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HEPATIC CANCER (N PARIKH, SECTION EDITOR)

Screening Indications and Treatments for Cholangiocarcinoma

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Abstract

Purpose of Review The goal of this review paper is to provide a comprehensive overview of cholangiocarcinoma (CCA) including its classification, epidemiology, risk factors, surveillance, diagnosis, and treatment.

Recent Findings Guidelines recommend CCA surveillance in PSC patients with MRI/MRCP or ultrasound and CA 19-9 every 6–12 months. Fluorescience in situ hybridization and next-generation sequencing improve the poor sensitivity of biliary brushings. Surgical resection with negative margins gives the best chance of survival, and liver transplantation is an option for patients with very early intrahepatic CCA and perihilar CCA.

Summary CCA is a deadly epithelial malignancy of the biliary-ductal system and is the second most common primary liver cancer. Surveillance should be offered to all patients with PSC. CCA carries poor prognosis, especially if resection or liver transplantion is not feasible. Novel biomarkers and therapeutic options such as molecularly targeted therapy and immunotherapy hold promise to improve the detection and outcome of CCA patients.

Keywords Cholangiocarcinoma · Primary sclerosing cholangitis · Surveillance · MRI/MRCP · CA 19-9 · ERCP · Biliary brushing · R0 resection · Chemotherapy · Locoregional therapy · Liver transplantation

Introduction

Cholangiocarcinoma (CCA) is an epithelial malignancy of biliary-ductal system, accounting for approximately 3% of all gastrointestinal malignancies and 10 to 20% of primary liver cancers [1]. CCA arises from various locations within the biliary tree and represents a diverse group of cancers with significant genetic heterogeneity and poor outcomes. CCAs are classified into intrahepatic, perihilar, and distal CCAs based on their anatomical locations. Intrahepatic CCA (iCCA) is defined as a CCA located within the liver proximally to the second degree bile ducts; perihilar CCA is localized to the area between the second degree bile ducts and the insertion of the cystic duct into the common bile duct; distal CCA is confined to the area between the origin of the cystic duct and ampulla of Vater [2]. Between the different types of CCA, perihilar CCA represents about 50%, distal CCA 40%, and iCCA less than 10% of all CCA cases [3]. Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a unique intrahepatic malignancy consisting of admixed elements of both HCC and CCA and is now acknowledged as a distinct subtype of CCA [4]. Unfortunately, CCA is associated with very high mortality, with 5-year survival as low as 10% [5].

The reported incidence rates of CCA in the USA are one or two cases per 100,000 person-years. The incidence rates of CCA increase with age, with a median age at diagnosis around 67 for iCCA and 72 for extrahepatic CCA [6]. There is a slight male predominance in CCA [7]. Age-adjusted incidence rates CCA are higher in Hispanic and Asian populations compared to non-Hispanic whites and Black people [8]. The number of new cases of CCA is increasing, mostly due to rising rates of iCCA. Between 1973 and 2012, the incidence rates of iCCA in the USA have increased significantly from 0.44 to 1.18 cases per 100,000, while the incidence rates of extrahepatic CCA increased only modestly from 0.95 to 1.02 per 100,000 [6]. There appears to be a similar trend of rising incidence rates of iCCAs and decreasing incidence of extrahepatic CCAs in many Western

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countries [8–10]. The reason for such disproportionate trends in the incidences rates of intrahepatic and extrahepatic CCAs is unclear. While some suggest changes in nomenclature and ICD classification as the primary reason [9], others attribute it to a concomitant increase in certain risk factors such as cirrhosis, alcoholic liver disease, and hepatitis C virus infection [11]. Given the significant mortality associated with CCA and its rising incidence throughout the world, more effective ways to identify and treat CCA are urgently needed. This review article will discuss surveillance of high-risk individuals, methods to diagnose CCA, and currently available treatment options.

