Cholangiocarcinoma: Disease State Overview

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Table of Contents

SECTION 1 Epidemiology and Etiology

SECTION 2 Diagnosis, Staging, and Prognosis

SECTION 3 Genomic Landscape

SECTION 4 Key Takeaways

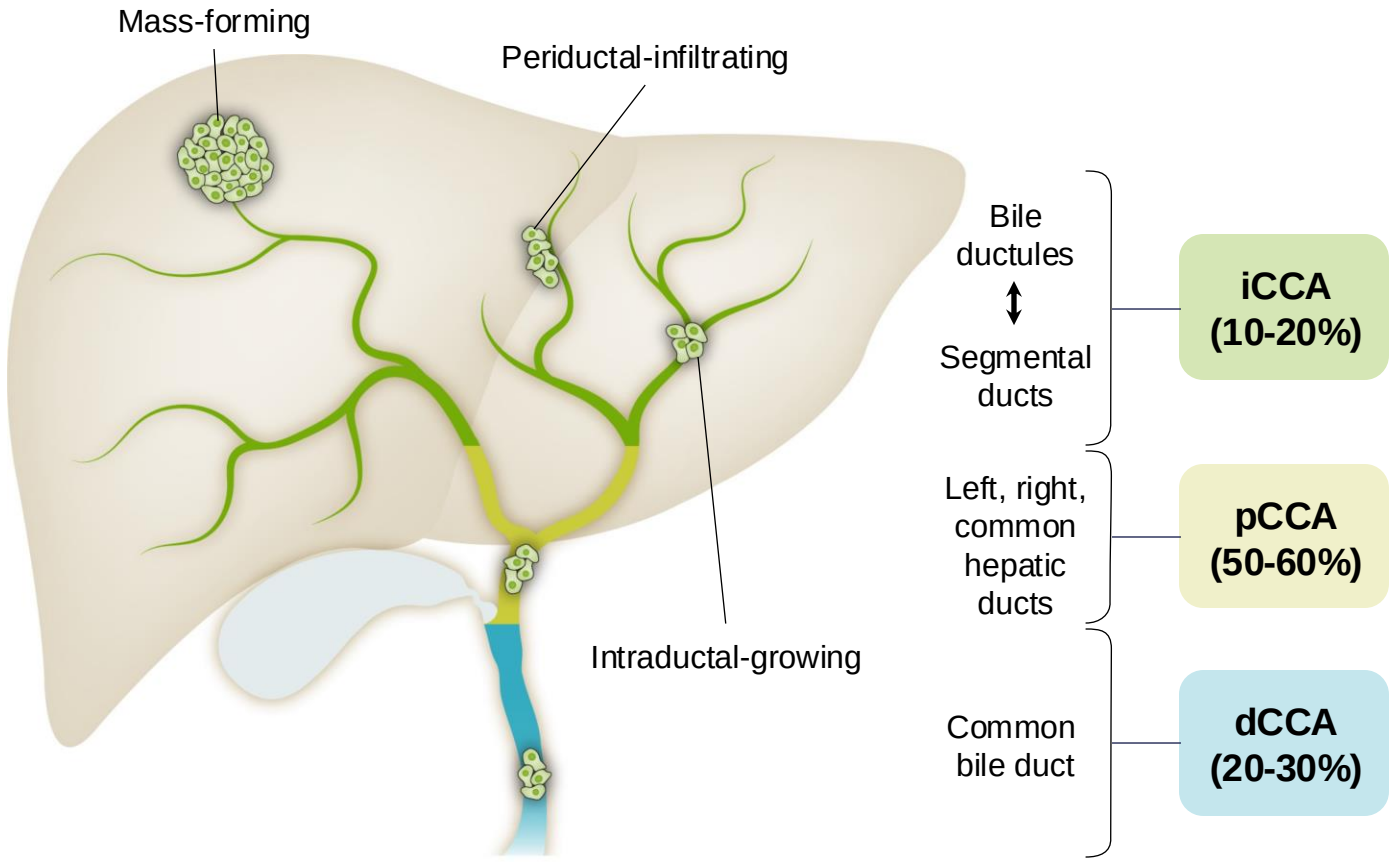
Click the section tab of interest to be taken to the corresponding portion of the deck

Epidemiology and Etiology

CCAs Are Heterogeneous Tumors Arising in the Bile Duct

- CCAs are heterogeneous epithelial tumors originating from cholangiocytes in the biliary tree[1-3]
- CCAs are classified into different anatomical subtypes based on location in the biliary tract:[1-4]
  - Intrahepatic
  - Extrahepatic, which is further divided into:
    - Perihilar
    - Distal
- Each anatomical subtype has different clinical and pathological characteristics, including different patterns of genomic alterations[1,2]

Anatomic classification of CCA[1]



dCCA, distal CCA; iCCA, intrahepatic CCA; pCCA, perihilar CCA.

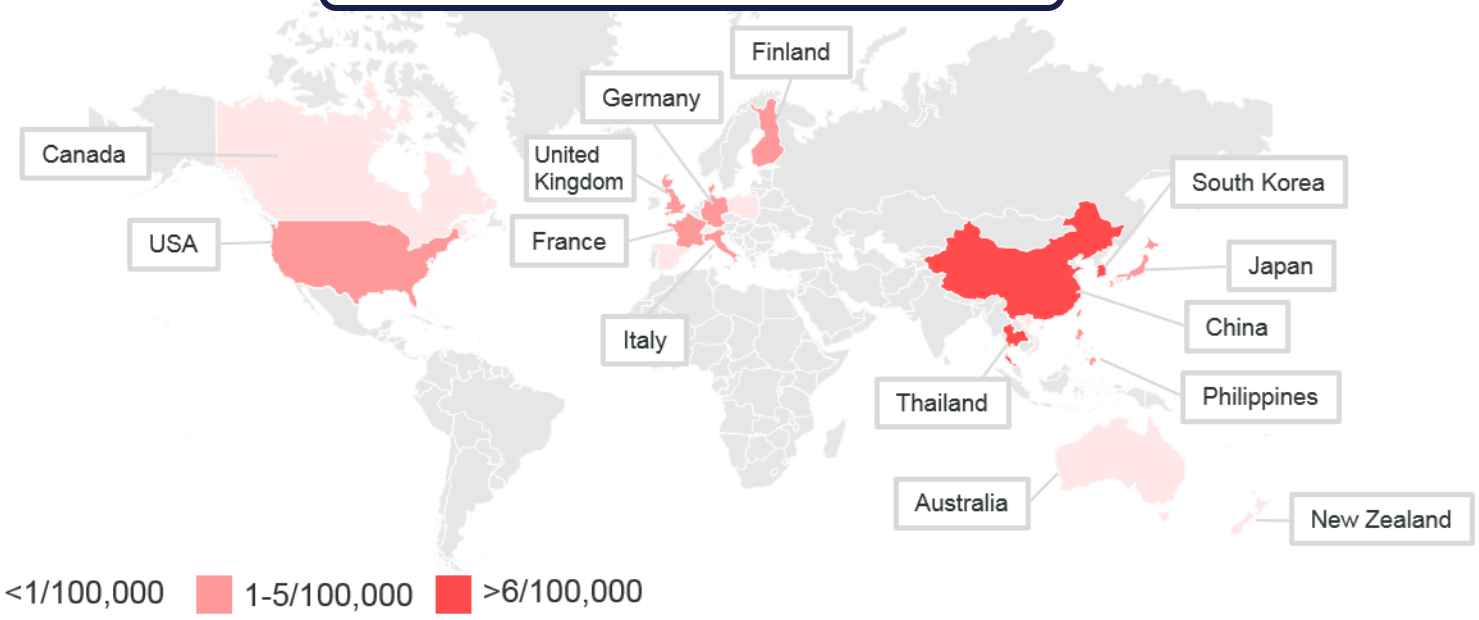
1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17:557-588. Figure reproduced under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/), only edits for style were made. 2. Blechacz B. *Gut Liver*. 2017;11:13-26. 3. Malenica I, et al. *Cancers (Basel)*. 2020;12:2190. 4. Huguet JM, et al. *World J Clin Cases*. 2019;7:1732-1752.

