Diagnosis and Current Challenges in Cholangiocarcinoma

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Disclosure

Received speaking honoraria from Astra Zeneca, Biologics, MSD and Hikma.

Background

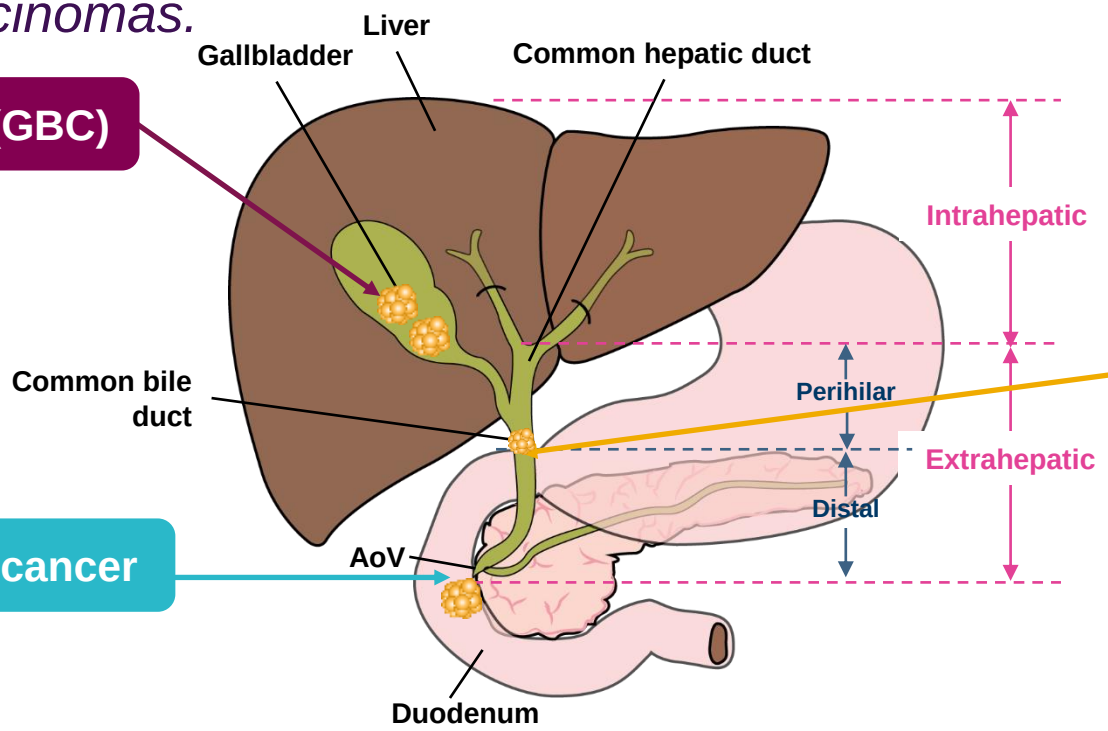
Diagnosis

Current challenges in the management of cholangiocarcinoma

BTC Arises From the Biliary Epithelium of the Small Ducts in the Liver Periphery (Intrahepatic) and the Main Ducts of the Hilum (Extrahepatic)[1]

BTC is a group of different diseases and can be subclassified as gallbladder carcinoma, bile duct cancer/cholangiocarcinoma and ampulla of Vater (AoV) cancer[1-3] Greater than 90% of BTC cases are adenocarcinomas.

Gallbladder carcinoma (GBC)



Cholangiocarcinoma (CC)

