Update on the Screening, Diagnosis, and Management of Cholangiocarcinoma

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Abstract: Cholangiocarcinoma (CCA) is a neoplasm of the biliary tract that has become increasingly prevalent throughout the world. Common risk factors for developing CCA include cirrhosis, primary sclerosing cholangitis, and trematode fluke infestation, although there are no set screening guidelines in high-risk groups. Lesions are typically identified via cross-sectional imaging and/or elevated serum carbohydrate antigen 19-9 levels, often followed by cytology or brushings with fluorescence in situ hybridization for confirmation. Treatments can vary among CCA subtypes but frequently involve systemic therapies such as gemcitabine and cisplatin with durvalumab or pembrolizumab. Targeted therapies may also be effective (eg, ivosidenib, pemigatinib, infigratinib, futibatinib) depending on the molecular alterations present. Resection is the most common surgical treatment for CCA, although liver transplantation is also an option in highly selected patients with liver-limited unresectable disease. Radiotherapy may also be a treatment option, as well as transarterial radioembolization (eg, yttrium-90), which is often utilized in combination with systemic therapy. Although patients with CCA have traditionally had a poor prognosis, recent advances in treatment, including new systemic therapies and increased utilization of liver transplantation, have improved expected survival. This article reviews screening modalities, pros and cons of diagnostic techniques, and therapies that are currently available to treat patients with CCA.

Keywords
Cholangiocarcinoma, bile duct neoplasms, intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, distal cholangiocarcinoma

Cholangiocarcinoma (CCA) is an adenocarcinoma that arises from the biliary tract. It is the second most common primary liver cancer, after hepatocellular carcinoma (HCC).[1] The incidence of CCA is highest in regions where trematode flukes are endemic, reaching 40 to 100 cases per 100,000 individuals.[2] Elsewhere, CCA rates

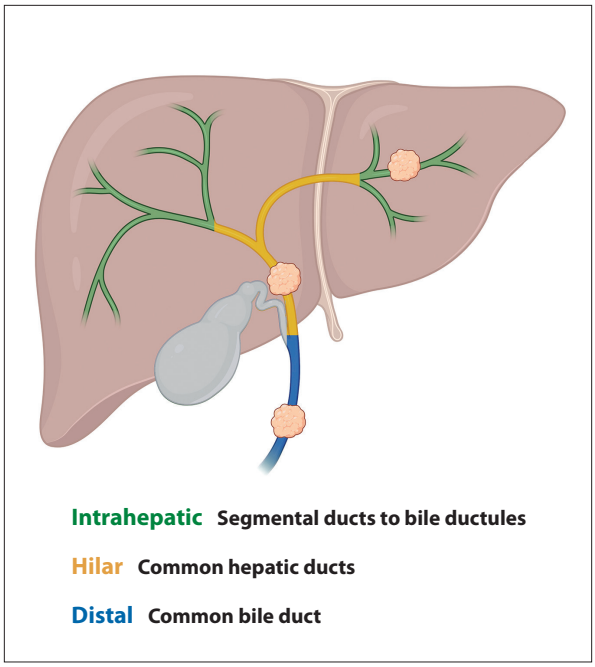

Figure 1. Cholangiocarcinoma subtypes based on anatomic location.

are approximately 0.4 to 2 per 100,000 persons.[1] Worldwide mortality rates range between 0.2 and 2 deaths per 100,000 person-years, with higher rates in men and in Europe, Japan, and Hong Kong.[3] CCA-related mortality rates are increasing in most countries,[3] including the United States.[4]

CCA is classified by its location as intrahepatic or extrahepatic, depending on the location of the bile ducts where the tumor originates. Specifically, intrahepatic CCA (iCCA) occurs in second-order bile ducts down to bile ductules. Extrahepatic disease can be further subclassified as distal (dCCA) or hilar (hCCA, also called perihilar CCA or Klatskin tumors) (Figure 1). Patients with extrahepatic CCA have lower mortality rates than patients with intrahepatic disease.[3]

