with alkaline phosphatase greater than twice normal with elevated gamma-glutamyl transferase and often bilirubin. Persistent biliary obstruction from tumor or iCCA can also result in elevated transaminases and prolongation of the international normalized ratio. Unfortunately, none of these tests have high specificity for CCA, and the differential diagnosis for this laboratory pattern is broad (**Table 1**). CCA incidence increases with age, most commonly presenting between 50 and 70; there is a slight male predominance, and people of Asian descent are at higher risk.[10] Although rare, its lethality demands a high level of suspicion.

Patients should be questioned for a history of gallstone disease, inflammatory bowel disease, or hepatitis. Substance abuse, travel, and family histories (for example, Lynch syndrome) should be taken. Symptoms such as weight loss, malaise, dark urine, clay-colored stools, or pruritis are nonspecific but suggest biliary obstruction with possible associated malignancy. Nonetheless, CCA is often clinically silent until an advanced stage, and cholangitis is a rare presentation.[11] Laboratory analyses should include Carbohydrate antigen 19-9 (CA 19-9), a tumor antigen with sensitivity for CCA of 50% to 70% at levels greater than 100 U/mL.[12] Its utility is limited due to false positives in the setting of cholangitis or other benign biliary disease. Likewise, 7% to 10% of patients do not express Lewis antigen and will not have an elevated CA 19-9. Other markers such as carcinoembryonic antigen (CEA), matrix metalloproteinase-7, and cytokeratin-19 fragment have been shown to be elevated in CCA[13] but suffer from a combination of low sensitivity, specificity, or availability in clinical practice. Some data suggest that combining all 4 markers could provide sensitivity and specificity greater than 90%,[14] but this is not guideline based and does not obviate eventual invasive testing. Immunoglobulin G4 elevations could suggest autoimmune

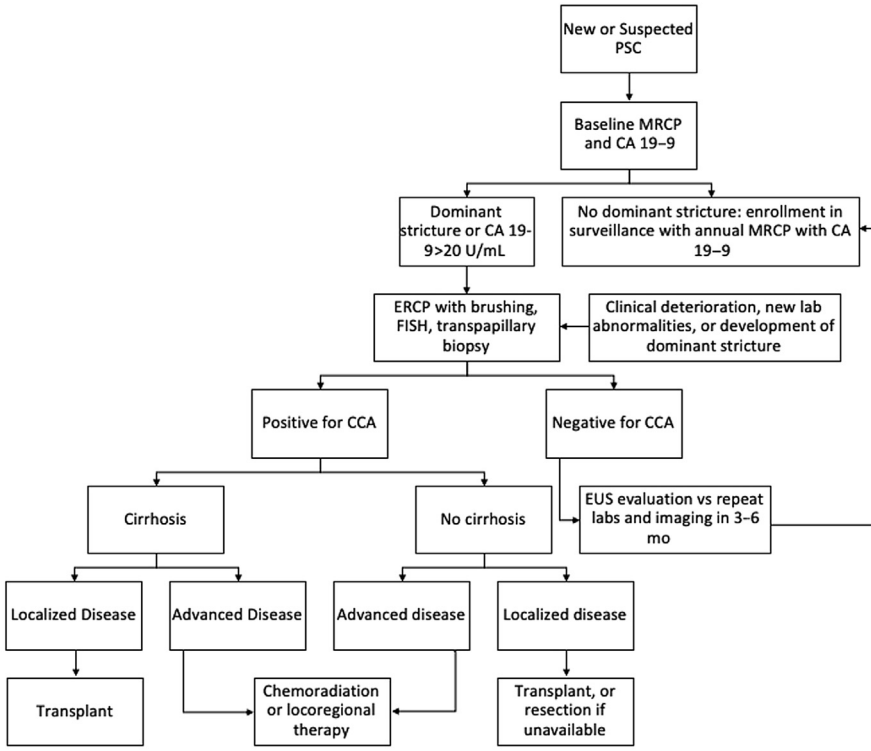

Fig. 3. Surveillance, diagnosis, and management of CCA in patients with PSC.

cholangiopathy, but is likewise nonspecific as elevations have been seen in CCA.[15] For this reason, unexplained elevation in liver enzymes should prompt further evaluation with imaging.