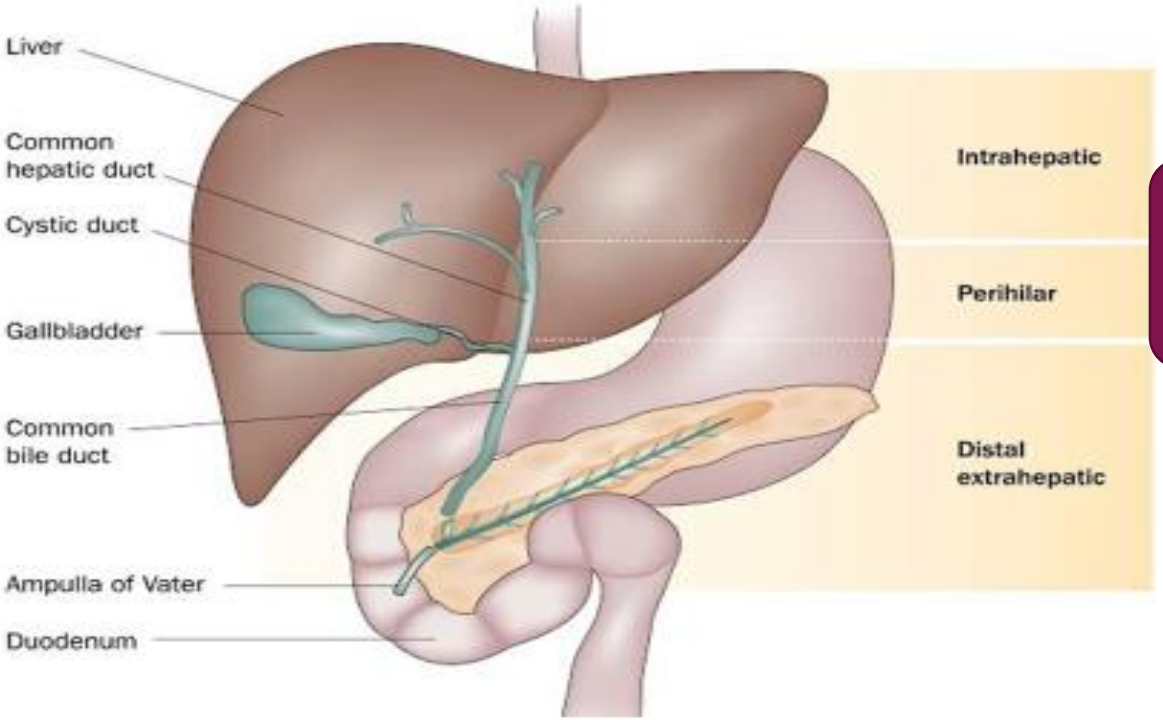
Ampulla of Vater (AoV) cancer

NOTE: AoV cancer will not be covered in detail in this asset as it is not included in the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®)[4] for BTC, and is often an exclusion criterion in major BTC clinical trials[5,6]

AoV = ampulla of Vater; BTC = biliary tract cancer; CC = cholangiocarcinoma; ESMO = European Society for Medical Oncology; GBC = gallbladder carcinoma; NCCN = National Comprehensive Cancer Network® (NCCN®).
References in the slide notes.

BILIARY TRACT CANCER

Cholangiocarcinoma Biology and Diagnosis



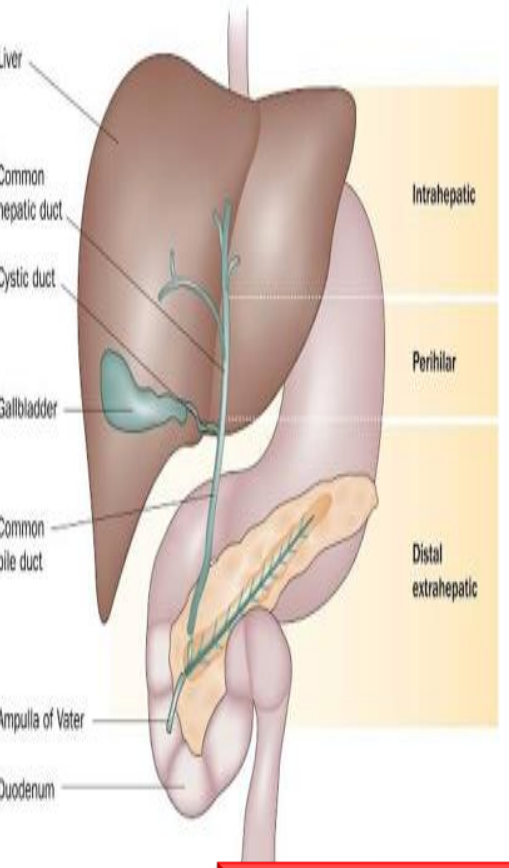
Biliary Tree

- **Rare, aggressive malignancy**
- 2nd most common primary liver malignancy[2]
- **Intrahepatic**: arises from the bile ducts inside the liver[1]
- **Extrahepatic**: includes *perihilar* and *distal* disease which arise from the bile duct outside the liver[2]
- Patients are typically asymptomatic in the early stages of the disease[3]
- >75% of patients have locally advanced or metastatic disease at diagnosis[4]