CCA cases can be divided into 3 growth patterns: mass-forming, periductal-infiltrating, and intraductal-growing. Most iCCAs are mass-forming, frequently appearing as a single solid lesion, although more advanced cases may be multifocal.[1,5] hCCAs tend to be periductal-infiltrating, where lesions grow along the axis of the common hepatic ducts[1] along Glisson capsule sheaths.[6] Intraductal-growing CCAs often have a papillary style of growth and tend to have better outcomes than the other two main anatomic growth patterns.[6] The goal of this article is to review current methods for screening and diagnosis of CCA, available treatments, and relevant recommendations by national and international medical societies.

Screening and Diagnosis of Cholangiocarcinoma

Identification of High-Risk Groups

Symptoms of CCA are often absent or nonspecific, including jaundice, abdominal pain, decreased appetite, weight loss, and night sweats.[1,7,8] Thus, the diagnosis of CCA usually stems from the identification of masses from imaging studies for other causes or symptomatic biliary strictures.[9] Approximately 20% to 40% of patients with iCCA receive their diagnosis incidentally.[1]

There is no consensus regarding which individuals should undergo regular screening for CCA. For example, the recommendations for CCA screening vary in patients with primary sclerosing cholangitis (PSC), who have a 1.5% chance of developing CCA per year postdiagnosis.[7] However, current American Association for the Study of Liver Diseases (AASLD) guidelines recommend annual screening in patients with PSC to monitor for CCA and gallbladder carcinoma using magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography, with or without serum biomarkers.[10] The American Gastroenterological Association recommends that adults with PSC undergo surveillance for CCA every 6 to 12 months.[11]

Imaging

iCCA lesions are frequently identified using computed tomography (CT) or MRI studies performed for HCC surveillance (Figure 2). Unenhanced or contrast-enhanced ultrasound may also be used.[12] In MRI studies, contrast is often more useful because it is better at distinguishing between iCCA and HCC lesions, the latter of which tends to rapidly take up contrast (arterial hyperenhancement), followed by delayed washout in the venous phase.[9] CCA tends to first be enhanced at its periphery followed by contrast washout in the center of the lesion, with delayed central enhancement.[13] Similarly, triple-phase CT scans provide greater diagnostic information than standard CT scans.[7] CT and MRI are also helpful because they can accurately identify which, if any, vessels are involved, which can be used to determine resectability and treatment planning with locoregional therapies.[12] It is important to note that it can be difficult to identify periductal-infiltrating CCAs using cross-sectional imaging.[14] Current American College of Gastroenterology guidelines recommend that patients suspected to have CCA on ultrasound screening should receive confirmatory MRI or CT scans.[7]

Imaging is also used in staging CCA spread beyond the liver and/or biliary tree, utilizing CT, MRI, or ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), which can identify distant metastases.[12] Most societies recommend abdominal MRI and chest, abdominal, and pelvic CT imaging to properly stage