In the patient presenting with symptoms or cholestatic liver enzyme elevation, the best test is a magnetic resonance/magnetic resonance cholangiopancreatography (MR/MRCP), which offers sensitivity of 88% and specificity of 75% to 85%. Addition of contrast increases sensitivity by 10%, so a contrast-enhanced study should be

Table 1
Differential diagnosis for common presenting symptoms and findings in cholangiocarcinoma

Cholestatic Liver Enzyme Elevation	Biliary Dilation or Stricture	Intrahepatic Mass
• Gallstone disease • Non-CCA malignant obstruction • Drug-induced liver injury • Primary biliary cholangitis • PSC • AIDS cholangiopathy • Cholestasis of pregnancy • Cholangitis • Autoimmune cholangiopathy	• Choledocholithiasis • PSC • Ampulla of Vater carcinoma • Pancreatic cancer • Secondary sclerosing cholangitis • Extrinsic gallstone compression (Mirizzi syndrome)	• HCC • Hepatic adenoma • Focal nodular hyperplasia • Hepatic hemangioma • Metastatic disease

performed in the absence of contraindications, such as renal failure or allergy.[16] Patients with renal failure should have a noncontrast MRCP rather than ultrasound. Findings of a mass, ductal dilation, stricture, contrast enhancement, and ductal wall thickening or irregularity should prompt invasive evaluation and tissue sampling.

Patients with Abnormal Liver Imaging

All patients who present with a biliary dilatation or a mass on imaging concerning for CCA should have an MRCP, ideally with contrast, as well as the laboratory workup above if not already performed. In a patient presenting with an intrahepatic mass, care must be taken to differentiate iCCA from other causes (see **Table 1**). Contrast-enhanced imaging characteristics help with this differentiation. Unlike the washout seen with hepatocellular carcinoma (HCC), iCCA tends to have progressive uptake in both the arterial and the venous contrast phases[17]; however, the classic heterogeneous uptake was only seen 70% of the time in 1 series,[18] and mixed tumors with both HCC and CCA can occur. MR can occasionally help with differentiation, but is not always definitive. Despite best efforts, CCA, especially intrahepatic, can still be mistaken for HCC, with 1 study reporting 1.5% of explants for presumed HCC actually representing early CCA.[19] Tumors less than 2 cm are less likely to have classic washout appearance to help delineate iCCA from HCC.[20] Any imaging assessment of an intrahepatic lesion concerning for iCCA should include a computed tomographic (CT) scan of the chest to assess for metastatic disease. The role of PET-CT is likely confined to metastatic disease.[21] If there is no evidence of distant metastasis and the lesion is concerning for iCCA, referral for surgical resection without biopsy is appropriate. In cirrhosis, a biopsy with endoscopic ultrasound (EUS) or percutaneously may be necessary for determination of transplant candidacy, despite a known risk of needle tract seeding. All patients with imaging findings concerning for iCCA should be referred early to a multidisciplinary team at a specialized center.

Perihilar or Extrahepatic Mass

Perihilar tumors less commonly present as a defined mass and more often appear nodular or infiltrating on cross-sectional imaging. CT is fairly accurate for detection of portal vein (sensitivity and specificity 89% and 92%) and hepatic artery (83% and 93%) involvement, whereas less accurate for lymph node detection (61% and 88%).[22] Still, MR/MRCP has become an essential and preferred evaluation tool for pCCA because of its ability to better characterize the biliary tree and extent of intrabiliary lesion.[16] Further anatomic subdivision of pCCA is by the Bismuth-Corlette classification.