1- RARE DISEASE

1 / 100,000

Cholangiocarcinoma Biology and Diagnosis



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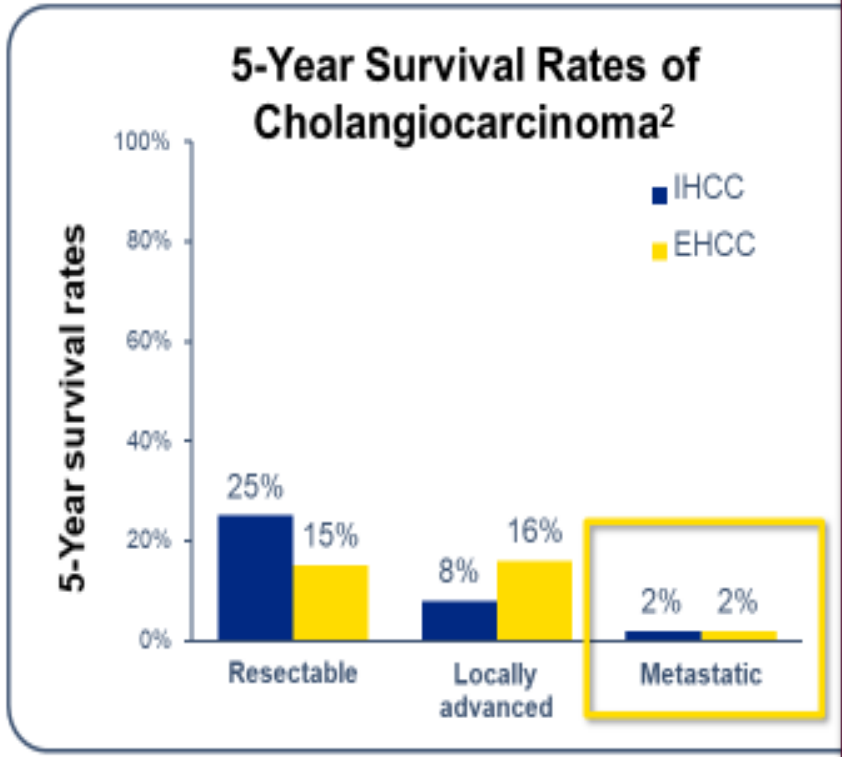
Poor Prognosis



In metastatic CCA median overall surviva
combination therapy, highlighting the need

APC, annual percentage change; EHCC, extrah
1. SEER Cancer Stats Facts: Common Cancer
staging/survival-by-stage.html. Accessed June
rcinoma
common.html. Accessed July 7, 2021. 2. American
Oncol. 2013;5(7):171-6.
www.cancer.org/

CHOLANGIOCARCINOMA "TARGET RICH DISEASE"

