Understanding Cholangiocarcinoma

CCA

A guide for diagnosing, testing, and treating patients with CCA

Treating cholangiocarcinoma

Cholangiocarcinoma (CCA) is a rare and aggressive cancer with a poor prognosis and with an increasing incidence. As our understanding of the molecular abnormalities driving CCA has increased, development of novel therapies has given promise to providing more treatment options for patients. This guide is a resource that may help you better understand and treat CCA.

Overview of cholangiocarcinoma (CCA)

Pathophysiology

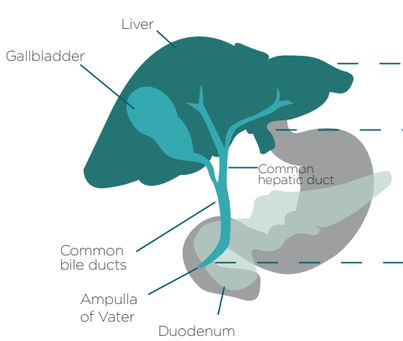
Cholangiocarcinoma, also known as bile duct cancer, originates from cholangiocytes (epithelial cells that line the biliary tree) and is categorized as either intrahepatic or extrahepatic according to the anatomic site of origin.[1-3]

CCAs categorized as extrahepatic (ECC) can be further divided into perihilar or distal[4]. Perihilar CCA is defined as a malignancy that arises in the right and/or left hepatic duct and/or at their junction, and distal CCA involves the common bile duct.[2]

CCAs classified as intrahepatic (ICC) are malignancies located in the periphery of the second-order bile duct.[2] The incidence rate of ICC may be significantly underestimated as approximately 20% of cancers of unknown primary origin involving the liver have been later attributed to ICC.[5] The 3 subtypes of CCA have distinct risk factors, epidemiological trends, pathophysiologies, clinical presentations, treatments, and prognoses.[2]

Subgroups of cholangiocarcinoma (bile duct cancer)

ANATOMICAL CLASSIFICATION OF CHOLANGIOCARCINOMAS[6]



		Percent of CCAs[4]	Incidence per 100,000[7]	Median Overall Survival[7,8]
INTRAHEPATIC	ICC	20%	0.9 (↑350% from 1973 to 2012)	12.6 months[a]
PERIHILAR EXTRAHEPATIC	ECC	50%-60%	1.9 (↑20% from 1973 to 2012)	8 months[b]
DISTAL EXTRAHEPATIC	ECC	20%-30%		

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ICC can also be misdiagnosed as cancer of unknown primary (CUP) cases; the true incidence of ICC **may be significantly underestimated.[5]**

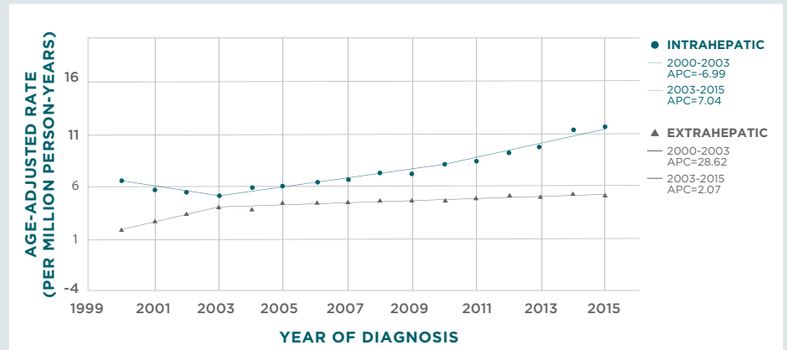
[a]mOS (time from randomization to death of any cause) for patients (N=109) diagnosed with advanced ICC who received first-line treatment with gemcitabine, cisplatin + gemcitabine, or cisplatin + gemcitabine + cediranib.[8]
[b]mOS for unselected patients (N=19,905) diagnosed with ECC from 1973 to 2008, who were included in the SEER 18 registry gemcitabine, cisplatin + gemcitabine, or cisplatin + gemcitabine + cediranib.[7]

Epidemiology

United States
CCA is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), comprising approximately 15% of all primary liver tumors and 3% of gastrointestinal cancers.[2] Based on cancer incidence rates obtained from the North American Association of Central Cancer Registries from 1999 to 2013, the number of new cases for cholangiocarcinoma increased with age. Adults aged ≥55 years have the highest rate of new cases of cholangiocarcinoma.[9]

The incidence of ICC in the United States increased by 165% in 30 years, from the 1970s to the 1990s, from 3.2 to 8.5 per million person-years.[1] The incidence for overall CCA calculated in the United States between 2000 and 2015 was 12.0 per million person-years. From 2003 to 2015, the annual percent change was 7.04% for ICC and 2.07% for ECC.[10]

Incidence of CCA in the United States[10]