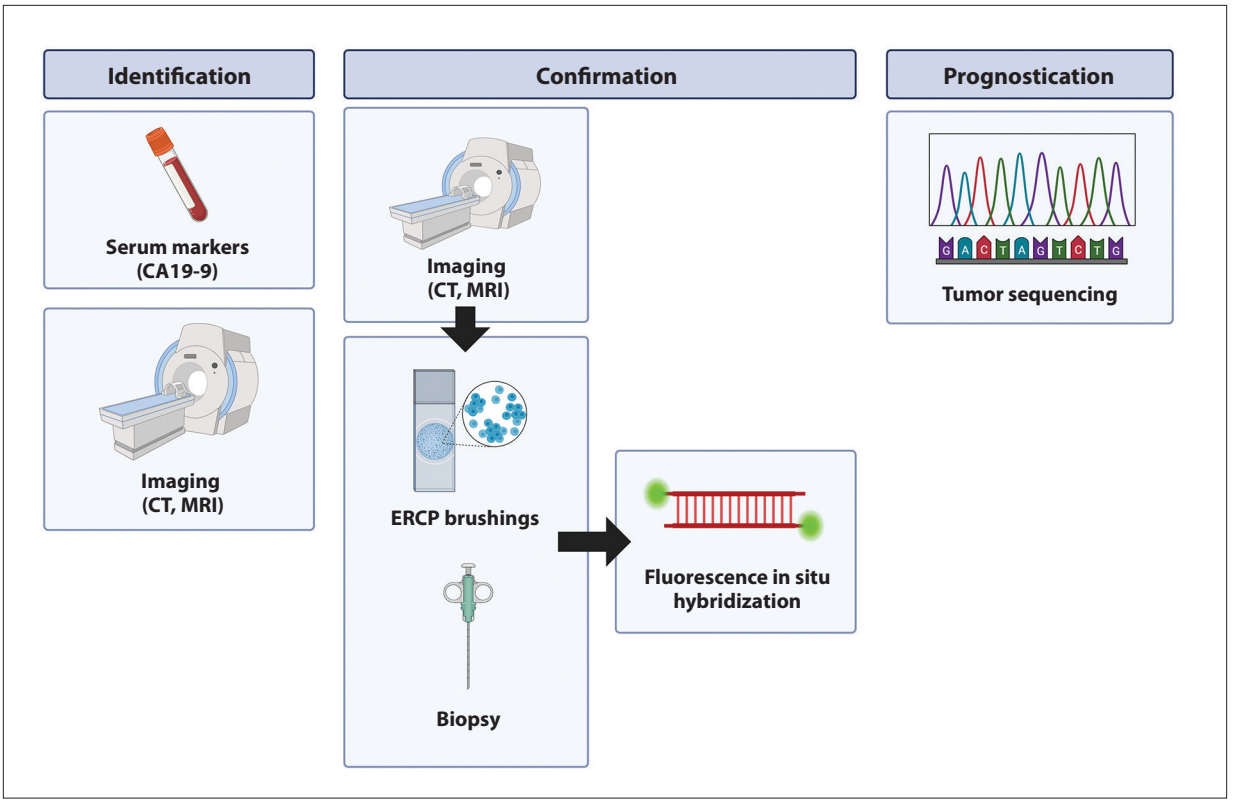

Figure 2. Modalities for screening and diagnosis of cholangiocarcinoma.

CA19-9, carbohydrate antigen 19-9; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; MRI, magnetic resonance imaging.

CCA once it is diagnosed.[15,16] It is important to note that ^{18}FDG-PET scans can have limited sensitivity in patients with CCA,[17] which limits their utility. Some societies, such as the European Society for Medical Oncology, do not recommend using PET scans in the diagnosis or staging of CCA.[18] Other societies, such as the AASLD, recommend using ^{18}FDG-PET for staging only and recommend against PET for CCA diagnosis.[10]

Carbohydrate Antigen 19-9

Carbohydrate antigen 19-9 (CA19-9) is the most frequently studied blood test used to screen for CCA. However, its sensitivity and specificity can be limited. For example, when using a cutoff of 20 U/mL, the sensitivity of CA19-9 was 78%, specificity was 67%, positive predictive value was 23%, and negative predictive value was 96%.[19] Moderate cutoffs of 37 U/mL result in a sensitivity of 77.14%, specificity of 84.78%, positive predictive value of 65.85%, and negative predictive value of 90.70%.[20] A cutoff of 129 U/mL provides a sensitivity of 78.6%, specificity of 98.5%, positive predictive value of 56.6%, and negative predictive value of 99.4% in patients with PSC.[21] Additionally, patients with PSC or biliary obstruction may have elevated CA19-9 levels without CCA,[15,22] so test results must be interpreted cautiously in this population. Combining CA19-9 with carcinoembryonic antigen may improve test performance,[23,24] but some guidelines only recommend the use of CA19-9.[10,18]