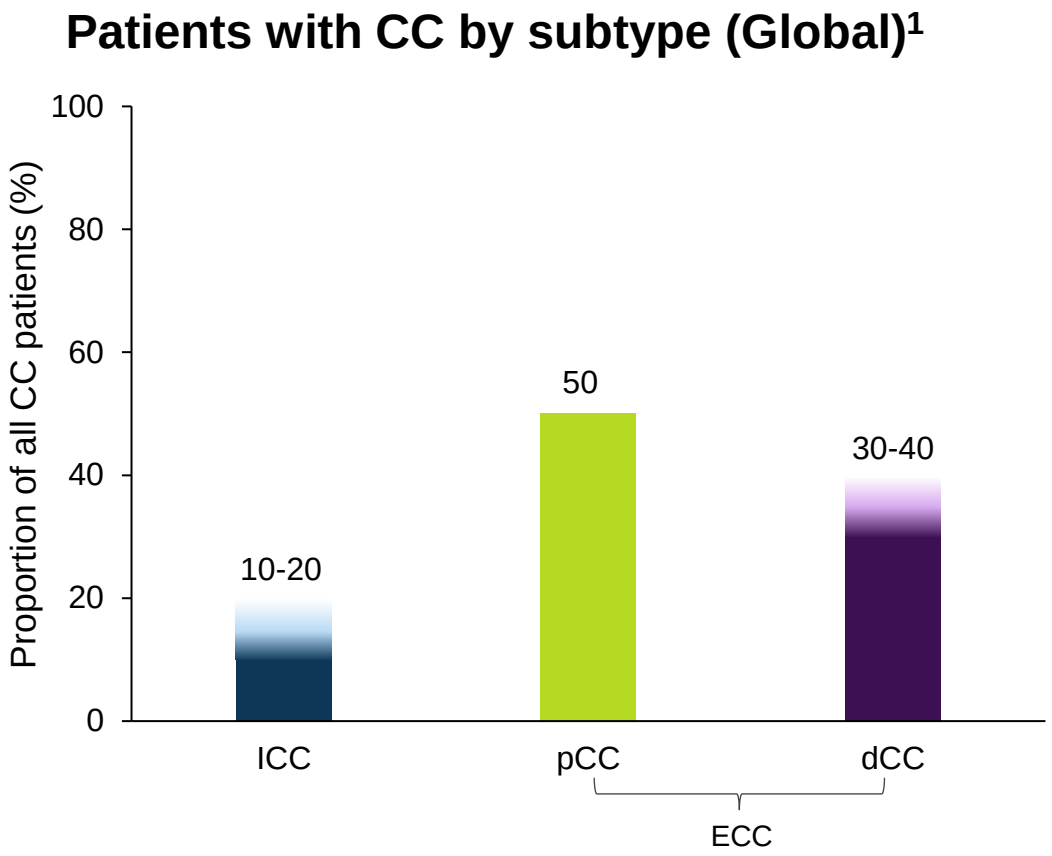
1-RARE

2- BAD

3- TARGET RICH

BTC Comprises 2% of all Human Cancers, but Accounts for ~10%–15% of All Primary Liver Cancers[1]

The proportion of patients with each BTC subtype varies, as does the proportion of patients with each specific CC subtype[1,2]



BTC = biliary tract cancer; CC = cholangiocarcinoma; dCC = distal cholangiocarcinoma; ECC = extrahepatic cholangiocarcinoma; ICC = intrahepatic cholangiocarcinoma; pCC = perihilar cholangiocarcinoma.
References in the slide notes.

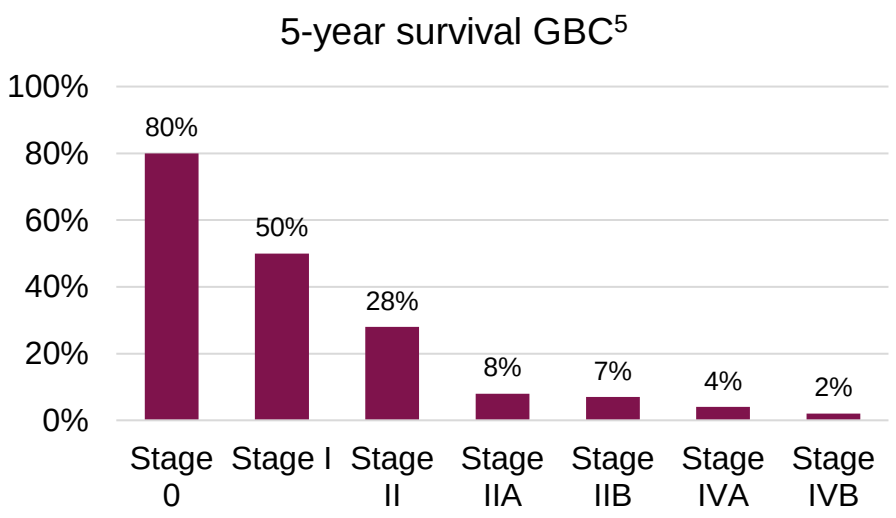
- Peaks at 7th decade. Median age at diagnosis is 67.
- 10-40% present with resectable disease.
- Most of patients with CCA present with advanced unresectable disease.

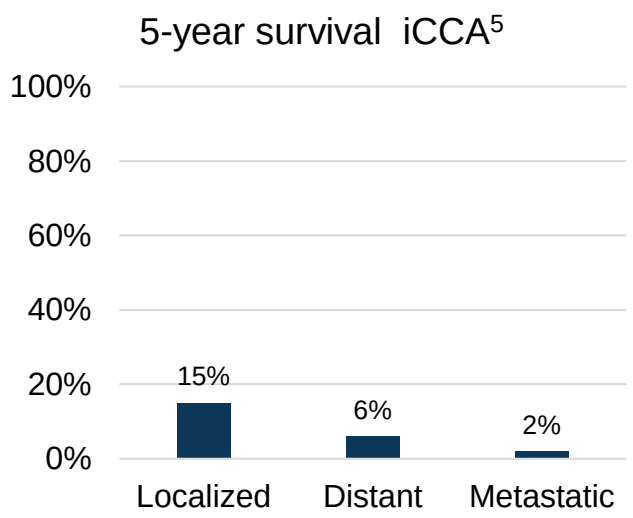
- Cidon EU. Resectable Cholangiocarcinoma: Reviewing the Role of Adjuvant Strategies.