In patients with imaging or symptoms concerning for pCCA, endoscopic retrograde cholangiopancreatography (ERCP) has become the test of choice for obtaining a tissue diagnosis. Multiple studies have shown low yield to cytology brushings alone.[23] Fluorescence in situ hybridization (FISH) increases the diagnostic yield of brushings[24] to approximately 35% or better.[25] Transpapillary biopsy in combination with FISH and brushing increases overall sensitivity to 82%,[26] whereas a recent study suggested improved diagnostic yield for combining FISH with single-operator cholangiography from 64.5% to 71.5% over transpapillary biopsy.[27] Intraductal ultrasound can be used as an adjunct for visual confirmation of difficult-to-characterize lesions. In expert hands, sensitivity has reached 93%, although its inability to collect tissue for cytology or detect regional adenopathy limits practical use.[28]

The use of EUS before or at the time of ERCP is somewhat controversial. Noninvasive EUS is likely helpful and has high sensitivity (90%–100%) for detecting an extrahepatic lesion, with increasing sensitivity in more distal tumors.[29] In addition, it likely

has a role in determining resectability of a tumor; in 1 series, EUS had 53% sensitivity and 97% specificity for unresectability[29] in part due to its excellent performance at identifying and sampling regional lymph nodes.[30] Fine needle aspiration (FNA) of the primary tumor also increases diagnostic yield. A recent metaanalysis including 294 patients with concern for malignant stricture noted improved diagnostic sensitivity of EUS-FNA over ERCP with transpapillary biopsy (75 vs 49%), albeit both had low negative predictive values.[31] EUS-FNA should be used in patients with an indeterminate initial ERCP; sensitivity in this setting ranges from 43% to 86%.[32] In 1 study, following an indeterminate ERCP with transpapillary biopsy with stepwise repeat, ERCP for intrinsic lesions or EUS-FNA for extrinsic lesions increased overall diagnostic yield to greater than 96%.[32] EUS-FNA does, however, raise concern for tumor seeding and should be avoided in patients who are possible transplant candidates. This concern is primarily in pCCA rather than dCCA, because the duodenal bulb is part of the surgical resection in the latter case. Although some studies have suggested that seeding is probably a clinically rare event,[33] it remains a contraindication for transplant at some centers, most notably the Mayo Clinic.[34] Overall strategy depends on tumor location, characteristics, and center expertise.

Patients with Primary Sclerosing Cholangitis

PSC is a chronic, inflammatory cholangiopathy characterized by progressive cholestasis, fibrosis, and stricturing.[35] It is strongly associated with inflammatory bowel disease, especially UC. Patients with PSC are twice as likely to develop cancer as the general population, and PSC is a known risk factor for multiple cancers, including CCA, colorectal, primary gallbladder, and HCC.[36] Unfortunately, it remains unclear which patients with UC will develop PSC and which of those will develop CCA.[37,38]

When referred a patient to rule out PSC or with a diagnosis of PSC, the clinician must have an immediate concern about the implications of CCA. Burden of CCA in this population is up to 1500 times the general population,[39] and despite this knowledge, most CCA is unresectable at diagnosis.[1] CCA is the largest cause of mortality in patients with PSC,[36] and the lifetime risk is approximately 10% to 15%, with annual incidence approximately 1%.[40] Early studies noted that approximately 50% of CCA is diagnosed within a year of PSC diagnosis,[41] and recent work suggests that the risk persists and is increased with longer disease course.[42] The fact that patients with PSC are often diagnosed with CCA early in their course suggests that many patients are diagnosed with PSC only after development of a dominant, malignant, stricture.

In newly diagnosed or suspected PSC, imaging with MRCP and laboratory testing including liver chemistries and a CA 19-9 are appropriate initial steps. These tests serve the dual purpose of identifying any possible malignant stricture and serving as a baseline in the case of laboratory, symptom, or imaging changes in the future. Most patients with PSC will at 1 time have a dominant stricture; although only about 25% of these will prove malignant,[43] ERCP with brushing/biopsy as discussed above is generally recommended to rule out CCA.