The Incidence of CCA Varies Significantly in Different Regions of the World

Account for **3%** of all GI tumors[1]

~15% of all primary hepatic tumors[1]

Incidence of CCA worldwide[1,2]



- The worldwide epidemiology of CCA is widely variable, with generally lower incidences in Western vs Asian countries[3]
- Parasitic infections are key risk factors in higher risk Southeast Asian countries, with South Korea, China, and Thailand having the highest incidence of CCA[1,4]
- Between 2000 and 2015 in the US, 63% of patients diagnosed with CCA were >65 years of age[5]

GI, gastrointestinal; US, United States.

1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2020;17:557-588. 2. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. Figure reproduced under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/), only edits for style were made. 3. Baria K, et al. *Gastro Hep Advances.* 2022;1:618-626. 4. Florio AA, et al. *Cancer.* 2020;126:2666-2678. 5. Gad MM, et al. *Clin Res Hepatol Gastroenterol*. 2020;44:885-893.

The Increasing Incidence of iCCA

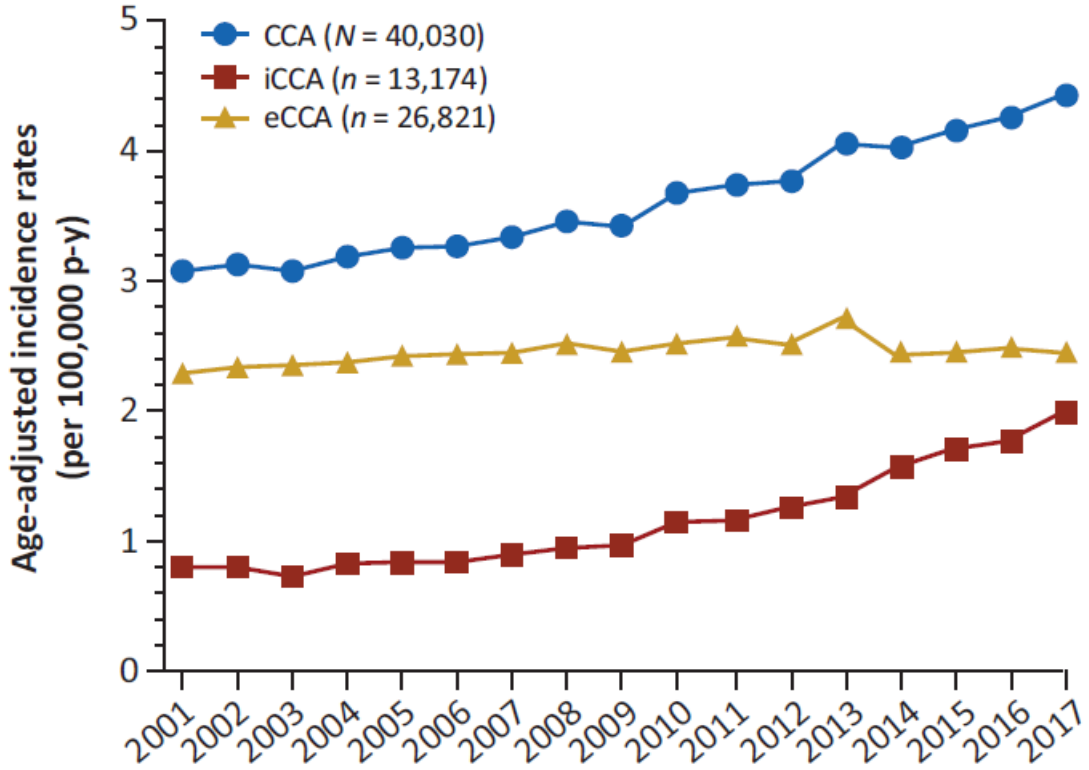
Year	Age-Adjusted Incidence of CCA
2001	3.08 per 100,000
2017	4.43 per 100,000

According to an analysis of the SEER database, the age-adjusted incidence rates of CCA have increased by almost 44% over the past ~20 years

Year	Age-Adjusted Incidence of iCCA	Age-Adjusted Incidence of eCCA
2001	0.80 per 100,000	2.28 per 100,000
2017	1.99 per 100,000	2.45 per 100,000

The overall growth in the incidence rate of CCA is largely attributable to iCCA, which has increased by 149% over the past ~20 years

Age-Adjusted Incidence of CCA, iCCA and eCCA in the USA (2001-2017, per 100,000 p-y)



p-y, person-years; SEER, Surveillance, Epidemiology, and End Results.

Most Cases of CCA Occur in the Absence of Evident Risk Factors

- The majority of CCAs (70%) occur sporadically without any apparent cause[1]
- However, there are risk factors strongly associated with CCA, the most relevant of which are PSC, liver flukes, and virus-related liver diseases[2]

Risk Factors Associated With CCA[1-3]

Parasitic infections

Liver flukes (from ingesting raw, undercooked, or pickled food; mostly in Southeast Asia)

- *Opisthorchis viverrini*
- *Clonorchis sinensis*

Coexisting liver/ duct diseases

- HBV-related diseases (mostly in Asia)
- HCV-related diseases (mostly in Western countries)
- Liver cirrhosis
- Gallstones
- Bile duct cysts
- Choledochal cysts

Bile duct autoimmune diseases

- PSC (with or without IBD; mostly in Western countries)

General

- Age >65 years
- Obesity
- Tobacco and alcohol use
- Aspirin use
- Printing factory chemicals
- Type 2 diabetes mellitus
- Hypertension

HBV, hepatitis B virus; HCV, hepatitis C virus; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

1. Kirstein MM, Vogel A. *Visc Med*. 2016;32:395-400. 2. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 3. Clements O, et al. *J Hepatol.* 2020;72:95-103.

CCA Is Asymptomatic Until Advanced Stages

- 20-25% of CCA diagnoses result from incidental findings (eg, abnormal liver function test results)[1,2]
- Symptoms of CCA are often nonspecific and are usually limited until the tumor grows and begins to block the bile duct[1-3]
- Symptoms also tend to depend on whether the cancer is intrahepatic or extrahepatic[3]
  - As eCCA is more likely to severely obstruct biliary drainage, it is more likely than iCCA to present with symptoms[3]
  - In patients with eCCA, 90% present with painless jaundice, and 10% present with acute cholangitis[3]

Symptoms of Advanced CCA[1-3]

- Jaundice
- Cholangitis
- Fatigue
- Light-colored/greasy stools
- Abdominal pain
- Weight loss/anorexia
- Nausea
- Night sweats

eCCA, extrahepatic CCA.

1. Banales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Forner A, et al. *Liver Int*. 2019;39(1 suppl):98-107. 3. Blechacz B, et al. *Nat Rev Gastroenterol Hepatol*. 2011;8:512-522.