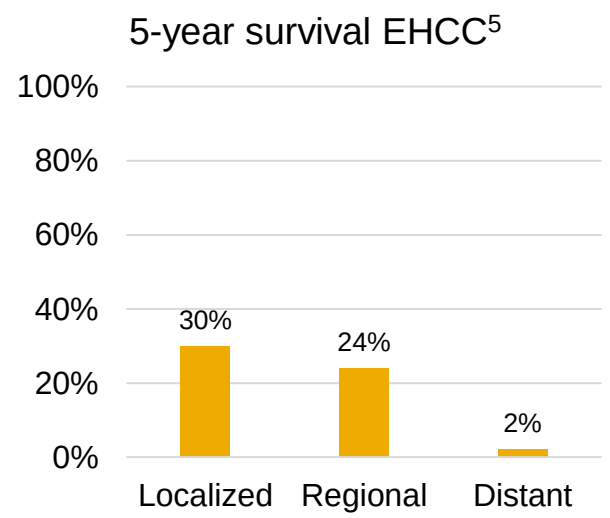
Prognosis and 5-year Survival Varies By Stage, Location and Sub-type of Disease[1,2]

Despite potentially curative resection for localized disease, there is a high rate of relapse post-resection[3]

More than 60% of BTC patients will be diagnosed with advanced disease, which is defined as inoperable (unresectable) or metastatic[4]