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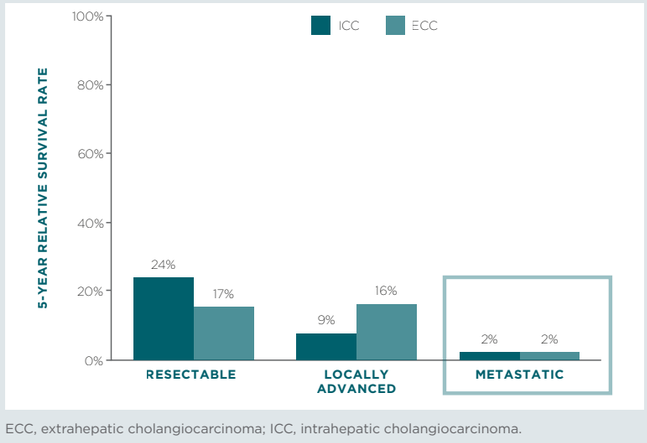
APC, annual percentage change.

Worldwide
The incidence and mortality of CCA have been increasing worldwide, though the reasons for this are not well defined.[1,2] Worldwide, the incidence rate of CCA ranges from 0.3 to 6 per 100,000 person-years. Mortality ranges globally from 1 to 6 per 100,000 person-years. Incidence rates do not include regions in Asia with >6 per 100,000 person-years, such as South Korea, China, and Thailand.[2] This difference of incidence rates between Asia and Western countries is mostly attributed to a higher prevalence of established risk factors such as parasitic infections.[11]

Prognosis

The 5-year overall survival (OS) rate for CCA (localized, regional, and metastatic disease) is 10%.[12] The 5-year OS for patients with metastatic intrahepatic CCA is 2%, which is due to most patients presenting with advanced stages.

5-Year survival rates for cholangiocarcinoma[12]



ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

Risk factors

Although a variety of risk factors are associated with CCA, most cases are not associated with established risk except in areas endemic for liver flukes.[11] In the United States and Europe, most cases are considered sporadic.[13]

The most common risk factors for CCA include[13]:

- **Cholestatic liver diseases** including primary sclerosing cholangitis immunodeficiency virus
- **Liver cirrhosis arising from any etiology**
- **Biliary stone disease**
- **Infections from viruses and parasites** including liver flukes, hepatitis B and C viruses, and human immunodeficiency virus
- **Inflammatory disorders** including inflammatory bowel disease, chronic pancreatitis, gout, and thyrotoxicosis
- **Exposure to toxins** such as alcohol and tobacco
- **Metabolic conditions** such as diabetes, obesity, and nonalcoholic fatty liver disease
- **Known genetic conditions** including Lynch syndrome and defects in bile salt transporter protein genes

Histology

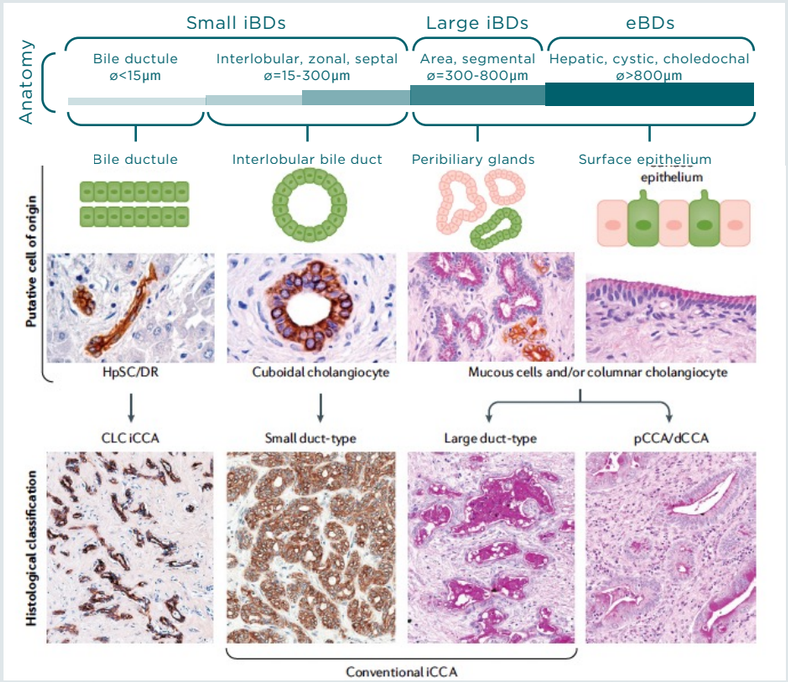
The majority of cholangiocarcinomas are classified as adenocarcinoma (>90%) with squamous cell carcinoma representing the remaining cases.[14] Morphologically, CCA demonstrates 3 main patterns based on gross appearance[15]:

- Mass–forming CCA is a mass lesion in the hepatic parenchyma
- Periductal–infiltrating ICC grows inside the duct wall and spreads longitudinally along the wall
- Intraductal–growing CCA is a polypoid or papillary tumor growing toward the duct lumen

The histological variants of cholangiocarcinoma cells reflect the phenotype of the involved duct and the putative cell of origin.[2] The histology of ICC can be further subdivided into small and large intrahepatic bile ducts based on size. The small intrahepatic bile ducts are composed of small cuboidal cholangiocytes, whereas large intrahepatic bile ducts consist of mucous and/or columnar cholangiocytes. Perihilar CCA and distal CCA originate from the lining epithelium and peribiliary glands.