CCA Risk Factors

While most CCAs arise de novo with identifiable risk factors, there are several well-established risk factors. Marked by chronic inflammation and cholestasis, primary sclerosing cholangitis (PSC) is the major risk factor for CCA in Western society. The lifetime chance of developing CCA among PSC patients ranges between 10 and 15%, and the risk of CCA among patients with PSC is increased 400-fold when compared with the general population [2, 12]. Approximately half of PSC-associated CCAs are diagnosed within the first 1–2 years of diagnosis of PSC [13, 14], and afterward, the yearly incidence rate is approximately 0.5–1.5% [15]. Bile duct cysts are rare congenital anomalies characterized by cystic dilatation of the bile ducts and are associated with up to 10–30% lifetime risk of CCA [7]. These cysts are often incidental findings on abdominal imaging or ERCP. In the absence of significant comorbidities that preclude surgery, patients with choledochal cysts (except type III, choledochocele) should be referred for surgical resection to minimize the risk of CCA [16]. Patients with Caroli disease and advanced liver disease should be evaluated for liver transplantation [16]. Hepatolithiasis, or intrahepatic stones, are thought to predispose to CCA by causing bile stasis, recurrent cholangitis, and chronic inflammation. Intrahepatic stones are rare in Western countries but common in parts of Asia and have been associated with 2–13% cumulative incidence of CCA in Asian countries [17]. Endemic to the Far East and Southeast Asia, the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* cause chronic parasitic infection of the bile ducts and significantly increase the risk of CCA [18]. Recently, cirrhosis and viral hepatitis B and C have also been recognized as risk factors for CCA, especially intrahepatic disease [2]. Potential risk factors with less evidence include inflammatory bowel disease, diabetes, obesity, gallstone disease, alcohol, and cigarette smoking [7]. Several genetic polymorphisms with increased risk of CCA development have been identified, including those encoding proteins participating in cell DNA repair (MTHFR, TYMS, GSTO1, and XRCC1), cellular protection against toxins (ABCC2, CYP1A2, and NAT2), or immunological surveillance (KLRK1, MICA, and PTGS2) [1].

CCA Surveillance

The latest guidelines from American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) both recommend CCA surveillance in PSC patients using ultrasound or MRI/MRCP in combination with serum CA 19-9 every 6 to 12 months [19, 20]. To date, PSC remains the only at-risk condition for which consensus guidelines on CCA surveillance have been published. There have been ongoing debates regarding the utility and cost-effectiveness of CCA surveillance in PSC patients, with no prospective studies that investigated its utility. Recently, a single-center retrospective cohort study of 830 PSC patients from the Mayo Clinic Rochester demonstrated that regular surveillance was associated with a significantly higher 5-year overall survival compared to no surveillance (68% vs. 20%; $p < 0.001$) [21••]. However, this study has not adjusted for lead time or length time bias. Several studies have investigated risk factors associated with increased development of CCA among PSC patients to identify the subset of PSC patients who would benefit most from aggressive surveillance strategies [22]. Older age at PSC diagnosis, smoking, alcohol use, elevated bilirubin, a longer duration of associated IBD, presence of colorectal cancer or dysplasia in patients with ulcerative colitis, proctocolectomy, variceal bleeding, and polymorphism of the NKG2D gene have been suggested to increase the risk of CCA in PSC patients [22–24]. However, these studies have not been rigorously validated, with only modest odds ratio (OR) for these risk factors [22]. Therefore, CCA surveillance strategies should be applied to all PSC patients.

Patients with other high-risk conditions are managed on a case-by-case basis. In 2015, the Kohn Kaen University in Northeast Thailand, a region with a high incidence of CCA secondary to liver fluke infestation, has started the "Cholangiocarcinoma Screening and Care Program" (CASCAP), a prospective cohort study of CCA surveillance on at least 150,000 individuals coming from high-risk areas for CCA [25]. This is a very promising study that will help build an extensive prospective database of CCA cases and lead to effective surveillance strategies in patients at risk of CCA [26].

Most CCA surveillance strategies in PSC utilize a combination of imaging modalities and serum carbohydrate antigen 19-9 [16, 19, 22]. Of the available imaging modalities, magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) is often the imaging method of choice with 89% sensitivity and 75% specificity [22]. A less expensive and more readily available alternative to MRI/MRCP, ultrasound has a sensitivity of only 57% but a specificity of 94% [27]. Computerized tomography is not recommended as a first-line screening modality due to the risk of exposure to radiation and contrast [22].