The AASLD and European Society for Medical Oncology recommend that patients with elevated CA19-9 levels undergo follow-up imaging for CCA.[10,18] The AASLD specifically recommends using multiphasic CT or MRI to detect primary and potential secondary tumors and distant metastases and confirm imaging findings with biopsy for a definitive diagnosis.[10]

Biopsy

Biopsies (percutaneous or endoscopic) and aspirates can be collected if suspicious lesions are identified on imaging studies. Endoscopic retrograde cholangiopancreatography (ERCP)-guided biopsy is the generally preferred method of collecting specimens for histology for suspected extrahepatic CCA.[15] Endoscopic ultrasound–guided biopsy is similar to ERCP, but uses ultrasound to image the biliary tract. Recent research has suggested that endoscopic ultrasound–guided biopsies may provide a more accurate sample than ERCP-guided biopsies for diagnosing biliary abnormalities.[25] Clinicians may also choose to perform

percutaneous biopsies, in which a needle (usually 18-21 gauge) is used to obtain a core tissue sample, usually guided by imaging.[12]

Although biopsy is the only way to obtain a definitive diagnosis of CCA, many providers avoid it owing to the risk of tumor seeding.[26,27] Therefore, percutaneous transperitoneal biopsy should not be used in patients who are potential candidates for liver transplantation (LT) in hCCA.[27] Additionally, a definitive tissue diagnosis may not inform the treatment plan, as a diagnosis of CCA can be presumptively made in some settings, such as hCCA patients. If these patients present with a malignant-appearing stricture less than 3 cm and CA19-9 levels above 100 U/mL, they are eligible for exception points for LT and do not need tissue biopsy confirmation.[7] Biopsy may also be contraindicated in patients with ascites and/or severe coagulopathy. However, the benefits of biopsy can outweigh the risks. For example, ERCP-guided biopsy is superior to brushings in diagnosing extrahepatic CCA.[15] Biopsies can also be useful if clinicians need to sequence the tumor to place the patient on a targeted therapy or in a clinical trial; hence, tissue biopsy is now standard of care for guiding therapy for iCCA.[10]

The decision to utilize biopsy to diagnose CCA must carefully weigh the risks and benefits to the procedure. Society recommendations for the utilization of biopsy in CCA diagnosis therefore reflect the nuances in this decision-making process. The American College of Gastroenterology only recommends biopsy in patients with inoperable tumors, with core biopsies preferred over fine-needle aspiration.[7] The AASLD states that core-needle biopsy is needed to make a definitive diagnosis of iCCA.[10] The US National Comprehensive Cancer Network recommends against biopsy if the CCA is potentially resectable.[15] Conversely, the British Society of Gastroenterology and International Liver Cancer Association recommend biopsy to obtain a definitive diagnosis prior to beginning any therapy.[15] The European Society for Medical Oncology recommends that all patients with CCA who are not surgical candidates undergo biopsy and molecular profiling to confirm their diagnosis and determine the best course of treatment.[16] Variability in society clinical guidelines and recommendations can affect diagnostic workup of patients, which in turn can affect the likelihood of detecting CCA at early stages.

Brushings and Cytology

In addition to histology, cytology can be used to positively identify CCA. Cytologic samples for CCA are most frequently obtained from biliary brush samples taken during ERCP.[28] Fine-needle aspiration can also be used to obtain material for cytologic analysis, but its utility may be restricted by the lesion's anatomic location. Additionally, core-needle biopsy generally provides more accurate results than fine-needle aspiration[29] and other cytologic methods. A 2022 meta-analysis reported that ERCP brushings have a pooled sensitivity of 56%, lower than biopsy, combined brushings and biopsy, and endoscopic ultrasound–guided fine-needle aspiration.[30]