It is notable that histological subtypes correspond to the molecular genetic characterization of CCA.[2] Small bile duct ICC can be characterized by isocitrate dehydrogenase-1/2 (*IDH1/2*) mutations or fibroblast growth factor receptor 2 (*FGFR2*) fusions. Large bile duct ICC, similar to ECC, shows a high frequency of mutations in *KRAS* and/or *TP53* genes.

Histological classification and putative cells of origin in cholangiocarcinoma[2]



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Pathological and molecular features of cholangiocarcinoma subtypes[2]

CCA TYPE	GROSS PATTERN	PRECANCEROUS LESION	UNDERLYING DISEASE	TISSUE MARKERS[a]	FREQUENT MUTATIONS[b]
ICC—CLC	Mass-forming	None	Viral, cirrhosis	NCAM	***IDH1***/2, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, ***TP53***, *SMAD4*
ICC—small duct type	Mass-forming	None	Viral, cirrhosis	NCAM, N-cadherin, SMAD4, $BAP1^{loss}$	***IDH1/2***, ***FGFR2* fusions**, *BAP1*, *BRAF*, *ARID1A*, *KRAS*, *TP53*, *SMAD4*
ICC—large duct type	Periductal infiltrating (±mass-forming) or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	$Mucin^{c}$, MUC5AC, MUC6, S100P, $SMAD4^{loss}$, BAP1	*IDH1/2*, *FGFR2* fusions, *BAP1*, *BRAF*, *ARID1A*, ***KRAS***, ***TP53***, *SMAD4*
pCCA & dCCA	Periductal infiltrating or intraductal growing	Biliary epithelial neoplasia, IPNB, ITPN, mucinous cystic neoplasm	Primary sclerosing cholangitis, liver flukes	Mucinb, MUC5AC, MUC6, S100P, $SMAD4^{loss}$, BAP1	*KRAS, TP53, SMAD4, ERBB3, PRKACA-PRKACB* fusions, *ELF3*

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CCA, cholangiocarcinoma; CLC, cholangiolocarcinoma; dCCA, distal cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; IPNB, intraductal papillary neoplasm of the bile duct; ITPN, intraductal tubulopapillary neoplasm; pCCA, perihilar cholangiocarcinoma.
[a]Markers from single-center experience; international criteria and consensus on a definite panel of markers are still needed.
[b]Most common mutations are bolded.
[c]Mucin refers to the histomorphological stain periodic acid–Schiff (PAS) or Alcian PAS.

Diagnosis and staging

Signs and symptoms

Patients with CCA are typically asymptomatic in the early stages of the disease.[2] The clinical features of CCA tend to depend on the location of the tumor.[1,2] The most common symptom of ECC is jaundice due to biliary tract obstruction. Patients with ICC are less likely to present with jaundice and usually present with nonspecific symptoms. Other symptoms of advanced CCA include asthenia, abdominal pain, malaise, nausea, anorexia, and weight loss.[2]

Patients with cholangiocarcinoma present with nonspecific symptoms[16]

Jaundice (90%)

Pruritus (66%)

Weight Loss (30% - 50%)

Abdominal Pain (30% - 50%)

Fever (up to 20%)

Clinical workup

A diagnosis of CCA should be considered if there are signs of biliary obstruction, such as jaundice, abnormal liver tests in a cholestatic pattern, and bile duct dilation on imaging studies.[16] A definitive diagnosis often requires multiple diagnostic modalities to distinguish CCA from other cancers, to establish the anatomic location, and to distinguish between benign and malignant strictures.[1] By the time patients receive a diagnosis of CCA, approximately 70% will have locally advanced or metastatic disease, which highly compromises therapeutic options and contributes to poor prognosis.[2]

Workup for suspected ICC[17]:

- Multiphasic abdominal/pelvic magnetic resonance imaging (MRI)/computerized tomography (CT) with IV contrast
- Liver function tests
- Surgical consultation
- Esophagogastroduodenoscopy and colonoscopy
- **Consider:** viral hepatitis serologies, testing for tumor biomarkers (CEA, CA 19-9, AFP), biopsy, and referral to a hepatologist

Workup for suspected ECC[17]:

- History and physical examination
- Multiphasic abdominal pelvic CT/MRI
- Chest CT with or without contrast
- Liver function tests
- Cholangiography (magnetic cholangiopancreatography [MRCP] is preferred)
- **Consider:** testing for tumor biomarkers (CEA, CA 19-9), endoscopic ultrasound after surgical consultation, and serum IgG4 to rule out autoimmune cholangitis

Imaging

When CCA is suspected, clinicians typically begin with ultrasonography to exclude gallstones.[18] The performance of CT and MRI can characterize the mass and evaluate bile duct dilation, vascular infiltration, and lymph node invasion to some extent.[19] The standard imaging modality for detecting CCA features and for staging is CT. MRI is considered to be superior to CT for diagnosis and staging; however, it lacks accuracy for the evaluation of tumor invasion along the bile duct. PET scan imaging is used to assess and evaluate distant metastasis.