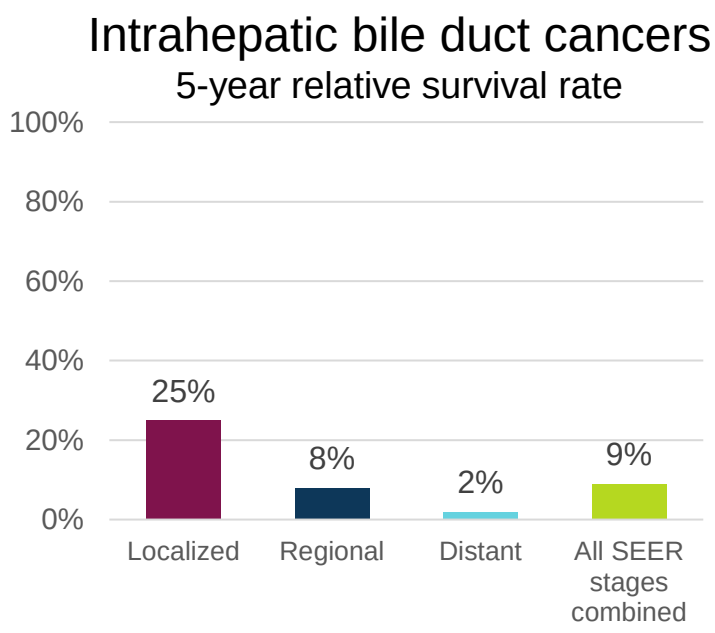


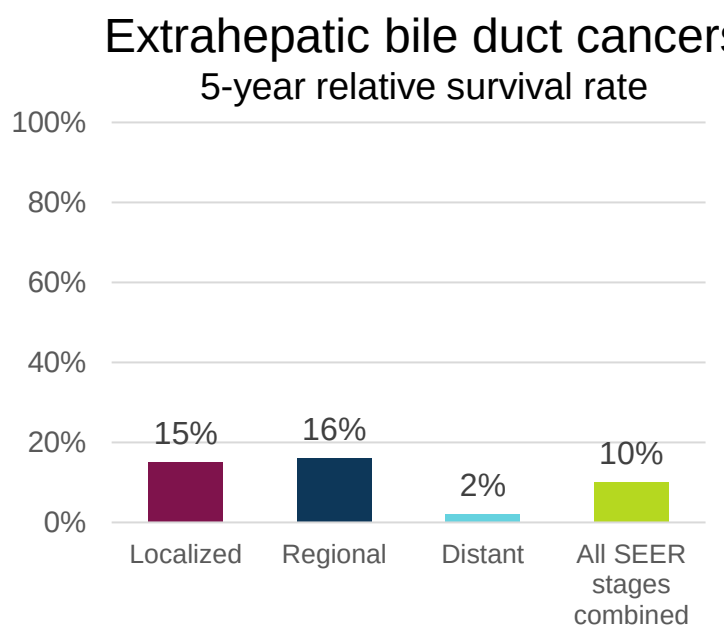


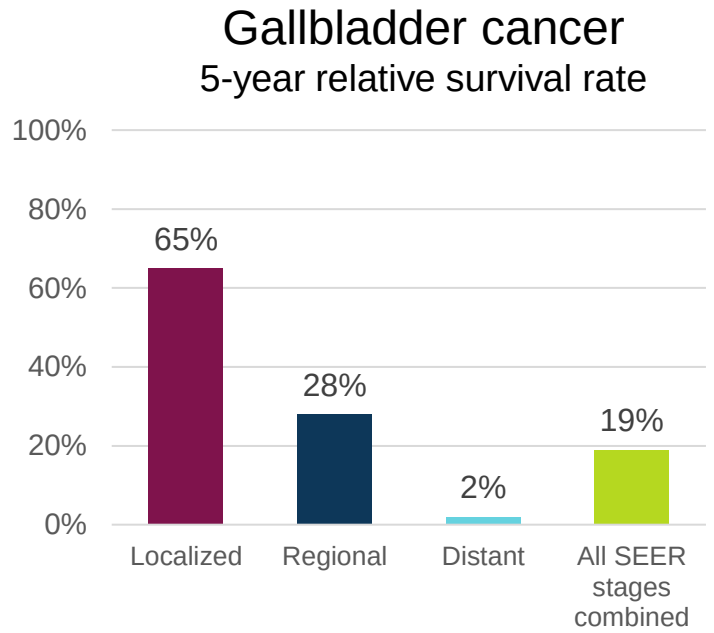
Abbreviations and references in the slide notes.

5-Year Relative Survival Rates for BTC[a]

Based on individuals diagnosed with bile duct cancers and gallbladder cancers in the United States between 2010 and 2016.[1,2]







[a]Excluding ampulla of Vater cancer.

BTC = biliary tract cancer.

1. American Cancer Society. Bile Duct Cancer Survival Rates. Accessed December 3, 2021. 2. American Cancer Society. Gallbladder Cancer Survival Rates. Accessed December 3, 2021.

Gallbladder Ca

These numbers are based on people diagnosed with cancers of the gallbladder between 2011 and 2017.

SEER stage	5-year relative survival rate
Localized	66%
Regional	28%
Distant	2%
All SEER stages combined	19%

Cholangiocarcinoma

Intrahepatic bile duct cancers (those starting within the liver)