Bile Duct Obstruction Is a Common and Serious Complication of CCA

Malignant biliary obstruction

- Complete surgical resection is the best potentially curative therapy[1]
- Many patients are not candidates for surgery and therefore require a palliative biliary stent[1,2]

Biliary stenting

- Palliative biliary stenting helps relieve obstructive cholestasis and its associated conditions, such as pruritus, cholangitis, and pain[1]
- Endoscopic stenting can restore biliary drainage in almost 90% of patients, with the advantage of providing a more noninvasive and comfortable patient experience compared with percutaneous transhepatic cholangiography[1,2]

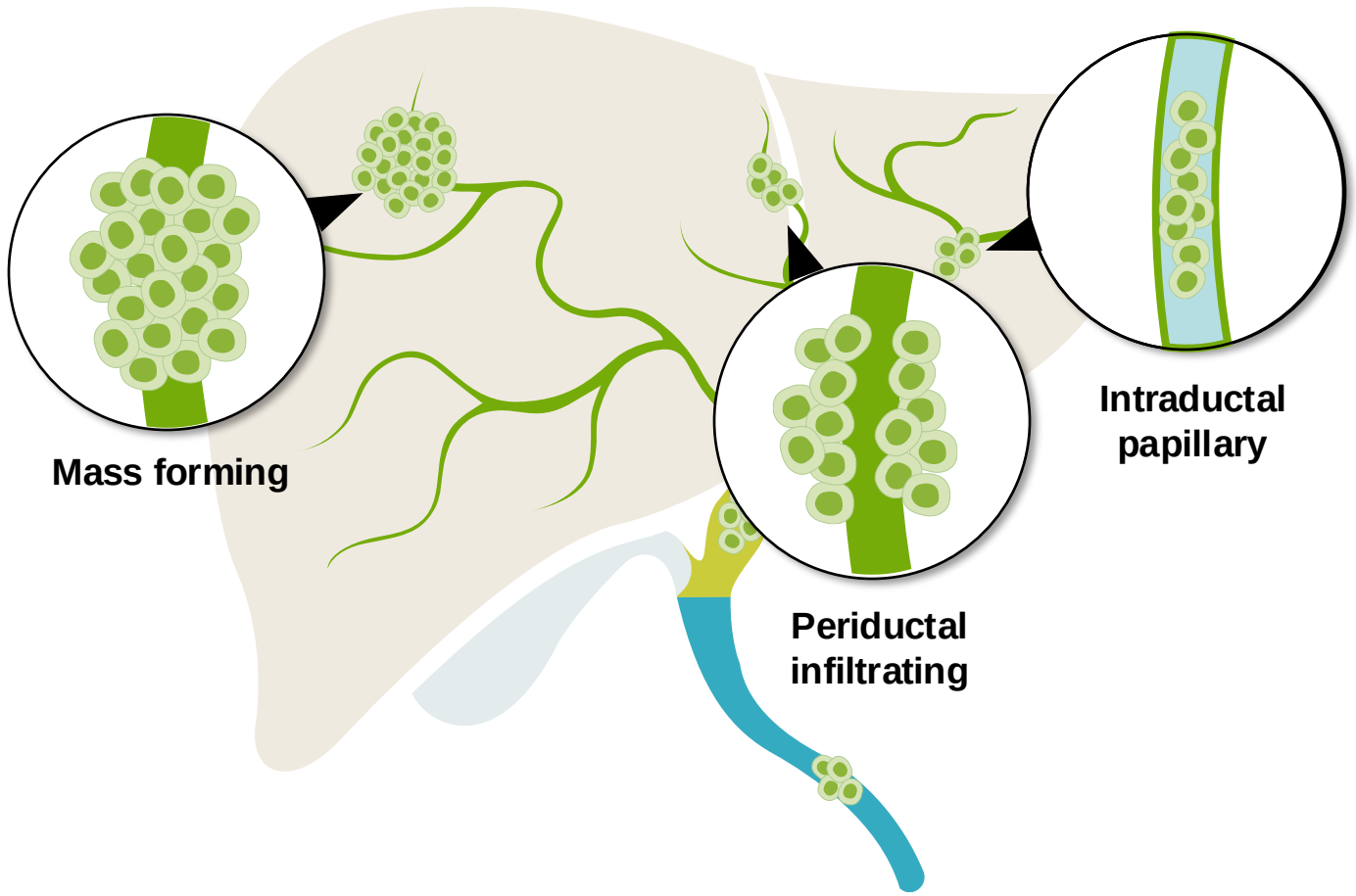
1. Kim JH. *Clin Endosc*. 2011;44:76-86. 2. Bertani H, et al. *World J Gastrointest Endosc*. 2015;7:582-592.

Diagnosis, Staging, and Prognosis

Growth Pattern and Cellular Classification of CCA

- CCAs are usually adenocarcinomas with varying degrees of differentiation; other histological subtypes are rare[1]
- CCA tumors present with 1 of 3 growth patterns according to anatomical location and morphology[1,2]
  - Mass forming
  - Periductal infiltrating
  - Intraductal papillary
- iCCAs predominantly present with a mass-forming (65%) growth pattern, followed by mixed-form (25%), periductal (6%), and intraductal (4%)[2]

CCA Growth Patterns[1,2]

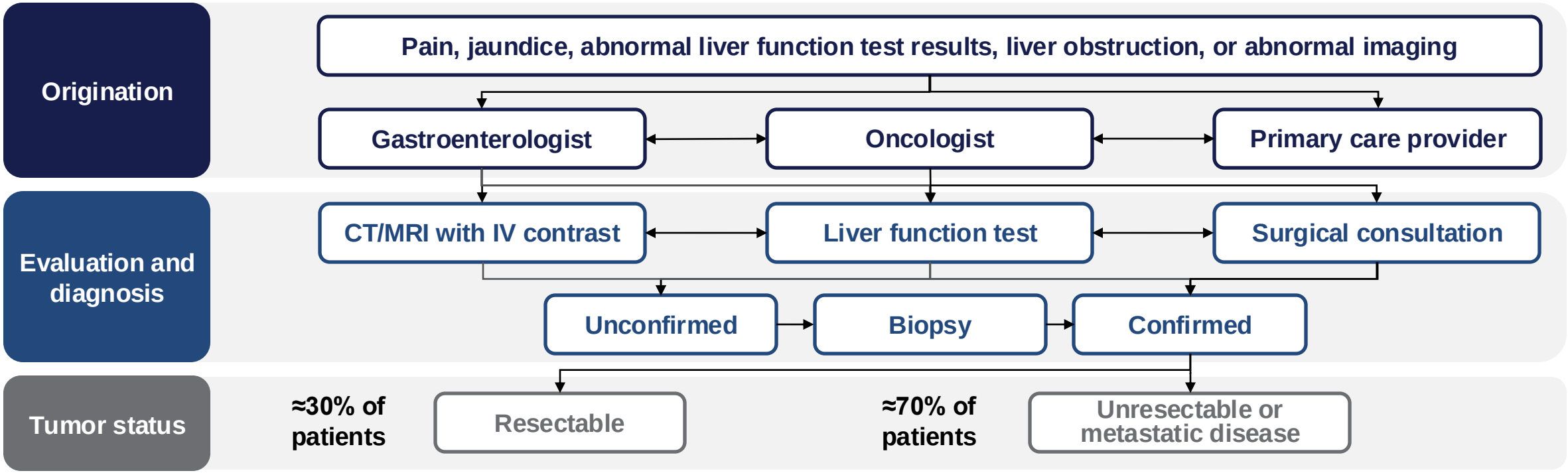


1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Vijgen S, et al. *Hepatobiliary Surg Nutr.* 2017;6:22-34.