> ***MRI combined with cholangiopancreatography offers noninvasive high sensitivity and allows the visualization of ductal and vascular structure, definition of tumor extent, and detection of distant metastases.[1]***

Additional imaging testing is suitable based on the clinical scenarios:

- Magnetic resonance cholangiopancreatography (MRCP) plays a differential diagnosis role for difficult cases of CCA.[19] It can also be used to evaluate the longitudinal invasion of ECC along the bile duct
- Endoscopic retrograde cholangiopancreatography (ERCP) allows for therapeutic intervention via stent placement.[1] Its leading role is for the pathological diagnosis and biliary drainage[19]

Biopsy

Tissue biopsy

Confirmation of a CCA diagnosis requires a tissue biopsy.[20] Liver biopsy for ICC is minimally invasive, performed percutaneously with ultrasound-guided imaging. This is the preferred method because of the widespread use of ultrasound and also because of low cost and time savings. The sensitivity of biopsy is dependent on the location and size of the tumor as well as the operator's expertise in conducting these types of biopsies.[21] A negative biopsy does not exclude diagnosis due to sampling error potential. Single-tissue sampling methods have sensitivities in low ranges for CCA detection.[22] However, combined triple-tissue sampling (TTS) including on-site bile aspiration cytology, brush cytology, and forceps biopsy has shown to provide improved diagnostic accuracy in CCA detection.

> ***Biopsy is mandatory to confirm a diagnosis of CCA.[20]***

Liquid biopsy

Liquid biopsy can be used to screen for therapeutic targets and drug resistance–conferring gene mutations on circulating tumor cells (CTC) and cell-free circulating tumor DNA (ctDNA).[23-25] This method provides an alternative to tissue biopsy for biomarker testing and may be valuable in detecting unique genomic metastases that are distant from the primary tumor and would not be picked up in a normal biopsy. However, it does not assess for non-DNA-based alterations, and it is a relatively new procedure needing additional validation trials. Compared with traditional biopsy, liquid biopsy has the following advantages[25,26]:

- Less invasive, less dangerous, and less expensive
- Faster recovery time
- May better capture tumor heterogeneity

> ***High concordance between tissue and liquid biopsy in ICC***
> *In an analysis of concordance between tissue and liquid biopsy, tumor tissue and corresponding ctDNA samples were collected from 23 CCA patients.[27] Blood/tissue concordance was 74% overall, 92% for ICC, and 55% for ECC.*

Blood biomarkers

There are no specific blood tests that diagnose CCA. Conventional liver function markers do not specifically indicate malignancy.[1] Patients suspected of cholangiocarcinoma should have tumor biomarkers checked. Important biomarkers include[1,28]:

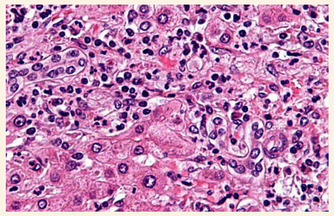
- Cancer antigen (CA) 19-9—also elevated in pancreatic, colorectal, and gastric cancers—and CA-125—elevated in around 40% to 50% of CCAs
- Carcinoembryonic antigen (CEA)—elevated in 30% of patients with CCA

Because of their low sensitivity and specificity, these biomarkers must be used along with other diagnostic tools to support a diagnosis of cholangiocarcinoma.[1,28] Other serum, plasma, bile, urine, and tissue markers have been linked to CCA, but none have established clinical utility.[28]

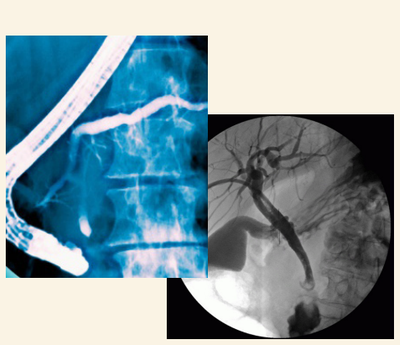
> ***About 40% of biliary tract cancers have potential targetable genetic driver mutations.[29]***

Diagnostic modalities for CCA

Imaging (CT, MRI, US): ultrasonography (US) is initially used to exclude gallstones, assess dilation of the biliary tract, and determine location of obstruction.[1] Computed tomography (CT) and magnetic resonance imaging (MRI) provide greater sensitivity



Histology: essential for definitive CCA diagnosis[4]



Endoscopic retrograde cholangiopancreatography (ERCP) *(left)* and percutaneous transhepatic cholangiography *(right)*: invasive procedures that allow for stricture sampling for brush cytology, tissue biopsy, or for stent insertion[1]

Diagnostic biomarkers: have low sensitivity and specificity.[1] The most commonly used biomarkers for CCA are cancer antigen 19-9 (CA 19-9), CA-125, and carcinoembryonic antigen (CEA)

Immunochemistry

It can be difficult to distinguish between ICC and ECC, but the two are pathologically distinct and should be differentiated based on patterns of biomarker expression.[2,30-32] Definitive diagnosis of ICC is fundamentally established by exclusion of other cancers and ECC. No biomarker is entirely specific for ICC. Immunohistochemical markers are used in combination to establish a definitive diagnosis.[30] There are both positive and negative histological markers used in the differential diagnosis of ICC.