The carbohydrate antigen 19-9 (CA 19-9) is currently the only available serum biomarker for CCA and is often used to complement the imaging studies for CCA surveillance. Using a

cutoff value of ≥ 20 U/mL, CA 19-9 in combination with imaging studies leads to significantly improved sensitivities compared to imaging alone (100% vs. 89% for MRI/MRCP; 91% vs. 57% for ultrasound), but at the cost of significantly reduced specificities (38% vs. 75% for MRI/MRCP; 62% vs. 94% for ultrasound) [27]. Using a higher cutoff value of 129 U/mL for CA 19-9 improves specificity but decreases sensitivity. Of note, approximately 7% of the general population with negative Lewis antigen will not produce CA 19-9 and can have falsely negative CA 19-9 despite having advanced CCA [28].

Endoscopic retrograde cholangiopancreatography (ERCP) has also been considered for CCA surveillance and has a sensitivity of 91% and a specificity of 66% when used alone, and a sensitivity of 100% and a specificity of 43% when combined with CA 19-9 at a cutoff value of 20 U/mL [27]. However, ERCP is not recommended for routine surveillance due to its procedural risks, and primarily reserved for further evaluation of abnormalities identified during surveillance, including dominant strictures, mass lesions, or increasing CA 19-9 levels [29]. Figure 1 shows a proposed algorithm for approach to surveillance and diagnosis of CCA in PSC patients.

CCA Diagnosis

Intrahepatic CCA

ICCA is an incidental finding in 20–25% of cases and typically presents as a mass lesion during routine imaging surveillance for HCC in cirrhosis patients [30••]. In the context of cirrhosis, distinguishing between HCC and iCCA can be challenging, but possible using multi-phase cross-sectional imaging techniques such as CT or MRI. While HCC classically exhibits arterial phase enhancement with delayed phase washout, iCCA demonstrates a pattern of the initial rim or peripheral arterial phase-enhancement followed by centripetal enhancement in the delayed phases [31–33]. A definitive diagnosis of iCCA requires histopathological analysis of a biopsy specimen with a panel of immunohistochemistry markers and cytokeratin profiles [34, 35]. ICCA can be further divided into two main histopathological subtypes: bile ductular-type (mixed) arising from small intrahepatic bile ducts, and bile duct-type (mucinous) arising from large intrahepatic bile ducts. The bile ductular-type iCCAs almost always present in mass-forming growth patterns [36]. The bile ductular-type iCCAs are frequently associated with viral hepatitis [37, 38]. On the other hand, the bile duct-type iCCAs can exhibit various growth patterns including mass-forming, periductal infiltrating, and intraductal growing [38]. The bile duct-type iCCAs are more frequently associated with PSC [37, 38]. This morphological classification is of clinical significance, as patients with bile ductular-type iCCA tend to have higher 5-year survival rates compared to patients with the bile duct-type iCCA [39].

Perihilar and Distal CCA

Unlike iCCAs which tend to be mass-forming, pCCAs and dCCAs usually present in a periductal-infiltrating form with narrowed perihilar or distal biliary ducts and irregular wall thickening and dilatation of intrahepatic bile ducts due to distal biliary obstruction [40]. These findings can be subtle and make it challenging to distinguish benign strictures from malignant strictures, particularly in PSC patients. Development of a new dominant stricture should raise serious concern for CCA, as one fourth of the dominant strictures are malignant