CCA Is A Diagnosis of Exclusion

- Diagnosis requires careful interpretation of clinical, radiological, and nonspecific histological and/or biochemical markers[1,2]
- CCA is usually diagnosed after metastasis when the disease is unresectable[2,3,5]

Diagnosis of CCA[1,2,4,5]



CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging.

1. Bañales JM, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261-280. 2. Blechacz B, et al. *Nat Rev Gastroenterol Hepatol.* 2011;8:512-522. 3. Valle JW, et al. *N Engl J Med*. 2010;362:1273-1281. 4. Razumilava N, Gores GJ. *Lancet*. 2014;383:2168-2179. 5. Valle JW, et al. *Cancer Discov.* 2017;7:943-962.

Staging of CCA Is Defined by the 8th Edition of the *AJCC Cancer Staging Manual* TNM Model

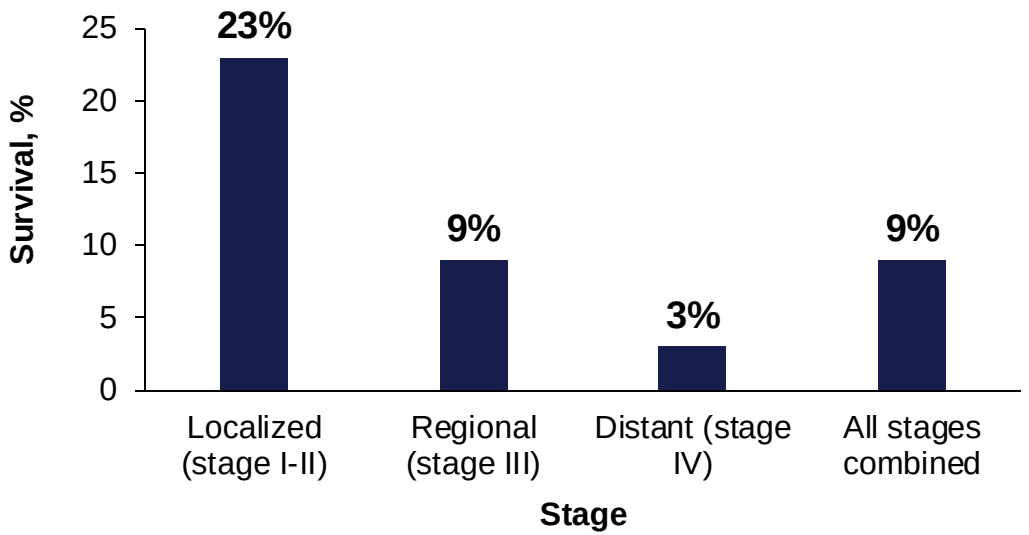
- iCCA, pCCA, and dCCA are staged using separate AJCC criteria[a]
- The different TNM criteria account for:
  - Location of the tumor (intrahepatic; proximity to the gallbladder, pancreas, duodenum, or other adjacent organs)
  - Potential areas of tumor invasion (eg, vasculature/arteries, peritoneum, muscles, adipose tissue)
  - Tumor size
  - Spread to specific local and regional lymph nodes

iCCA		pCCA		dCCA	
Stage	**TNM**	**Stage**	**TNM**	**Stage**	**TNM**
0	Tis N0 M0	0	Tis N0 M0	0	Tis N0 M0
IA-B	T1 N0 M0	I	T1 N0 M0	I	T1 N0 M0
II	T2 N0 M0	II	T2 N0 M0	IIA	T1 N1 M0 T2 N0 M0
				IIB	T2 or 3 N1 M0 T3 N0 M0
IIIA	T3 N0 M0	IIIA/B	T3/4 N0 M0	IIIA	T1-3 N2 M0
IIIB	T4 N0 M0 Any T N1 M0	IIIC	Any T N1 M0	IIIB	T4 N0-2 M0
IV	Any T any N M1	IVA IVB	Any T N2 M0 Any T any N M1	IV	Any T any N M1

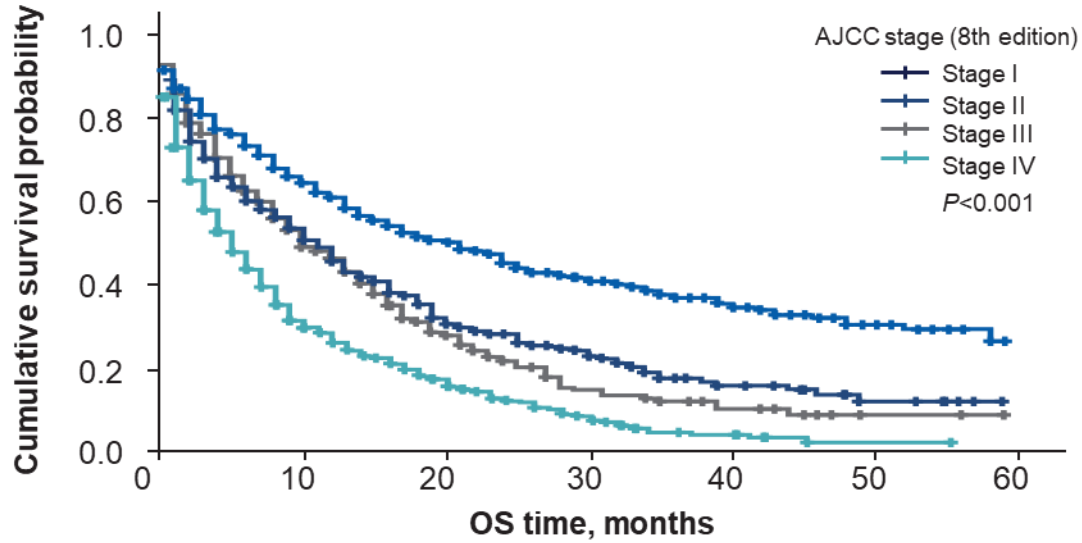
[a] Original source is the *AJCC Cancer Staging Manual,* 8th Edition (2017) published by Springer International Publishing.
AJCC, American Joint Committee on Cancer; Tis, carcinoma in situ; TNM, tumor, node, metastasis.
Liao, et al. *Arch Pathol Lab Med*. 2021 May 1;145(5):543-553.

5-Year Survival Rates Among Patients With CCA Remain Poor

5-Year Survival by Stage of iCCA (SEER 2012-2018)[1]



iCCA OS by Stage[2]



Median OS rates for iCCA

Resectable	Unresectable	Stage IV disease
≈3 years[3-8]	≈12-15 months[9-11]	≈9 months[12]

Graph reproduced from Meng Z-W, et al. *Oncotarget*. 2017;8(60):101165-101174. Copyright 2017. Licensed under a CC-BY Creative Commons Attribution 3.0 International License (https://creativecommons.org/licenses/by/3.0/).

OS, overall survival.