Select immunohistochemical markers used in combination to establish a definitive diagnosis of ICC

Diffuse positive staining[30]	• CK7 (found in >80% of ICCs, also expressed in other carcinomas)[15,30,31] • CK19 (found in >80% of ICCs; also expressed in other carcinomas)[30,31] • MOC31 (found in >80% or ICCs, 2X greater expression than in hepatocellular carcinomas)[31] • AE1/AE3[33] • Albumin in situ hybridization (positive in >90% of ICCs, differentiates from other CCAs)[5]
Negative or slightly positive staining[30]	• GATA3 (found in <10% of ICCs)[34] • TTF-1 (more common in lung cancers)[30,35] • CDX-2 (more common in colon and esophageal cancer, found in <30% of ICCs)[15,30,36] • DPC4 (common in pancreatic adenocarcinomas that have metastasized)[33] • BRST-2 (GCDFP-15)/ Estrogen and progesterone receptors (indicative of breast cancer)[30]

Staging

The tumor (T), regional lymph node infiltration (N), and the presence of distant metastases (M) classification system from the American Joint Committee on Cancer (AJCC), known as the TNM system, includes a separate staging system for intrahepatic, perihilar, and distal bile duct tumors.[2,20] The system does have some limitations despite offering a clinically meaningful classification correlated with prognosis.[2] There are important epidemiologic, etiologic, and biologic differences between the CCA subtypes.[21]

Staging of cholangiocarcinoma using the AJCC TNM classification system[20]

	dCCA	pCCA	ICC
Primary tumor (T)			
TX	Primary tumor cannot be assessed	Primary tumor cannot be assessed	Primary tumor cannot be assessed
T0	n/a	No evidence of primary tumor	No evidence of primary tumor
Tis	Carcinoma in situ/ high-grade dysplasia	Carcinoma in situ/ high-grade dysplasia	Carcinoma in situ (intraductal tumor)
T1	Tumor invades the bile duct wall with a depth <5 mm	Tumor confined to the bile duct, with extension up to the muscle layer fibrous tissue	—
T1a	—	—	Solitary tumor ≤5 cm without vascular invasion
T1b	—	—	Solitary tumor >5 cm without vascular invasion
T2	Tumor invades the bile duct wall with a depth 5-12 mm	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, tumor invades adjacent hepatic parenchyma	Solitary tumor with intrahepatic vascular invasion or multiple tumors (with or without vascular invasion)
T2a	—	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue	—
T2b	—	Tumor invades adjacent hepatic parenchyma	—
T3	Tumor invades the bile duct wall with a depth >12 mm	Tumor invades unilateral branches of the portal vein hepatic artery	Tumor perforating the visceral peritoneum
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery	Tumor invades the main portal vein, its branches bilaterally, the common hepatic artery; unilateral second-order biliary radicals with contralateral portal vein hepatic artery involvement	Tumor involving local extrahepatic structures by direct invasion

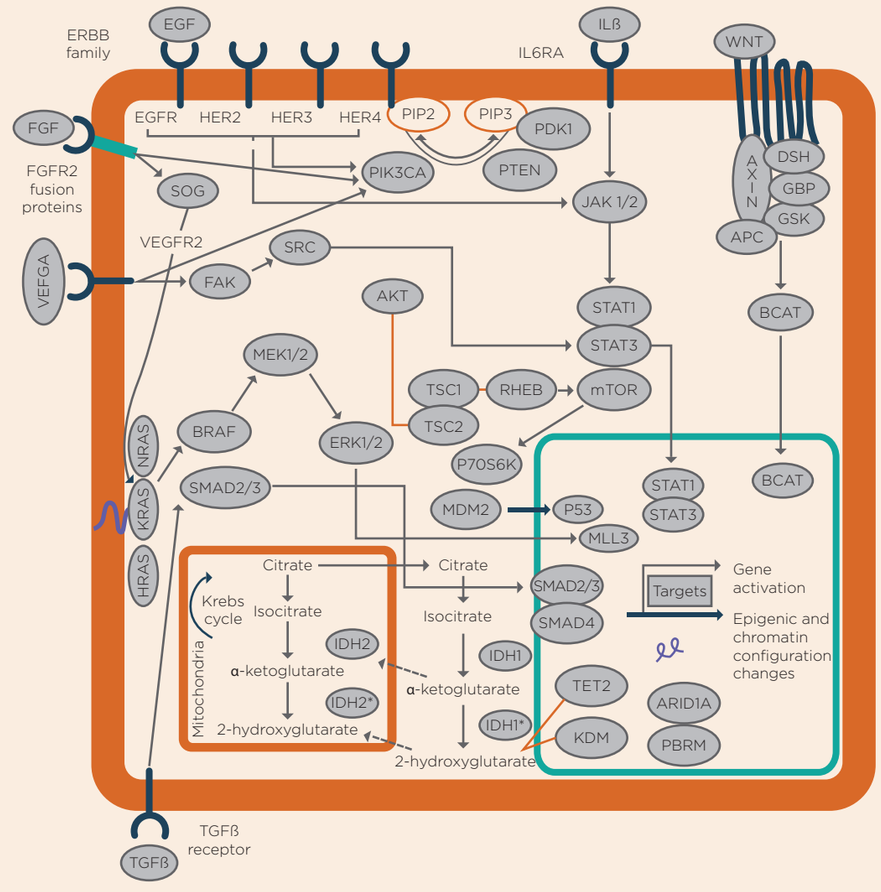
Staging of cholangiocarcinoma using the AJCC TNM classification system (cont'd)[20]