Society guidelines for the clinical use of brushings and cytology vary depending on the anatomic location of the CCA. Per AASLD guidelines, percutaneous fine-needle aspiration should not be utilized in patients with hCCA because of the high risk of tumor seeding.[10] For patients with suspected hCCA or dCCA, the guidelines recommend using ERCP brushings combined with fluorescence in situ hybridization (FISH; detailed in the following section). When paired with FISH, the sensitivity, specificity, and accuracy of cytology increase.[14]

Fluorescence In Situ Hybridization

FISH is an important tool in differentiating CCA from nonmalignant biliary strictures in cytologic analysis. This technique utilizes fluorescent DNA probes to identify cells with chromosomal abnormalities associated with malignancy,[31] which cytology may otherwise fail to identify. Commercially available kits mark sections located near the centromeres of chromosomes 3, 7, and 17 and in the band 9p21.[31-33] Cells that show 2 fluorescent dots for each probe are disomic, but if there are at least 3 dots for a probe, the cell is polysomic. Brushing samples with multiple polysomic cells are highly indicative of CCA.[34]

Traditional cytology has a sensitivity of 21% to 50% and a specificity of 98% to 100%, which increase to 35% to 89% and 91% to 100%, respectively, when FISH is added.[14] In patients with PSC, a meta-analysis has reported that FISH has a pooled sensitivity of 68% and a pooled specificity of 70%.[35] When malignancy is identified using positive cytology or FISH results, sensitivity increases to 89% and specificity increases to 97%, with an area under the curve of 0.931.[32] The AASLD currently recommends that FISH be used during cytologic analysis of ERCP brushings to aid in the diagnosis of CCA, as traditional cytology may not yield accurate results.[10]

Management of Cholangiocarcinoma

General Principles

Table 1 summarizes the treatments that are currently available for different types of CCA. Regardless of the anatomic type of a patient's CCA, treatment strategies are usually the same. For example, the majority of patients undergo systemic therapy. European Society for Medical Oncology and American Society of Clinical Oncology guidelines recommend the use of surgery and adjuvant capecitabine for early-stage CCA.[15,16] First-line treatment

Table 1. Treatments Available for Different Types of Cholangiocarcinoma

Treatment type	Intrahepatic cholangiocarcinoma	Hilar cholangiocarcinoma	Distal cholangiocarcinoma
Systemic therapies	Yes	Yes	Yes
Resection	Yes	Yes	Yes
Radiotherapy	Yes	Yes	
Locoregional therapy	Yes		
Liver transplantation	Yes[a]	Yes[a]	

[a]In highly selected patients under institutional protocols.

for locally advanced or metastatic CCA had historically been gemcitabine and cisplatin. Most recently, guidelines have been updated to recommend gemcitabine, cisplatin, and durvalumab (Imfinzi, AstraZeneca), with maintenance durvalumab,[16] based on the TOPAZ-1 trial.[36] The KEYNOTE-966 trial has shown similar improvements in progression-free and overall survival in advanced biliary tract cancers with gemcitabine, cisplatin, and the programmed death 1 pathway inhibitor pembrolizumab (Keytruda, Merck).[37] Other systemic therapies may also be used depending on the molecular alterations of the patient's CCA, including ivosidenib (Tibsovo, Servier Pharmaceuticals) for patients with isocitrate dehydrogenase 1 mutations and pemigatinib (Pemazyre, Incyte), infigratinib, or futibatinib for fibroblast growth factor receptor 2 fusions. FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) can also be effective against biliary tract cancers, as can pembrolizumab. Systemic therapies can also be used as neoadjuvant bridging treatments to LT.[15]

Treatment for CCA also depends heavily on whether the disease is resectable. Complete surgical removal of diseased tissue offers the only chance of cure. However, resectability of any hepatic tumor depends on its location relative to vascular and biliary structures, as well as the size of the future liver remnant following surgery. Patients with decompensated cirrhosis and/or portal hypertension are not eligible for liver resection. Well-compensated patients with cirrhosis, especially patients with Child-Pugh A cirrhosis, can undergo hepatic resection if expected to have a functional liver remnant of at least 40%.[38] The goal of any liver cancer resection is to remove the tumor with negative (R0) margins while still maintaining an adequate functional liver remnant with sufficient blood flow and a biliary drainage. However, many hCCA lesions are unresectable because of vascular involvement near the hilum.[26] Patient survival at 5 years postresection is approximately 25% to 50%, although survival rates increase if R0 resection is achieved, which occurs in 70% to 80% of patients.[39]