SEER stage	5-year relative survival rate
Localized	24%
Regional	9%
Distant	2%
All SEER stages combined	9%

Extrahepatic bile duct cancers (those starting outside the liver)

(This includes both perihilar and distal bile duct cancers.)

SEER stage	5-year relative survival rate
Localized	17%
Regional	16%
Distant	2%
All SEER stages combined	10%

Risk Factors of BTC :

Primary Sclerosing Chlolangisits(Autoimmune)

Fibropolycystic liver disease (Congenital)

Cholelithiasis

Alcoholic liver disease

Metabolic RF like Obesity.

Risk Factors of BTC

Lynch syndrome

BAP1 tumor predisposition syndrome:

Increased risk of cholangioca has been reported in families that carry germline missense variants of the *BRCA*-associated protein 1 (*BAP1*) gene.

Risk Factors of BTC

Parasitic infections: **Clonorchiasis** and **Opistorchiasis** infections

HIV

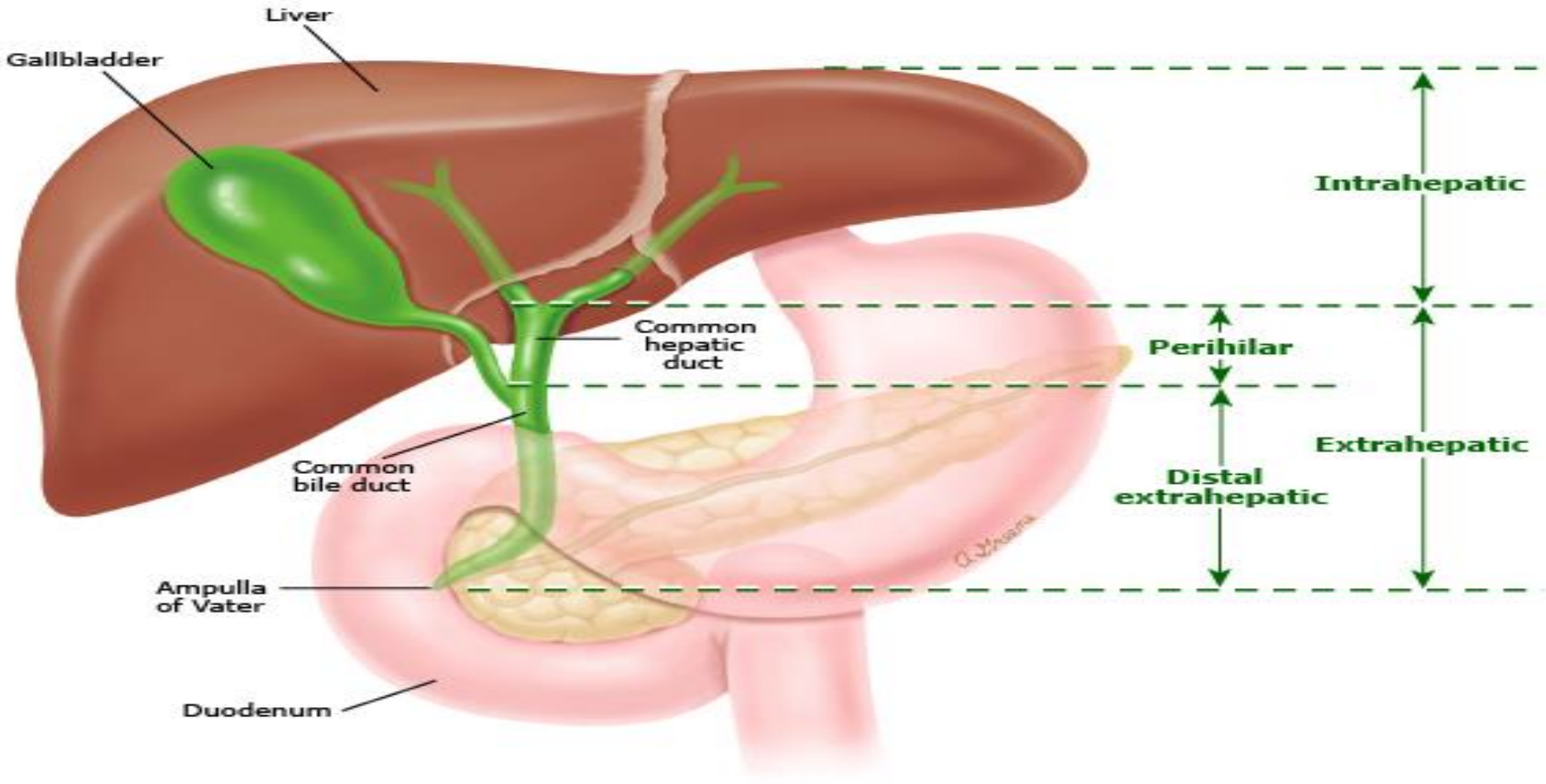
HEP B and C infections.