	dCCA	pCCA	ICC
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis	No regional lymph nodes metastasis	No regional lymph nodes metastasis
N1	Metastasis in one to three regional lymph nodes	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes	Regional lymph nodes metastasis present
N2	Metastasis in four or more regional lymph nodes	Four or more positive lymph nodes from the sites described for N1	—
Distant metastasis (M)			
M0	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis present
Prognostic stage groups			
0	Tis, N0, M0	Tis, N0, M0	Tis, N0, M0
I	T1, N0, M0	T1, N0, M0	—
Ia	—	—	T1a, N0, M0
Ib	—	—	T1b, N0, M0
II	T1, N0, M0	T2a-b, N0, M0	T2, N0, M0
IIa	T1N1/T2N0, M0	—	—
IIb	T2N1/ T3N0/T3N1, M0	—	—
IIIa	T1-3, N2, M0	T3, N0, M0	T3, N0, M0
IIIb	T4, Any N, M0	T4, N0, M0	T4, Any N, M0/ Any T, N1, M0
IIIc	—	Any T, N1, M0	—
IV	Any T, Any N, M1	-	Any T, Any N, M1
IVa	—	Any T, N2, M0	—
IVb	—	Any T, Any N, M1	—

Genetic alterations in CCA

Several molecular pathways may be genetically altered in CCA.[37] Genetic profiling via next-generation sequencing (NGS) has advanced the understanding of the heterogeneous mutational landscape in CCA.[4] Results from genetic profiling provide both prognostic and predictive information. About 40% of biliary tract cancers (ICC, ECC, and gallbladder cancer) have potential targetable genetic driver mutations.[29] Molecular pathways implicated in CCA include isocitrate dehydrogenase (IDH) alterations, the fibroblast growth factor receptor (FGFR) pathway, and chromatin modifiers, which influence cell proliferation and survival.[37]

Several molecular pathways may be genetically altered in CCA[37,a]



[a]Activation links are described with black arrows. Negative links are described as red lines. Red asterisk identifies the mutated variant of the protein.

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IDH1

The IDH1 enzyme is involved in cellular metabolism—catalyzing the reversible conversion of isocitrate to alpha-ketoglutarate (alpha-KG) and NADP+ to NADPH.[38]

Studies have identified *IDH1* mutations in 13% to 25% of patients with ICC.[3,37,39] *IDH1* mutations result in the overproduction and build-up of D-2-hydroxyglutarate (2HG).[40] This 2-HG overproduction stimulates abnormal metabolism and epigenetic dysregulation. There is evidence that these mutations block normal hepatocyte differentiation and increase the pool of hepatic progenitor cells, which can lead to cancer cell formation. *IDH1* mutations are not associated with prognosis in patients with ICC.[3]

FGFR

FGFR is a tyrosine kinase that regulates cell proliferation, differentiation, migration, and apoptosis.[41,42]

Genetic aberrations in the *FGFR* pathway, including amplification, activating mutations, or chromosomal translocations/fusions, contribute to tumorigenesis.[43] Several *FGFR2* gene fusions with multiple genomic partners have been identified and occur in about 10% to 16% of patients with ICC. In a study using comprehensive genetic profiling of 412 cases of ICC, patients with *FGFR2* mutations had increased overall survival compared with those with wild type *FGFR2*.[44]

BRAF

BRAF is a proto-oncogene and member of the rapidly accelerated fibrosarcoma (RAF) kinase family that serves as a key component of the RAS/RAF/MEK/ERK (MAPK) proliferation signaling pathway.[45,46] As one of the most commonly mutated kinases, BRAF is found in about 6% of human cancers and 5% to 22% of CCA cases.[45-47] The most common *BRAF* gene mutation in cancers is a V600E mutation.[46]

Higher rates of *BRAF* mutations have been reported in ICC than ECC, and larger studies suggest *BRAF* mutations may be exclusive to ICC.[2,47] A decreased overall survival in patients with ICC who have *BRAF* mutations has been reported.[48]