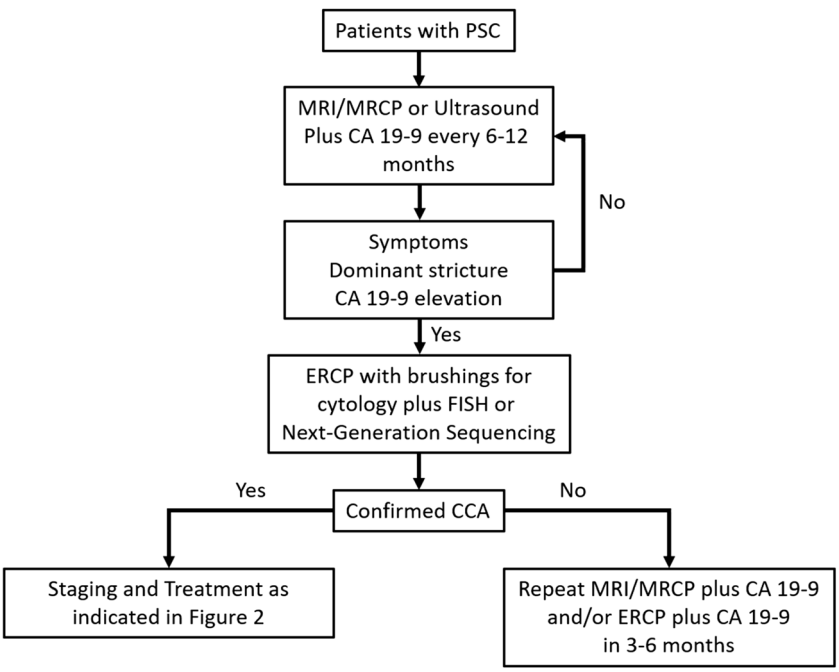

Fig. 1 Recommended CCA surveillance algorithm in patients with PSC. CA 19-9 carbohydrate antigen 19-9, CCA cholangiocarcinoma, ERCP endoscopic retrograde cholangiopancreatography, FISH fluorescence in situ hybridization, MRI magnetic resonance imaging, MRCP magnetic resonance cholangiopancreatography, PSC primary sclerosing cholangitis

[41, 42]. However, CCA may present in patients without an obstructive stricture, so their absence does not exclude malignancy [29]. Therefore, patients who develop dominant strictures, increasing CA 19-9 levels, or any other clinical features concerning for CCA should undergo ERCP with biliary brushing samples for cytological analysis [19, 20, 30]. Endoscopic ultrasonography (EUS) can also effectively diagnose and stage pCCAs (83% sensitivity) and dCCAs (100% sensitivity) [43], but fine-needle aspiration (FNA) during EUS carries a significant risk of tumor seeding leading to peritoneal metastases [44].

In patients with PSC, bile duct brushing cytology has a very high specificity of 97%, but limited sensitivity of 43% for the diagnosis of p/dCCA [45]. The addition of fluorescence in situ hybridization (FISH) analysis to the brush specimen has enhanced the diagnostic performance of conventional cytology. Developed in 2015, an optimized set of FISH probes targeting the 1q21, 7p12, 8q24, and 9p21 loci can detect CCA and other pancreatobiliary malignancies in PSC patients with improved sensitivity of 65% and specificity of 91% [46]. Moreover, next-generation sequencing (NGS) for various oncogenic targets including *KRAS*, *TP53*, *SMAD4*, and *CDKN2A* can further improve the diagnostic performance of biliary brushing [47]. In a study of bile duct brushing specimens from 74 patients, combination of cytology and NGS resulted in the highest sensitivity (85%), compared to cytology alone (67%), and combination of cytology and FISH (76%) [47]. Finally, a variety of emerging "liquid biopsy" techniques such as circulating tumor DNA, microRNAs, and extracellular vesicles in bile and serum demonstrate great promises in enabling diagnosis of CCA without directly obtaining biliary cytology [48].

CCA Treatment

Intrahepatic CCA

The treatment approach for CCA is summarized in Fig. 2. The prognosis of iCCA is very poor, with nearly no survivors at 3 years without surgery [49]. For patients with localized iCCA, complete surgical resection of the tumor with negative histologic margins is the only treatment option to achieve possible cure [49]. Patients with localized iCCA who undergo complete surgical resection have significantly higher median survival compared to those who do not undergo surgery (44 months vs 8 months; $p < 0.01$) [50]. In a single-center series, the median overall survival for R0-resected iCCA patients was as high as 80 months, with 5-year survival of 63% [3]. Unfortunately, many iCCA patients are found to have unresectable disease at the time of diagnosis due to presence of intrahepatic metastases, involvement of major blood vessels, extensive regional lymphadenopathy, or distant metastases [49]. Around 30% of iCCA patients deemed to have potentially resectable disease are found to be unresectable upon staging laparoscopy [51, 52]. Besides, a significant proportion of patients with localized iCCA who may obtain substantial survival benefit from cancer-directed surgery do not undergo surgery. According to a retrospective cohort study of the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2003, only 37% of iCCA patients with localized disease underwent cancer-directed surgery [50]. The barriers to receiving appropriate care in patients with localized iCCA remain to be determined.