1. American Cancer Society. Accessed August 2024. https://www.cancer.org/content/dam/CRC/PDF/Public/8554.00.pdf. 2. Meng Z-W, et al. *Oncotarget*. 2017;8:101165-101174. 3. Buettner S, et al. *Onco Targets Ther*. 2017;10:1131-1142. 4. Endo I, et al. *Ann Surg*. 2008;248:84-96. 5. De Jong M, et al. *J Clin Oncol*. 2011;29:3140-3145. 6. Amini N, et al. *J Surg Oncol*. 2014;110:163-170. 7. Koerkamp BG, et al. *J Am Coll Surg*. 2015;221:1041-1049. 8. Chung YJ, et al. *J Korean Surg Soc*. 2013;85:212-218. 9. Schartz DA, et al. *J Vasc Interv Radiol*. 2022;33:679-686. 10. Bridgewater J, et al. *J Hepatol*. 2014;60:1268-1289. 11. Ray CE Jr, et al. *J Vasc Interv Radiol*. 2013;24:1218-1226. 12. Valle J, et al. *N Engl J Med*. 2010;362:1273-1281.

Genomic Landscape

Genomic Alterations in CCA May Be Associated With Prognosis

- A prospective study was performed as part of the ICGC and analyzed 489 CCA samples from patients in 10 countries[a]
- Integrative clustering analysis revealed 4 sample clusters which were characterized by different clinical features and genetic, epigenetic, and gene-expression patterns – Cluster 4 is notable as it was comprised of Fluke-Neg, iCCA tumors with FGFR alterations

Cluster	1	2	3	4
Genomic alterations	• Highest SNV burden • Enriched in *TP53, ARID1A, BRCA1/2* mutations • Enriched in H3K27 me3-associated promoter mutations	Enriched in *TP53*		• Enriched in *BAP1* and *IDH1/2* mutations • Enriched in *FGFR* alterations
Copy number alterations	*ERBB2* amplification		↑ Highest CNA burden 1p, 2p, 2q, 7p, 16p, 19q, 20q	
Gene expression	↑ *ERBB2* ↑ TET1 ↓ EZH2	↑ CTNNB1, WNT5B, AKT1	↑ • Immune-related pathways • *PD-1, PD-L2,* and *BTLA*	↑ *FGFR1 FGFR2 FGFR3 FGFR4*
Methylation phenotype	CpG island hypermethylated			CpG shore hypermethylated
Prognosis	Poorer prognosis			Better prognosis

Survival analysis showed improved survival in CCAs of clusters 3 and 4 compared with other clusters

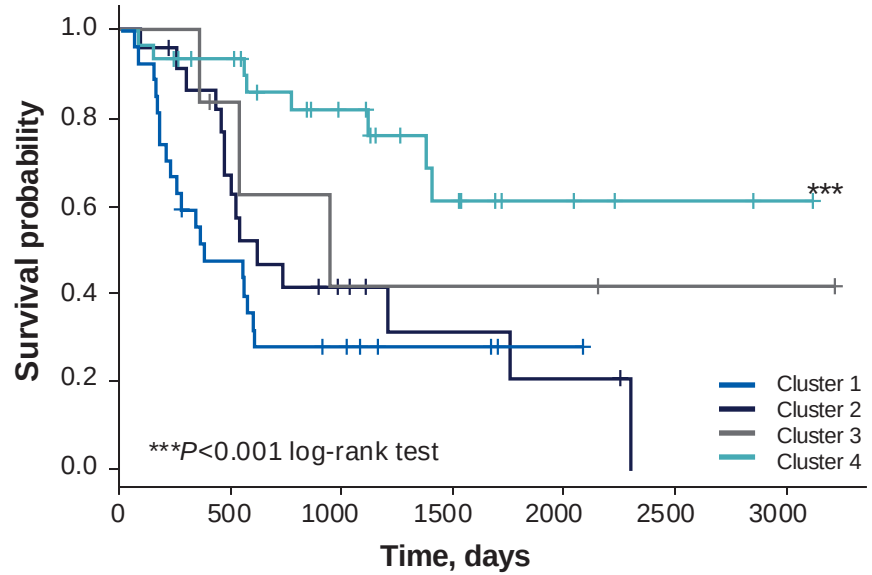


Image Adapted from Cancer Discov, Copyright © 2017, Volume 7/Issue 10, Pages 1116-1135, Jusakul A, et al, Whole-genome and epigenomic landscapes of etiologically distinct subtypes of cholangiocarcinoma, with permission from AACR.

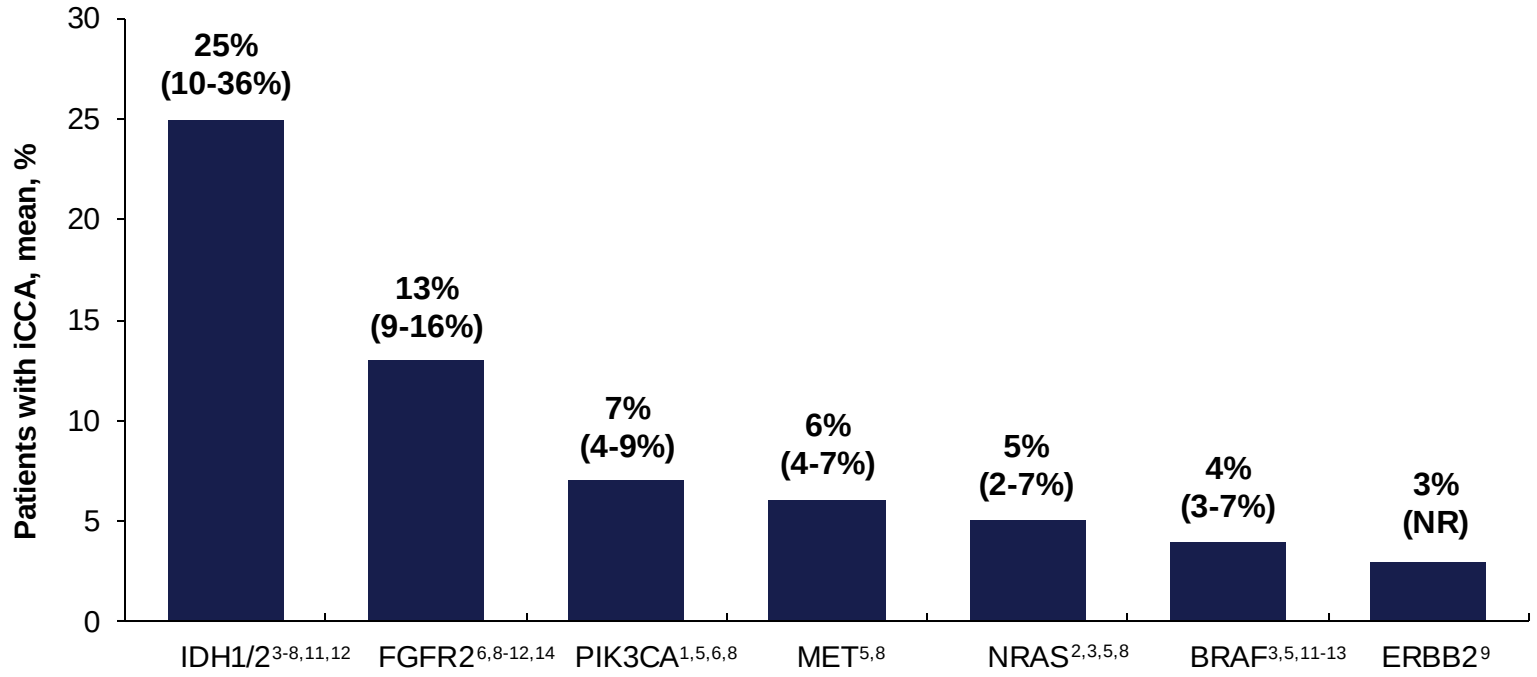
[a] Samples were analyzed using 4 different genomic platforms capable of detecting somatic mutations, somatic copy-number alterations, mRNA expression, and DNA methylation patterns.