Molecular testing

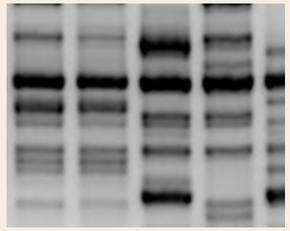
The National Comprehensive Cancer Network® (NCCN®) has recommendations for molecular testing in CCA.[17] Molecular testing is recommended to potentially guide targeted treatment for unresectable or metastatic CCA. Primary treatment options for patients with unresectable or metastatic CCA include:

1) Clinical trial
2) Systemic therapy
3) Best supportive care
4) Other primary treatment options:
   - External beam radiation therapy (EBRT) with concurrent fluoropyrimidine for patients with unresectable ICC or ECC
   - Locoregional therapy (EBRT or arterially directed therapies) for patients with unresectable ECC or with metastatic or unresectable ICC
   - Palliative EBRT for patients with unresectable ECC

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) suggests[17]:

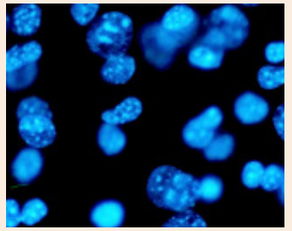
- **Given emerging evidence regarding actionable targets for treating cholangiocarcinoma, molecular testing of unresectable and metastatic tumors should be considered**

Several molecular profiling techniques are available for genetic biomarker testing[49]



Polymerase chain reaction (PCR)-based single-gene test

Amplifies and quantifies a portion of a targeted DNA molecule



In situ hybridization (ISH)

Detects gene deletions, amplifications, translocations, and fusions

Includes chromogenic ISH (CISH) and fluorescence ISH (FISH)

Immunohistochemistry (IHC)

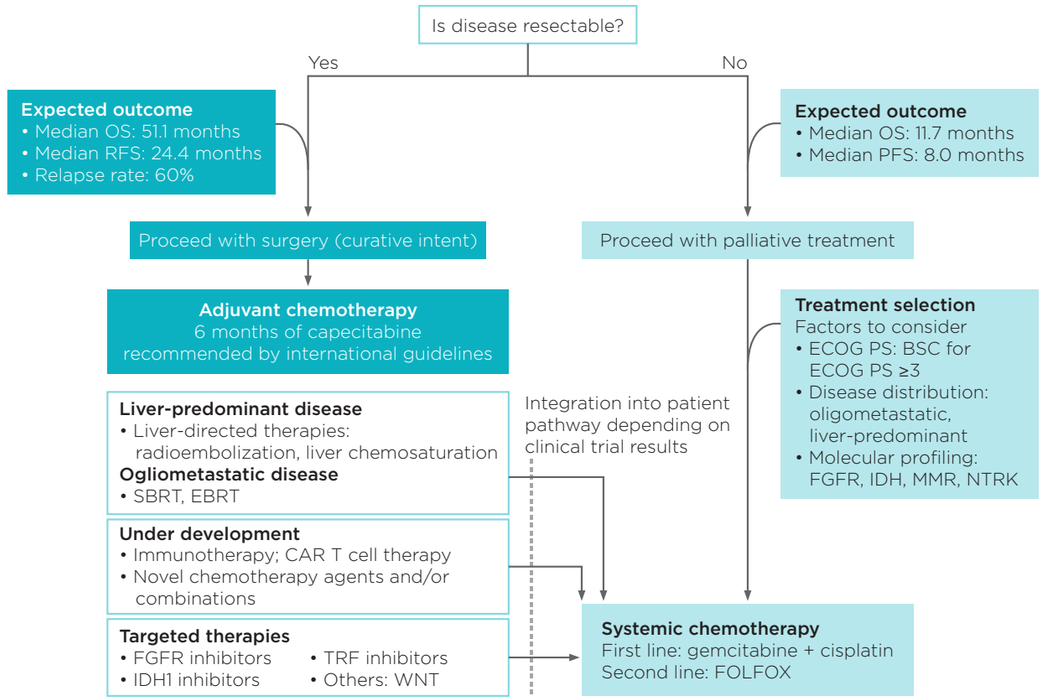
Determines level of protein expression

Next-generation sequencing (NGS)

Detects DNA mutations, copy number variations, and gene fusions across the genome

Treatment options and outcomes

Current decisions and management of patients with CCA according to formal guidelines[2]



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BSC, best supportive care; CAR, chimeric antigen receptor; EBRT, external beam radiation therapy; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, folinic acid, 5-fluorouracil, and oxaliplatin; MMR, DNA mismatch repair; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SBRT, stereotactic body radiation therapy.