Definitive surveillance guidelines for this population have proven elusive.[39] As previously reported, the 1% annual incidence of CCA in PSC is roughly the same as HCC in cirrhosis, which could serve to justify a surveillance program.[44] At the moment, expert consensus supports annual or semiannual CA 19-9 with either abdominal ultrasound or preferably MRCP.[45] Because of the high rate of elevated CA 19-9 in benign PSC as well as elevation in other diseases, such as cholangitis,[46] care must be taken not to rely solely on laboratory data. A new dominant stricture or CA 19-9 greater than 20 U/mL should prompt ERCP with brush cytology, FISH, and biopsy. In patients with PSC, FISH has a high false positive rate[47] but still provides useful diagnostic

information. A recent study of surveillance for all hepatobiliary cancer in PSC found that patients enrolled in surveillance programs had lower all-cause mortality and that CCA was diagnosed with smaller lesions and less nodal involvement; surveilled patients received more liver transplants (LT) and had higher survival even in the absence of transplantation.[48] Despite this, the most recent consensus guidelines out of the United Kingdom fail to recommend routine surveillance.[49]

No medication or supplement, including ursodeoxycholic acid[50] or curcumin,[51] has been consistently shown to decrease risk of CCA. Patients are likely to ask about such options, but at this time the evidence is insufficient to advise their use. With curcumin, promising in vitro data suggested possible antitumorigenicity, but a resultant small clinical trial failed to show any change in cholestatic markers.[52] Smoking and alcohol avoidance is recommended, even in the absence of cirrhosis.

MANAGEMENT OPTIONS

The primary management strategies for CCA include surgical resection, LT, systemic chemotherapy, and locoregional therapy. Multidisciplinary expert involvement is critical to quickly identify those patients for whom potentially curative resection or transplant is available.

Surgical Resection

Surgery is the only potentially curative management of CCA. Typically, resection is reserved for patients without retroperitoneal or periceliac node involvement, no main portal vein or hepatic artery invasion, no invasion of adjacent organs, and no distant metastasis. There are other individualized factors that can limit resection candidacy beyond the scope of this review. Only approximately half of patients with iCCA present with tumors that are considered candidates for resection, and recurrence rates are high with 5-year survival ranging from 40% to 60% even with R0 resection.[53] Likewise, metastatic disease not seen on imaging can be discovered during attempted surgical resection. Some experts recommend preresection diagnostic laparoscopy,[54] but this is controversial. Portal lymphadenectomy may be needed for some patients. Vascular involvement, large tumor size, lymphadenopathy, and positive resection margin are among the factors predicting recurrence.[55] Surgery for more distal tumors is likewise complex. Whipple procedures are generally performed for dCCA; even with R0 resection (negative microscopic margins), 5-year survival is approximately 27%.[56] Surgical options for pCCA are related to Bismuth classification, but often involve lobectomy, bile duct resection, lymphadenectomy,[57] and hepaticojejunostomy.[58] Overall, recurrence rates (70%–80%) and 5-year survival (30%–50%)[59] have improved for resection of pCCA likely because of improved patient selection[60] and improved surgical technique.[61] Those treated with neoadjuvant therapy who become surgically resectable likely have similar outcomes to those with primary resectable disease.[62]

Because of the high recurrence rates, adjuvant chemoradiotherapy is often used. Previous retrospective or nonrandomized studies demonstrated mixed results with a possible trend toward survival benefit especially in those with R1 or lymph node–positive resection.[63] Randomized phase 3 data from the PROTIGE[64] and BILCAP[65] trials have conflicting results, exacerbated by heterogeneous study populations. PROTIGE randomized 196 patients with biliary cancer (including primary gallbladder) and R0 or R1 resections to receiving gemcitabine and oxaliplatin; there was no difference in relapse-free survival or mortality with a median follow-up of 46.5 months, including in subgroup analysis of iCCA and eCCA. In BILCAP, 447 patients were

randomized to postoperative capecitabine or observation with median follow-up of 51 months. There was no overall survival (OS) improvement by the intention-to-treat analysis, but sensitivity and per-protocol analyses suggested a benefit. Even though both BILCAP and PROTIGE were technically negative studies, their trends toward significance may lead to increased usage of adjuvant capecitabine or gemcitabine.