BTLA, B and T lymphocyte associated; CNA, copy number alteration; ICGC, International Cancer Genome Consortium; PD1, programmed cell death protein-1; PDL2, programmed cell death ligand 2; SNV, single nucleotide variant.

Jusakul A, et al. *Cancer Discov.* 2017;7:1116-1135.

Common Alterations in iCCA

Approximate Incidence (Range) of Common Alterations Targetable With Approved or Late-Stage Experimental Drugs



Individual studies have reported other potentially oncogenic alterations in iCCA[2-13]

- *ARAF*
- *ARID1A*
- *BRCA1/2*
- *BAP1*
- *CDKs* (eg, *CDKN2A/B*)
- *EGFR*
- *ERBB2/HER3*
- *KRAS*
- *NF1*
- *TP53*
- *PTEN*
- *ROS1*

≈50% of iCCAs have genomic alterations that could be used to personalize therapy[8,11,15,16]

NR, not reported.

1. Riener M-O, et al. *Genes Chromosomes Cancer.* 2008;47:363-367. 2. Deshpande V, et al. *BMC Cancer.* 2011;11:60. 3. Borger DR, et al. *Oncologist.* 2012;17:72-79. 4. Wang P, et al. *Oncogene.* 2013;32:3091-3100. 5. Voss JS, et al. *Hum Path*. 2013;44:1216-1222. 6. Jiao Y, et al. *Nat Genetics.* 2013;45:1470-1473. 7. Chan-On W, et al. *Nat Genetics.* 2013;45:1474-1478. 8. Ross JS, et al. *Oncologist.* 2014;19:235-242. 9. Graham RP, et al. *Hum Pathol*. 2014;45:1630-1638. 10. Arai Y, et al. *Hepatololgy.* 2014;59:1427-1434. 11. Sia D, et al. *Nat Commun.* 2015;6:6087. 12. Javle M, et al. *Cancer.* 2016;122:3838-3847. 13. Sia D, et al. *Gastroenterology*. 2013;144:829-840. 14. Krook MA, et al. *J Clin Oncol.* 2020;15(suppl):3620. 15. Lowery MA, et al. *Clin Cancer Res*. 2018;24:4154-4161. 16. Chun SY, Javle M. *Cancer Contr*. 2017;24:1-7.

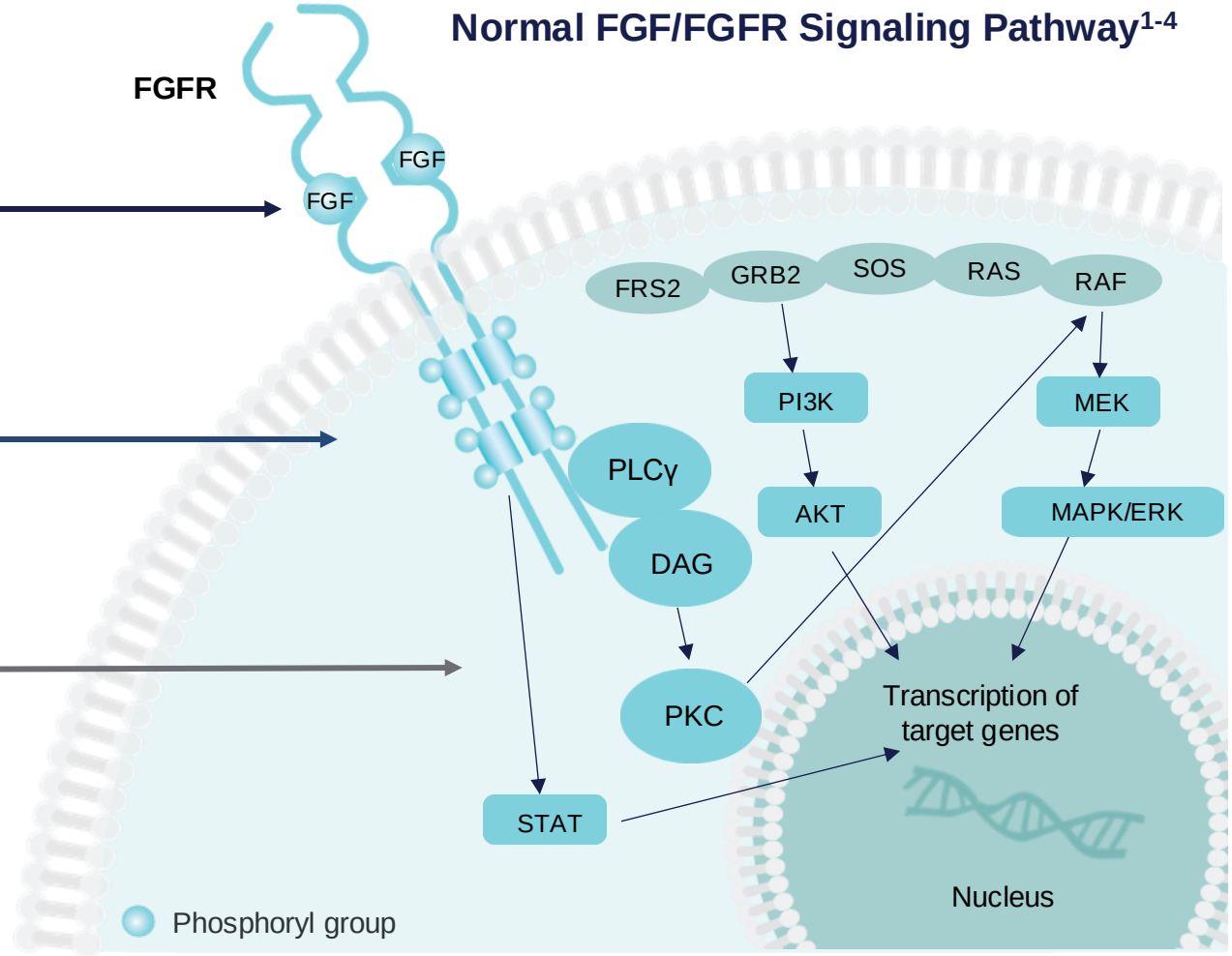
The FGF/FGFR Signaling Pathway Plays a Central Role in Multiple Cellular Processes[1-4]

Binding of FGF ligands (FGF1 to 23) to their cognate FGF receptors (FGFR1 to 4) leads to receptor dimerization[1,2]

Receptor dimerization induces cross-phosphorylation and activation of the FGFR kinases[1-3]

FGFR kinases activate downstream signaling pathways implicated in cellular processes such as proliferation, survival, migration, and angiogenesis[1,2]

Normal FGF/FGFR Signaling Pathway[1-4]