Resectable disease: Surgery

Surgery is potentially curative in CCA; however, due to most patients (~70%) being diagnosed at late stages, it is often not feasible.[2] For patients eligible for surgery, the goal is a complete margin-negative resection (R0) with an adequate future liver remnant.[2,21] Practice guidelines recommend resection only for solitary tumors. Surgical approaches vary depending on the anatomic site of the tumor.[21]

Distal cholangiocarcinoma

- Surgical approach includes pancreaticoduodenectomy (Whipple procedure) with removal of the head of the pancreas, the first part of the duodenum, the gall bladder, and the bile duct.[2] The 5-year survival rates ranges from 16% to 52% in patients with complete resection[50]

Intrahepatic cholangiocarcinoma

- Surgical approach involves hepatic resection to achieve negative resection margins.[32] The 5-year overall survival rates depend on positive or negative surgical margins, which can be 4.7% or 39.8%, respectively.[51] Recurrence rates are significantly lower for patients with negative resection margins than for those with positive margins (53.9% and 73.6%, respectively)

Perihilar cholangiocarcinoma

- To improve liver function and avoid post-hepatectomy liver failure, pre-operative drainage of the liver remnant is performed.[2] The reported 5-year survival rates following complete resection ranges between 20% and 42%[50]

NCCN

NCCN Guidelines® state[17]:

- **For intrahepatic CCA: Complete resection is the only potentially curative treatment for patients with resectable disease, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis**
- **For extrahepatic CCA: Complete resection with negative margins is the only potentially curative treatment for patients with resectable disease**

Resectable disease: Chemotherapy and chemoradiotherapy

Neoadjuvant
Neoadjuvant therapies have been used in patients with large, locally advanced unresectable intrahepatic CCAs who can be converted to potentially resectable disease.[52] Surgical resection could be considered in this setting. For neoadjuvant therapy, there are limited clinical trial data to define a standard regimen or definitive benefit.[17] According to NCCN Guidelines, there is no preferred regimen. Options listed as other recommended regimens are 5-FU, capecitabine, gemcitabine, 5-FU/oxaliplatin, capecitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/cisplatin, gemcitabine/cisplatin/albumin-bound paclitaxel, or gemcitabine/oxaliplatin.

Adjuvant
The use of chemotherapy or chemoradiotherapy has been associated with survival benefit in patients with biliary tract cancer, especially in patients with lymph node positive disease.[17] Capecitabine is the preferred chemotherapy agent for 6 months based on the results from the BILCAP study.[2] Options listed as other recommended regimens are gemcitabine, gemcitabine/capecitabine, gemcitabine/cisplatin, 5-FU, 5-FU/oxaliplatin, capecitabine/oxaliplatin, or capecitabine/cisplatin.[17] The role of chemoradiotherapy remains unclear but might be of benefit in patients with pCCA or dCCA.[2]

Unresectable or metastatic disease: Palliative chemotherapy

Consider the following 3 aspects for determination of chemotherapy[2]:

- Patient fitness assessed in terms of ECOG PS (patients with an ECOG PS of 3 or higher are not likely to benefit from treatment and should be managed with best supportive care)
- Disease distribution
- Accessibility of tumor profiles

The combination of cisplatin and gemcitabine is a preferred systemic therapy option for the primary treatment of unresectable or metastatic CCA.[17] Other first-line options are 5-FU, capecitabine, gemcitabine, 5-FU/oxaliplatin, 5-FU/cisplatin, capecitabine/cisplatin, capecitabine/oxaliplatin, gemcitabine/albumin-bound paclitaxel, gemcitabine/capecitabine, gemcitabine/oxaliplatin, gemcitabine/cisplatin/albumin-bound paclitaxel, and durvalumab/gemcitabine/cisplatin.

FOLFOX (folinic acid, fluorouracil, and oxaliplatin) is the preferred option for subsequent-line systemic therapy for unresectable or metastatic CCA if disease progresses.[17] Other recommended options are fluorouracil/irinotecan (FOLFIRI), regorafenib, liposomal irinotecan/fluorouracil/leucovorin, and durvalumab/gemcitabine/cisplatin.

Unresectable or metastatic disease: Targeted therapies

The use of targeted therapies is useful in certain circumstances following disease progression:

IDH1
A landmark study of an IDH1 inhibitor provided level A evidence for the efficacy of targeted therapy in CCA and supports standard molecular profiling of tumor tissues in this cancer.[2] *IDH1* mutations are found in up to 20% of of intrahepatic cholangiocarcinoma cases in the United States.[39,53]

FGFR
Mutations in *FGFR2* fusions have been found in 13% to 14% of intrahepatic CCAs[17] and have been associated with a favorable prognosis.[44] The first approval of a targeted therapy in CCA was a *FGFR1*, *FGFR2*, and *FGFR3* inhibitor.[54]

NOTES

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CCA

- CCA is the second most common primary liver cancer and is associated with a poor prognosis.[2]
- Largely due to a lack of specific symptoms, most patients (~70%) are diagnosed at late stages, when the disease is unresectable.[2]
- Practice guidelines recommend molecular testing of unresectable or metastatic tumors.[17]
- A preferred first-line systemic therapy option for unresectable CCA is the combination of gemcitabine + cisplatin.[17]
- Targeted systemic therapy options are available for subsequent-line treatment for certain mutations (*IDH1* and *FGFR2*).[2,17,54]