Liver Transplantation

CCA was long considered a contraindication to transplantation (LT), but has been reevaluated as an option in selected patients with pCCA because of high recurrence and mortality rates after surgical resection. In an early study evaluating surgical options for CCA, LT was associated with the lowest rate of recurrence, albeit with high overall rates in part because of the high number of stage IV patients included.[58] However, in the absence of posttransplant adjuvant therapy such as radiation, recurrence rates are untenable for both pCCA[66] and iCCA[67]; 1 study reported recurrence of approximately 50% within 1 year.[68] For context, in HCC within Milan criteria, 1-year recurrence-free survival for LT surpasses 80%.[69] Fortunately, the addition of neoadjuvant chemoradiation for patients with unresectable pCCA has allowed transplantation to become a viable option again,[70] with 5-year recurrence-free survival of 65%.[71] In response, the Mayo Clinic Protocol for patient selection and neoadjuvant chemoradiation therapy has been adopted by the United Network of Organ Sharing and allows allocation of transplant exception points for pCCA similar to that of HCC after review by the National Liver Review Board.[72] To date, no randomized controlled trial has evaluated transplantation versus resection for pCCA. Similar rates of success for LT in iCCA have been difficult to achieve; guidelines recommend against LT in this population.[5] Recent data, largely from explants with unintentionally discovered iCCA, have renewed interest in LT for early iCCA,[73] but overall recurrence rates remain higher even for pathologically early iCCA.[19] A prospective trial is currently underway (NCT02878473).[74]

In PSC, CCA is often detected at a more advanced stage and with more underlying liver disease, complicating surgical management. Diffuse, difficult-to-discern disease could make a resection specimen clear of disease, while dysplasia persists elsewhere.[75] Randomized data are lacking, but several small studies have evaluated orthotopic liver transplantation for dysplasia or CCA in PSC, sometimes with the addition of radiotherapy[76] or chemotherapy.[77] In addition, coincident Whipple procedure is often performed.

Treatment of Locally Advanced or Unresectable Disease

In patients without surgically resectable disease, palliative chemotherapy or locoregional therapy can be offered. Since the ABC-02 trial, the mainstay of therapy has been gemcitabine in combination with cisplatin, offering a mean OS of 11.7 months compared with 8 months with gemcitabine alone.[78] Almost all patients eventually fail this therapy, and no standard second-line regimen exists. Second-line therapies with gemcitabine or combining 5-fluorouracil with either oxaliplatin or irinotecan have shown additional OS of approximately 13 months in retrospective studies.[79,80] A recent randomized study of supportive care or 5-fluorouracil plus oxaliplatin for any advanced biliary cancer demonstrated improved (25.9 vs 11.4%) 12-month OS with chemotherapy.[81] Tyrosine kinase inhibitors against vascular endothelial growth factor-2 have shown disappointing results in small studies.[82] Some patients will require ERCP with stenting to normalize serum bilirubin before chemotherapy.

Most mortality in CCA is due to local progression and obstruction rather than distant metastasis,[83] so patients without resection options should be considered for locoregional disease control.

Palliative stenting improves biliary drainage and quality of life at the expense of increased cholangitis occurrence; endoscopically placed self-expanding metal stents are generally thought to be superior to plastic stents or percutaneous stents for this purpose.[84,85] Endoscopic radiofrequency ablation[86] in combination with stenting may improve survival in pCCA and eCCA and likely improves stent patency.[87] Similarly, photodynamic therapy[88] may reduce stent blockage and has some mortality benefit. Lack of head-to-head comparison with other methodologies or high-quality studies precludes these therapies being guideline based; an individualized approach is needed with pCCA and dCCA, and they are not effective for iCCA.[89]