Liver transplantation has been considered contraindicated in iCCA patients due to poor outcomes and high rates of recurrence. In 2003, an analysis of liver transplantation outcomes for iCCA in the European Liver Transplant Registry revealed poor 1-, 3-, 5-, 8-, and 10-year survival rates of 58%, 38%, 29%, 23%, and 21% [53]. However, a retrospective multicenter study in 2014 demonstrated excellent 1-, 3-, and 5-year post-transplantation survival rates of 100%, 73%, and 73% in a specific subset of cirrhosis patients with "very early" iCCA, defined as single tumors ≤ 2 cm in diameter [54]. A subsequent follow-up study with a larger, international, multicenter cohort of patients confirmed the improved liver transplantation outcome in patients with very early iCCA, with 1-, 3-, and 5-year survival rates of 93%, 84%, and 65% compared 79%, 50%, and 45% in patients with "advanced" iCCA (single tumor > 2 cm or multifocal disease) [55]. Therefore, liver transplantation appears to be an effective treatment option for a subset of localized iCCA patients with early disease.

Patients with advanced iCCA who are not candidates for resection or liver transplantation may benefit from systemic chemotherapy, radiation therapy, placement of a hepatic artery infusion pump (HAIP), and locoregional therapies. For patients receiving chemotherapy, a combination regimen of gemcitabine plus cisplatin is superior to gemcitabine alone, with significantly improved time to progression (8 months vs. 5 months) and overall survival (11.7 months vs. 8.1 months) [56]. A recent National Cancer Data Base study of unresectable iCCA patients showed that combined chemoradiation therapy was associated with significantly higher median overall survival compared to chemotherapy alone (13.6 vs. 10.5 months, $p < 0.001$) [57]. A SEER database study also showed that palliative radiotherapy is associated with significantly improved overall and cancer-specific survival in patients with unresectable iCCA [58]. Locoregional therapies, including transarterial chemoembolization (TACE), transarterial radioembolization (TARE) also have a role in the management of unresectable iCCA. TACE leads to the improved median overall survival of 12 to 15 months compared to 5 to 8 months without treatment [59–61]. Transarterial radioembolization (TARE) using yttrium-90 microspheres is also an effective and safe option with a median overall survival of 11 to 22 months [62]. Targeted therapy using HAIP is

another option for unresectable iCCA, where the patient receives a continuous infusion of fluorodeoxyuridine. In a single-center study of 525 patients with iCCA from 2000 to 2012, patients who received combined HAIP and systemic chemotherapy had a significantly improved overall survival compared to patients who received chemotherapy alone (30.8 vs. 18.4 months, $p < 0.001$) [63]. In addition, several patients receiving HAIP were downstaged from unresectable to resectable disease and underwent complete resection with a median survival of 37 months [63].