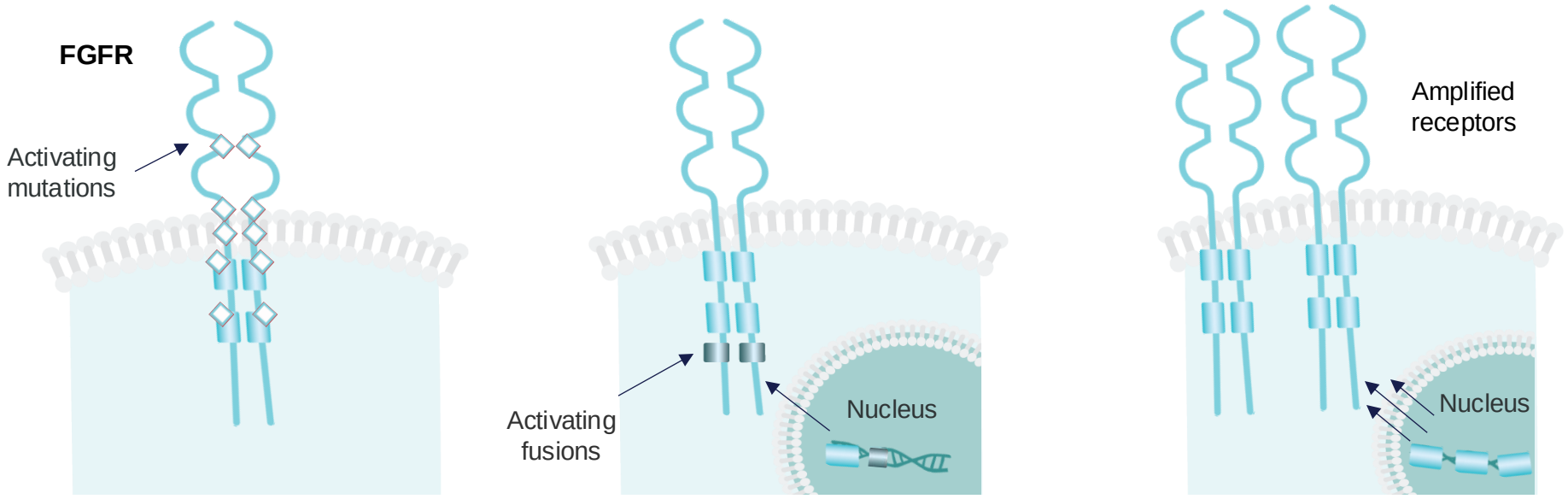
AKT, protein kinase B; DAG, diacylglycerol; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FRS2, fibroblast growth factor receptor substrate 2; GRB2, growth factor receptor-bound protein 2; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLCγ, phospholipase C-gamma; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SOS, son of sevenless; STAT, signal transducer and activator of transcription.

1. Babina IS, Turner NC. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Sarabipour S, Hristova K. *Nat Commun*. 2016;7:10262. 4. Touat M, et al. *Clin Cancer Res*. 2015;21:2684-2694.

Deregulation of FGFR Signaling Is Implicated in Tumorigenesis

- Aberrant FGFR signaling mediates tumorigenesis by enhancing proliferation, migration, survival, invasion, and angiogenesis[1,2]
- Different genomic alterations may result in tumorigenic FGFR signaling[1]

Activating Mutations	Chromosomal Rearrangements	Gene Amplifications
Leading to constitutive activation of the kinase domain or ligand-independent receptor dimerization	Translocations resulting in gene fusions that allow ligand-independent receptor dimerization	Inducing protein overexpression, receptor accumulation and activation of downstream signaling pathways



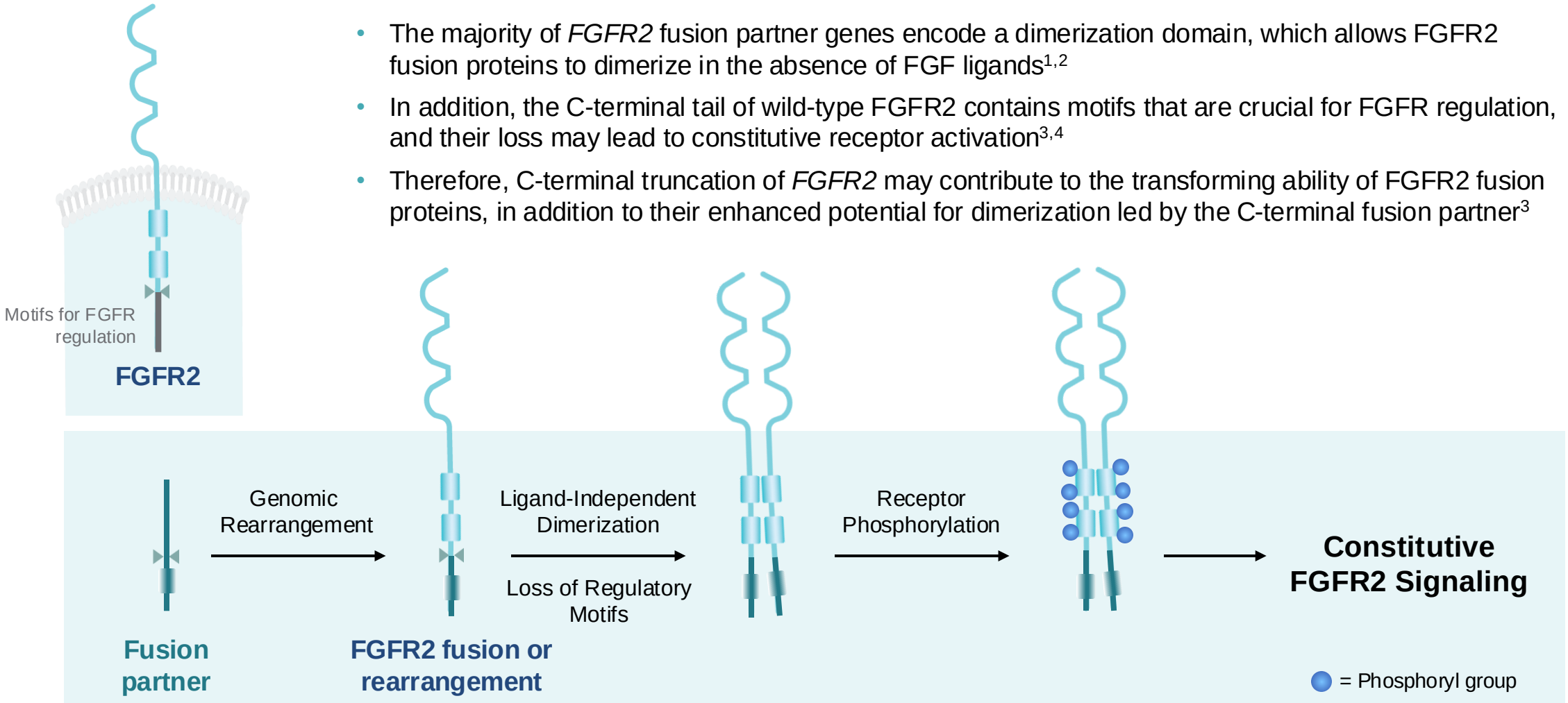
FGFR2 Gene Fusions:

- Occur in 9-16% of patients with iCCA[3-6]
- Are detected early in disease progression, suggesting that *FGFR2* fusions serve as oncogenic drivers[7]

1. Babina I, Turner N. *Nat Rev Cancer*. 2017;17:318-332. 2. Turner N, Grose R. *Nat Rev Cancer*. 2010;10:116-129. 3. Rizvi S, Borad MJ. *J Gastrointest Oncol*. 2016;7(5):789-796. 4. Graham RP, et al. *Hum Pathol.* 2014;45:1630-1638. 5. Farshidfar F, et al. *Cell Rep*. 2017;18(11):2780-2794. 6. Ross JS, et al. *Oncologist*. 2014;19:235-242. 7. Krook MA, et al. *J Clin Oncol*. 2020;15(suppl):3620.