Intrahepatic Cholangiocarcinoma

For patients with resectable iCCA, resection is often the first-line treatment. Patients with cirrhosis who undergo regular imaging to screen for HCC may be diagnosed with early iCCA lesions, which may be resectable in the absence of portal hypertension. However, resection may not be an option in advanced disease and patients who manifest symptoms of portal hypertension. Patients with resectable tumors are in the minority, making up only approximately 15% of iCCA cases, according to Surveillance, Epidemiology, and End Results database analysis.[40] Patient survival after resection for iCCA generally ranges between 30% and 55% at 5 years in contemporary studies, with higher survival rates in patients who undergo R0 resection.[41]

LT is an option for highly selected patients with unresectable iCCA. Initial guidelines suggested limiting LT to patients with a single lesion no more than 2 cm in diameter, reporting 1-, 3-, and 5-year overall survival rates of 93%, 84%, and 65%, respectively, in patients meeting these size criteria.[42,43] However, recent studies have shown that patients with locally advanced, liver-limited iCCA with a single lesion greater than 2 cm in diameter or multiple lesions can have overall survival rates of 100%, 71%, and 57% at 1, 3, and 5 years, respectively, post-LT.[44,45] These patients were treated with neoadjuvant systemic therapy (usually gemcitabine-cisplatin) and had radiographically stable lesions for 6 months. Response to neoadjuvant therapy acted as a measure of tumor biology, allowing patients with large but amenable iCCA tumors to undergo LT. Unlike for hCCA, there is no standardized process for awarding deceased donor liver allocation exception points to patients with iCCA, which limits their access to transplant. Living donation may be a viable option for these patients if carefully selected.

In direct comparisons between resection and LT for iCCA, patients receiving LT generally have superior overall and recurrence-free survival.[41] Transplantation provides R0 resection of all lesions, including lesions that are

Table 2. Mayo Clinic Selection Criteria for Patients With Hilar Cholangiocarcinoma

Eligibility requirements for liver transplantation for hilar cholangiocarcinoma[a]
• Biliary stricture that appears malignant in imaging and meets at least 1 of the following criteria: – Biopsy or cytology-proven hilar cholangiocarcinoma – CA19-9 >100 U/mL in patients who do not have cholangitis – Aneuploidy (fluorescence in situ hybridization)
• Unresectable lesion
• Lesion <3 cm in diameter in cross-sectional imaging
• No intrahepatic or extrahepatic metastases
• Regional lymph node biopsies negative for malignancy
• No transperitoneal biopsy of the lesion performed

CA19-9, carbohydrate antigen 19-9.
[a]Patients meeting these requirements are eligible for United Network for Organ Sharing exception points.

too small to be detected via imaging, and thus eliminates potential lesions left in the functional liver remnant after resection. When resection or LT is performed for iCCA, the British Society of Gastroenterology, European Society for Medical Oncology, International Liver Cancer Association, and National Comprehensive Cancer Network guidelines recommend conducting a portal lymphadenectomy, as lymph node metastasis is often present in these patients.[15]

With the advent of chemoimmunotherapy combinations and targeted agents, patients with unresectable iCCA now have multiple treatment options. Systemic therapy for iCCA most frequently consists of capecitabine, gemcitabine, cisplatin, or a combination thereof.[16] Recent trials over the past 5 to 10 years have resulted in newly approved, effective systemic treatments for iCCA, including many targeted therapies.[46] Combination transarterial radioembolization and systemic therapy (yttrium-90 with gemcitabine and cisplatin) has shown promise as a first-line treatment in a phase 2 trial, with overall survival rates of 75% at 1 year and 45% at 2 years.[47]