Vascular therapies, including transarterial chemoembolization (TACE), hepatic artery infusion (HAI) of chemotherapy, and yttrium-90 (^{90}Y) radioembolization, have been used for disease control and occasional conversion to resectability, especially for iCCA. Of these, the most evidence exists for ^{90}Y therapy, which uses catheter-delivered radiolabeled microspheres.[90] Response rates in iCCA vary from 5% to 36% with median survival increases of approximately 9 to 22 months.[91] Small studies have suggested prolonged benefit when combined with systemic chemotherapy.[92] Recently, a French multicenter single-arm prospective study (MISPHEC)[93] treated 41 patients with locally advanced disease with cisplatin, gemcitabine, and ^{90}Y. They noted a 39% response rate, with 20% of enrolled patients able to subsequently undergo R0 resection and progression-free survival (PFS) of 14 months. Given the efficacy and relatively minimal toxicity of ^{90}Y, it is considered second-line therapy by some experts.[57] Potential hepatotoxicity means it is currently not recommended for patients with cirrhosis. Randomized trial data comparing TACE, HAI, and ^{90}Y are lacking but potentially forthcoming.[94]

Radiation therapy with external beam radiation or stereotactic body radiotherapy (SBRT) is often offered for unresectable tumors. Survival data are mixed, but it appears that there is some benefit to high-dose radiotherapy.[95] SBRT may offer similar marginal disease control, with 1 study finding a PFS of 10 months among patients with either iCCA or pCCA.[96] A recent systematic review noted that although most studies of SBRT are not robust, efficacy appears to approach that of chemotherapy alone for survival and disease control.[97]

The recent proliferation of tumor genomic testing and new technologies, such as immunotherapy, likely will impact management of unresectable disease in the coming years. The heterogeneity of CCA makes standardization difficult, but some tumors demonstrate programmed cell death protein-1 ligand and mismatch repair protein deficiency, representing possible targets for immunotherapy.[98] Early phase studies of immunotherapy in unresectable patients have shown some promise,[99] and multiple clinical trials are currently enrolling.[100] It is reasonable to consider tumor genomics and enrollment in clinical trials for patients with advanced CCA and good performance status.

SUMMARY

CCA is a heterogeneous and highly lethal cancer that lacks reliable disease markers and often presents with symptoms late in its course and in an unresectable state. Patients with known PSC should be enrolled in a surveillance program early in their course. In any patient with symptoms or biochemical evidence of cholestasis, laboratory testing with CA 19-9 and imaging with abdominal ultrasound or preferably MRCP

should be performed. CT exposes patients to radiation without added diagnostic efficacy, whereas CEA and other tumor markers can be collected but with probable minimal clinical benefit. Imaging is especially crucial to delineate between other causes of cholestasis or obstruction, localizing CCA as intrahepatic, perihilar, or distal, and guiding management.

A suspicious lesion on MR generally demands invasive testing for tissue confirmation. A possible exception would be a patient with cirrhosis whom is a transplant candidate. ERCP with brush cytology, FISH, and transpapillary biopsy is generally preferred for tissue acquisition. EUS is useful for more distal tumors, lymph node evaluation or sampling, and in the setting of a negative ERCP. Other tools, such as intraductal ultrasound, cholangioscopy, or percutaneous biopsy, have utility in specific settings.

Most important in the diagnosis and staging of CCA is deciding on resection and transplant candidacy, because these are the only potentially curative therapies. Patients with advanced liver disease are not candidates for resection. Transplantation is available for select patients with local perihilar disease undergoing neoadjuvant chemoradiation per the Mayo Clinic Protocol and offers acceptable cure rates. Without resectable disease, prognosis is generally dismal. For patients with good performance status, systemic chemotherapy with gemcitabine/cisplatin and locoregional therapy provides some survival benefit and occasionally can shrink tumors enough to offer surgical resection. The choice of locoregional therapy depends on patient characteristics, presence of distant metastases, location of CCA, and center expertise. For patients with poor performance status, palliative stenting is a viable option to provide some symptom control.

Further advances in this field are necessary. Ongoing topics of research include noninvasive markers of disease, head-to-head comparison of adjuvant therapies, better delineation of appropriate transplant candidates, targeted systemic therapy such as immunotherapy, and improved surveillance methods for patients with PSC.

DISCLOSURE

Dr A.P. Buckholz and Dr R.S. Brown have nothing to disclose.

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