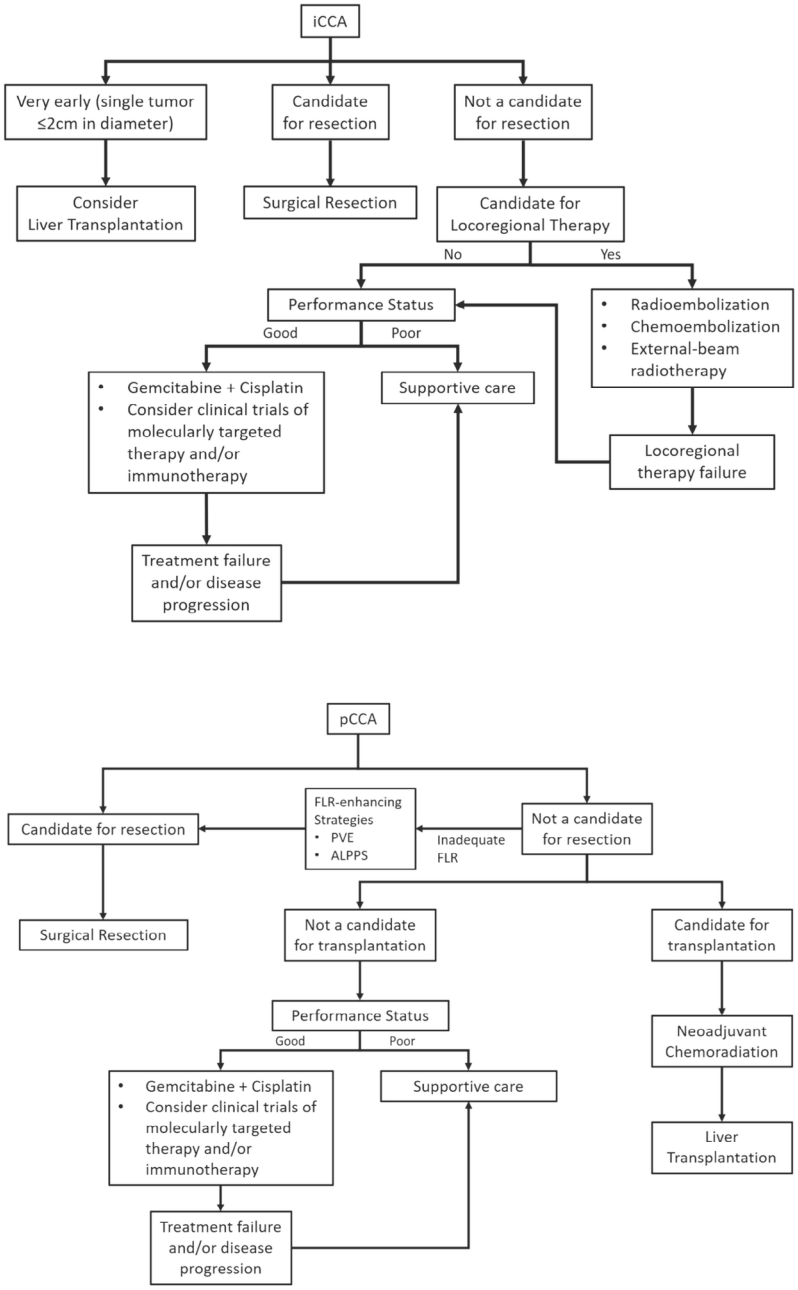

Fig. 2 Proposed clinical management algorithms for adult patients with cholangiocarcinoma. **a** For patients with intrahepatic cholangiocarcinoma. **b** For patients with perihilar cholangiocarcinoma. Patients with underlying PSC are discouraged from undergoing surgical resection regardless of their tumor anatomy, due to their chronic parenchymal disease and a field defect that cannot be eliminated by resection, as long as patients are eligible for liver transplantation. **c** For patients with distal cholangiocarcinoma. ALPPS associating liver partition and portal vein ligation for staged hepatectomy, dCCA distal cholangiocarcinoma, FLR future liver remnant, iCCA intrahepatic cholangiocarcinoma, pCCA perihilar cholangiocarcinoma, PVE portal vein embolization