FGFR2 Fusions or Rearrangements May Trigger Ligand-Independent Receptor Dimerization and Constitutive FGFR Signaling, Possibly Driving Tumorigenesis

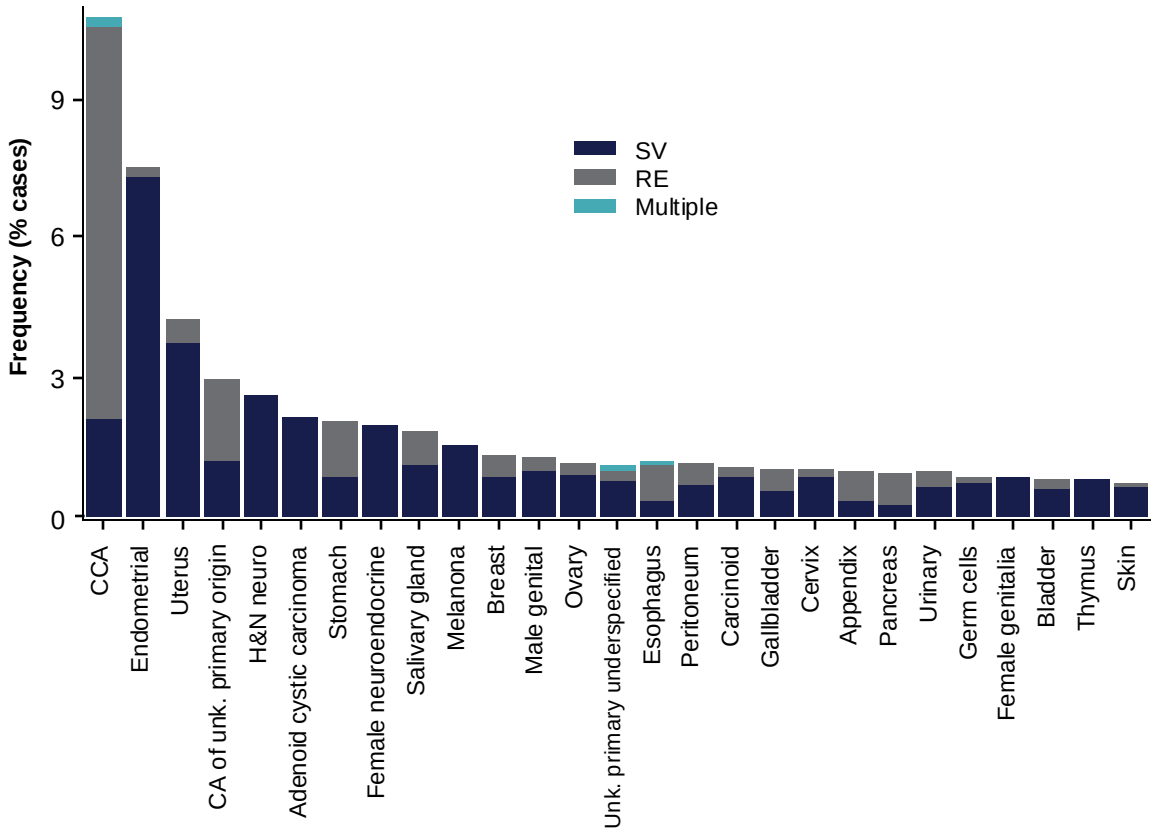
- The majority of *FGFR2* fusion partner genes encode a dimerization domain, which allows FGFR2 fusion proteins to dimerize in the absence of FGF ligands[1,2]
- In addition, the C-terminal tail of wild-type FGFR2 contains motifs that are crucial for FGFR regulation, and their loss may lead to constitutive receptor activation[3,4]
- Therefore, C-terminal truncation of *FGFR2* may contribute to the transforming ability of FGFR2 fusion proteins, in addition to their enhanced potential for dimerization led by the C-terminal fusion partner[3]



1. Gallo LH, et al. *Cytokine Growth Factor Rev*. 2015;26:425-449. 2. Wu YM, et al. *Cancer Discov*. 2013;3:636-647. 3. Li F, et al. *Cytokine Growth Factor Rev*. 2020;52:56-67.
4. Lorenzi MV, et al. *Oncogene*. 1997;15:817-826.

Oncogenic *FGFR2* Fusions or Rearrangements Are Common Alterations in CCA

Distribution of *FGFR2* Alterations by Tumor Type[1]



- *FGFR2* genomic alterations were identified in 1.7% of tumor samples from ≈350,000 patients who underwent Foundation Medicine CGP during routine clinical care[1]
- *FGFR2* SVs and rearrangements were most frequently observed in samples from patients with CCA[1]
- Most *FGFR2* alterations in CCA were gene fusions following chromosomal rearrangement[1]
- Other *FGFR2* mutations were also observed in CCA biopsies in this and other studies[1-3]

CA, carcinoma, CGP, comprehensive genomic profiling; H&N, head and neck; RE, rearrangement/fusion; SV, short variant mutation; unk, unknown.

1. Murugesan K, et al. *ESMO Open*. 2022; 6:100641. 2. Javle MM, et al. ASCO 2019. Poster 4087. 3. Silverman IM, et al. *Cancer Discov*. 2021;11:326-339.

Other Targetable Mutations in iCCA

IDH mutations

- IDH is an essential enzyme for cellular respiration in the TCA cycle[1,2]
- Mutations in *IDH* have been implicated in tumorigenesis, cell maintenance, and proliferation[1,3]

BRAF mutations

- *BRAF* mutations result in constitutive BRAF activation and uncontrolled signaling via the MAPK pathway[4]
  - The MAPK pathway regulates cell signaling from transmembrane growth factor receptors, leading to cell proliferation[5-7]
- *BRAF* mutations have been identified in approximately 5% of patients with CCA, predominantly those with iCCA[8]

BRAF, B-Raf proto-oncogene, serine/threonine kinase; IDH, isocitrate dehydrogenase; TCA, tricarboxylic acid cycle.

1. Fujii T, et al. *Discov Med*. 2016;21:373-380. 2. Presner JR, Chinnaiyan M. *Nat Med.* 2011;17:291-299. 3. Takeishi K, et al. *Cancer Cell.* 2015;28:773-784. 4. Cantwell-Dorris ER, et al. *Mol Cancer Ther.* 2011;10:385-394. 5. Dibb NJ, et al. *Nat Rev Cancer*. 2004;4:718-727. 6. Sánchez-Torres, et al. *Transl Lung Cancer Res.* 2013;2:244-250. 7. Beeram M, et al. *J Clin Oncol*. 2005;23:6771-6790. 8. Silverman IM, et al. ASCO 2019 abstract 4080.

Key Takeaways

Key Takeaways

- CCA is a rare malignancy of the biliary tract occurring both inside (iCCA) and outside (eCCA) the liver; despite its rare occurrence, the overall incidence of iCCA has increased in recent years[1,2]
- Diagnosis remains a challenge due to a lack of symptoms and known risk factors for most patients, limited value of tumor markers, and overlap with other disease states (eg, pancreatic cancer, PSC)[3]
- Approximately 30% of patients with a diagnosis of iCCA have resectable disease, yet more than half of patients who undergo resection will experience a relapse[4,5]
  - Prognosis for patients with a diagnosis of CCA remains poor, with median survival rates in resectable and unresectable disease of ≈3 years and 12-15 months, respectively[4,6-8]
- Genomic analyses of CCA tumors have identified actionable oncogenic mutations[9]
  - Alterations in *FGFR* and *IDH* have been identified in ≈9-16% and ≈ 25% of patients with iCCA, respectively[9-15]

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