Hilar Cholangiocarcinoma

Treatment for hCCA depends on whether the patient's disease is resectable, although resection is not an option for many patients. LT is an option for highly selected patients with unresectable hCCA. The Mayo Clinic criteria (Table 2) limit LT to patients with unresectable lesions less than 3 cm in radial diameter and without metastatic disease. In the initial series, LT candidates received neoadjuvant external beam radiation therapy combined with 5-fluorouracil chemosensitization, with some also receiving capecitabine systemic therapy.[48] Patient survival rates in this study were 88% at 1 year and 82% at 5 years post-LT. Updated studies have reported 1-, 3-, and 5-year overall survival rates of 91%, 69%, and 62%, respectively.[49] Patient outcomes improve with center experience.[50]

Systemic therapies are also available for patients with hCCA. The Mayo Protocol, which is followed by many centers, recommends oral capecitabine following intraductal radiation until the patient undergoes LT.[48] On the other hand, several combination regimens such as gemcitabine and cisplatin and other agents are used in nonresectable and non-LT candidates.

Radiotherapy can also be an effective treatment for patients with locally advanced hCCA. Chemoradiotherapy can provide good local control of hCCA with or without brachytherapy.[51] As mentioned previously, chemoradiotherapy is also used as neoadjuvant treatment in LT candidates with hCCA.[48] Radiotherapy can also be used to treat local recurrence or metastatic disease, although it carries the risk of radiation-related toxicity and is generally contraindicated in patients who previously received this form of therapy.[39]

Distal Cholangiocarcinoma

Surgery for dCCA, the only curative treatment for this disease, involves a Whipple procedure (pancreaticoduodenectomy) that removes the common bile duct as well as the head of the pancreas.[16] As with hCCA and iCCA, the aim of resection is to achieve negative margins and complete removal of disease.[52] Lymph nodes that drain the area are also removed during surgery. Preoperative placement of a biliary stent may be necessary to facilitate bile drainage, particularly if the patient's plan of care involves chemotherapy.[53] Neither resection nor LT is generally required for treatment of dCCA, but may be considered for well-selected patients with tumors involving multiple anatomic areas of the biliary tree (eg, LT with en bloc or staged Whipple resection). Patients undergoing resection for dCCA have a 5-year survival rate of approximately 24%, and survival is significantly better for patients with R0 margins (median survival, 48 months) vs R1 margins (median survival, 9 months; P=.042).[54]

Patients who are not surgical candidates may receive systemic therapy. Although few studies have focused specifically on patients with dCCA, several have investigated outcomes of patients with CCA or pancreaticobiliary cancers.[52] Capecitabine has been shown to be effective in a wide range of biliary tract cancers,[55] and its use in this population is recommended by the American Society of Clinical Oncology.[56] Gemcitabine has been shown to effectively treat dCCA,[57] as can chemoradiotherapy with

gemcitabine and oxaliplatin.[58] However, other research has shown that these treatments have no effect on survival in patients with biliary tract cancer.[59] FOLFOX and combination gemcitabine/cisplatin/durvalumab with or without tremelimumab (Imjudo, AstraZeneca) may also be treatment options for patients who do not respond to capecitabine.[60,61]

Summary

CCA is the second most common primary liver cancer, with growing incidence worldwide. Early detection is paramount owing to poor survival rates, particularly in patients with advanced disease. Initial diagnosis is usually made using imaging in conjunction with elevated CA19-9 levels. Confirmatory biopsy is needed to make a definitive diagnosis, but biopsy is avoided in many patients for clinical reasons. Treatment largely depends on whether the CCA is resectable, and LT is an option for highly selected patients with hCCA or iCCA. New systemic therapies to treat CCA have emerged over the past 5 to 10 years, improving outcomes for patients with unresectable disease.

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