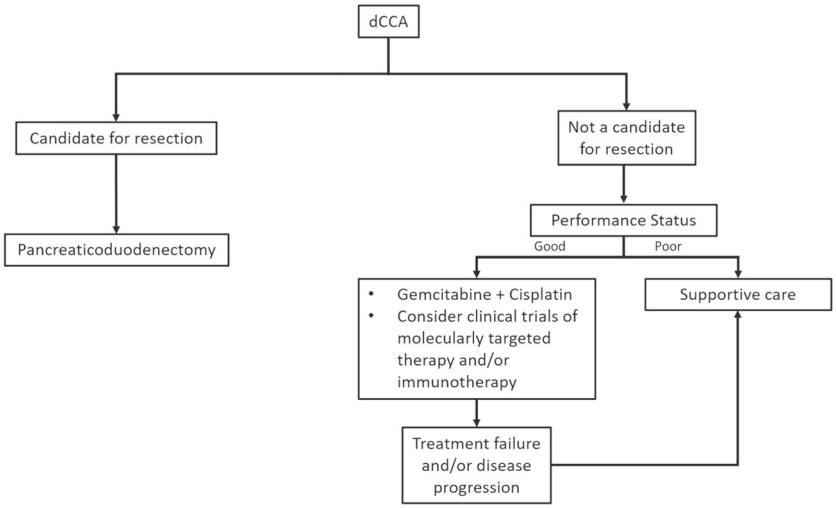

Fig. 2 (continued)

Perihilar CCA

For patients with pCCA, surgical resection gives the best chance of long-term survival and potential cure. Resection with curative intent often involves lobar or extended lobar hepatic and bile duct resection, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy [64]. Patients with successful R0 resection have 5-year survival rates ranging from 25 to 50%, while patients with positive margins have significantly worse 5-year survival ranging from 0 to 23% [65••, 66]. The resectability of non-metastatic pCCA depends on the biliary and vascular reconstruction options and the ability to leave adequate hepatic parenchyma. Thus, patients with tumor extension into the liver without a target for restoring biliary continuity, and patients with atrophy of the anticipated remnant liver are not considered to be candidates for surgical resection [66]. Of note, patients with underlying PSC are discouraged from undergoing surgical resection regardless of their tumor anatomy, due to their chronic parenchymal disease and a field defect that cannot be eliminated by resection as long as patients are eligible for liver transplantation [30]. Advancements in surgical techniques such as extended lobectomy and vascular reconstruction, and strategies to enhance remnant liver volume including portal vein embolization (PVE) and the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) now allow resection of a significant proportion of pCCA tumors previously considered unresectable [30]. Future liver remnant (FLR) is the percentage of remaining functional liver volume after surgical resection and is used to predict the risk of developing posthepatectomy liver failure. In general, FLR ≥ 20% in otherwise healthy liver is an acceptable cutoff with good postresection outcomes, while higher FLR cutoff around 30–40% are needed for patients with steatosis, cholestasis, and cirrhosis [67]. For pCCA patients with inadequate or borderline FLR, preoperative strategies such as PVE and ALPPS effectively improve FLR by inducing hypertrophy of the contralateral side and enable successful R0 resection [68, 69]. For patients with margin-positive or node-positive resection, adjuvant chemoradiation appears to be associated with more prolonged 5-year overall survival compared with resection alone (36.5% vs. 28.2%, $p < 0.001$) [70].

A small subset of patients with unresectable pCCA may be candidates for liver transplantation following neoadjuvant chemoradiation. In the absence of other contraindications to liver transplantation, selection criteria for this protocol include a radial diameter of the tumor < 3 cm, and absence of lymph node, intrahepatic or extrahepatic metastasis [71]. This strategy is an attractive treatment option for patients with any PSC associated pCCA or de novo pCCA who are not candidates for resection. Eligible patients undergo an intensive neoadjuvant regimen consisting of external beam radiation, brachytherapy, radiosensitizing therapy, and/or maintenance chemotherapy followed by liver transplantation [72]. pCCA patients across 12 US centers who participated in this protocol had a 65% recurrence-free survival after 5 years, showing it to be a highly effective option for these patients [72].

Patients with locally advanced, unresectable tumors are mainly treated with chemoradiation with or without intraluminal chemotherapy and have a poor median survival ranging from 11 to 15 months [66]. Patients with metastatic disease or locoregional recurrence are treated with systemic chemotherapy using gemcitabine and cisplatin as first-line agents [66].

Distal CCA

Similar to patients with iCCA and pCCA, complete R0 resection with negative margins offers the best chance of survival for patients with dCCA. Surgical resection usually involves a pancreaticoduodenectomy or Whipple procedure, which successfully achieves R0 resection in 78% [3]. The overall 5-year survival of dCCA patients is 23% and only increases to 27% with

R0 resection [3]. Adjuvant chemoradiation or systemic chemotherapy following R0 resection does not appear to offer any survival benefit compared with no adjuvant treatment [73]. Postoperative chemoradiation with or without systemic chemotherapy may have a beneficial role for patients with R1 resection and/or node-positive disease, as several retrospective single-center studies suggest modest improvements in local control and overall survival [74–76]. For patients with unresectable or metastatic dCCA, palliative chemotherapy using gemcitabine and cisplatin can be offered, but the median survival is less than 1 year [77].

Conclusion and Future Directions

CCAs are anatomically distinct and genetically heterogeneous epithelial malignancy of the biliary ductal system with an extremely high mortality rate. Several risk factors associated with CCA development have been identified, although a significant number of CCAs arise de novo without a clear precipitant. Currently available guidelines recommend CCA surveillance for PSC patients using MRI/MRCP or ultrasound and CA 19-9 every 6 to 12 months. iCCA can be suspected based on specific contrast enhancements of a mass lesion on cross-sectional imaging and diagnosed with histopathological analysis of a biopsy specimen. pCCA and dCCA often present in subtle, periductal-infiltrating forms, and require a high level of suspicion especially when a new, dominant stricture is found. ERCP with cytological analysis of biliary brushing specimen is highly specific but lacks sensitivity for diagnosing pCCA and dCCA. Incorporation of FISH and next-generation sequencing to cytology have significantly improved the sensitivity of biliary brushings. Currently, complete surgical resection with negative margins is the treatment option that provides the best chance of long-term survival and potential cure for all three types of CCA. Liver transplantation can be an effective treatment option for certain patients with very early iCCA or PSC induced pCCA or de novo unresectable pCCA. Those with advanced disease who are not candidates for resection or liver transplantation can be treated with gemcitabine and cisplatin-based chemotherapy, but have very poor survival.

Advancements in genomic and proteomic technologies hold great promises for the discovery of novel diagnostic and therapeutic modalities that can establish a precision medicine approach to CCA. Innovative "liquid biopsy" biomarkers such as circulating tumor DNA, DNA-methylation markers, microRNAs, and extracellular vesicles in bile and serum are expected to enable CCA diagnosis without biliary cytology [48]. Comprehensive whole-exome and transcriptome sequencing in a large cohort of CCA patients have revealed a variety of genetic driver mutations which could be candidates for molecularly targeted therapies [78]. Clinical trials investigating various targeted therapies have shown promising preliminary data for FGFR inhibitors and IDH1/IDH2 inhibitors, as well as immunotherapies [30].

Compliance with Ethical Standards

Conflict of Interest Joseph C. Ahn and Ju Dong Yang each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations *ACG,* American College of Gastroenterology; *AGA,* American Gastroenterological Association; *ALPPS,* Associating liver partition and portal vein ligation for staged hepatectomy; *CA 19-9,* Carbohydrate antigen 19-9; *CASCAP,* Cholangiocarcinoma Screening and Care Program; *CCA,* Cholangiocarcinoma; *cHCC-CCA,* Combined hepatocellular-cholangiocarcinoma; *dCCA,* Distal cholangiocarcinoma; *ERCP,* Endoscopic retrograde cholangiopancreatography; *EUS,* Endoscopic ultrasound; *FISH,* Fluorescence in situ hybridization; *FLR,* Future liver remnant; *FNA,* Fine-needle aspiration; *HAIP,* Hepatic artery infusion pump; *iCCA,* Intrahepatic cholangiocarcinoma; *MRCP,* Magnetic resonance cholangiopancreatography; *MRI,* Magnetic resonance imaging; *NGS,* Next-generation sequencing; *pCCA,* Perihilar cholangiocarcinoma; *PSC,* Primary sclerosing cholangitis; *PVE,* Portal vein embolization; *SEER,* Surveillance, Epidemiology, and End Results; *TACE,* Transarterial chemoembolization; *TARE,* Transarterial radioembolization

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