Diagnosis

Diagnosis

- Labs: Liver profile, CA19-9.
- Staging: CT CAP.
- MRI/MRCP: Perihilar
- ERCP/EUS: Distal extrahepatic CCA

Anatomic classification of cancers of the human biliary tract



Classifications defined by: American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition, Amin MB (Ed), Chicago: Springer Science+Business Media, LLC, 2017.

UpToDate®

Major Challenges?

Patient related

Presentation: Most patients present at late stage.

(10-40%) present with resectable disease. Cidon et al 2016.

Fitness for treatment. ? 20-30% not fit.

Aggressive biology

Desmoplastic reactions

A growth of fibrous connective tissue around tumor cells.

Desmoplasia is the result of increased synthesis o extracellular matrix proteins and collagen by stromal cells.

It is considered to be a reaction and response of the host tissue against invasive cancer cells.

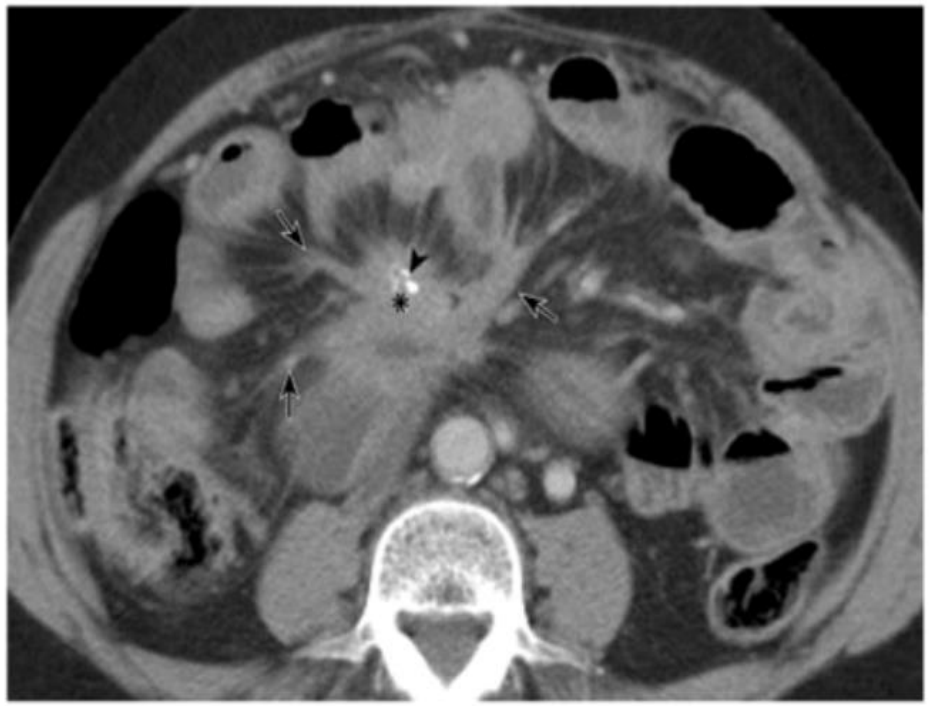


Figure 2. Desmoplastic reaction. The characteristic des-

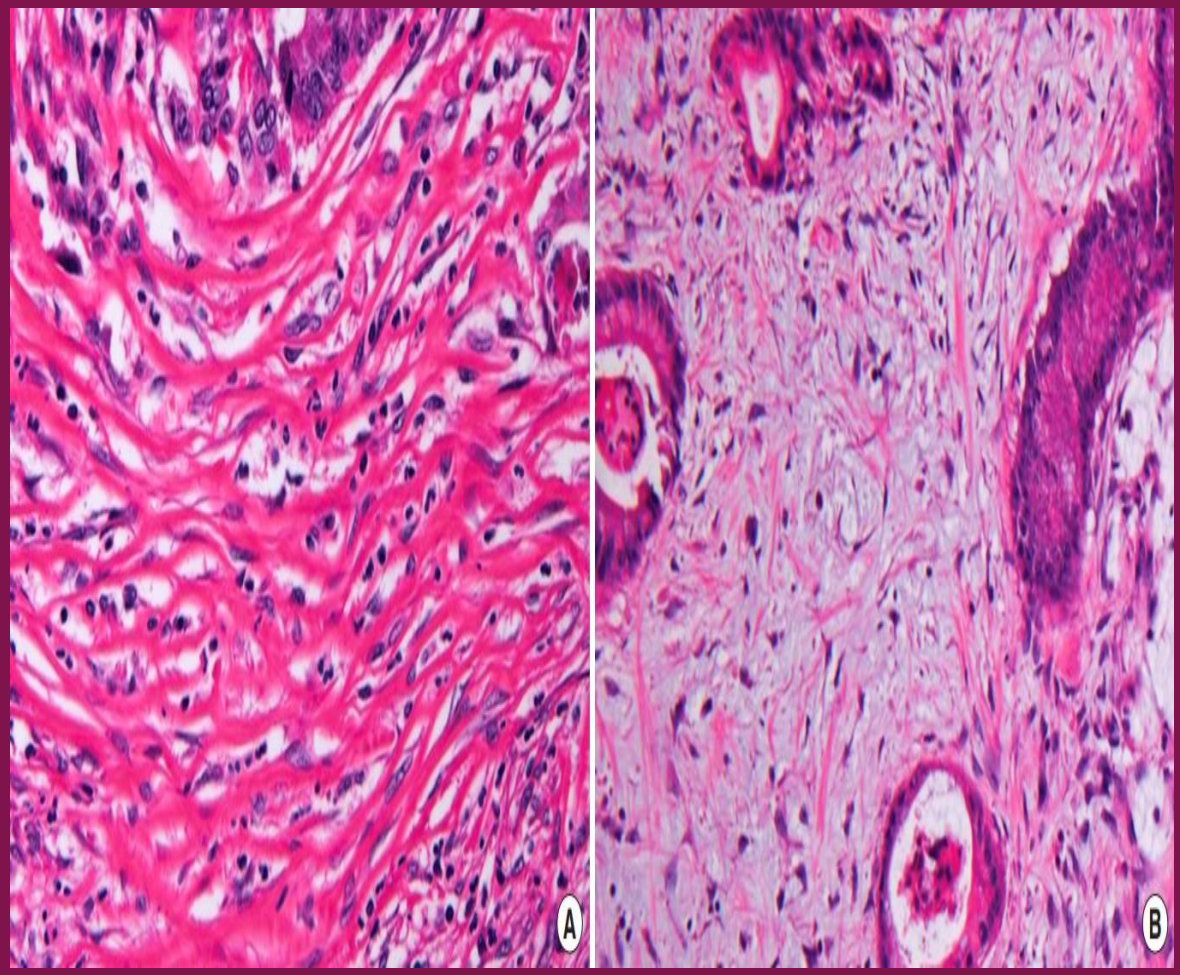
Aggressive biology

Desmoplastic reactions

Dramatic accumulation of α-smooth muscle actin positive cancer-associated fibroblasts (α-SMA+CAFs)

+ increased production of extracellular matrix proteins, pro-invasive growth factors and cytokines, anti-angiogenic factors, and matrix modifying enzymes.

The biological relevance of the desmoplastic response to cancer is still unclear.



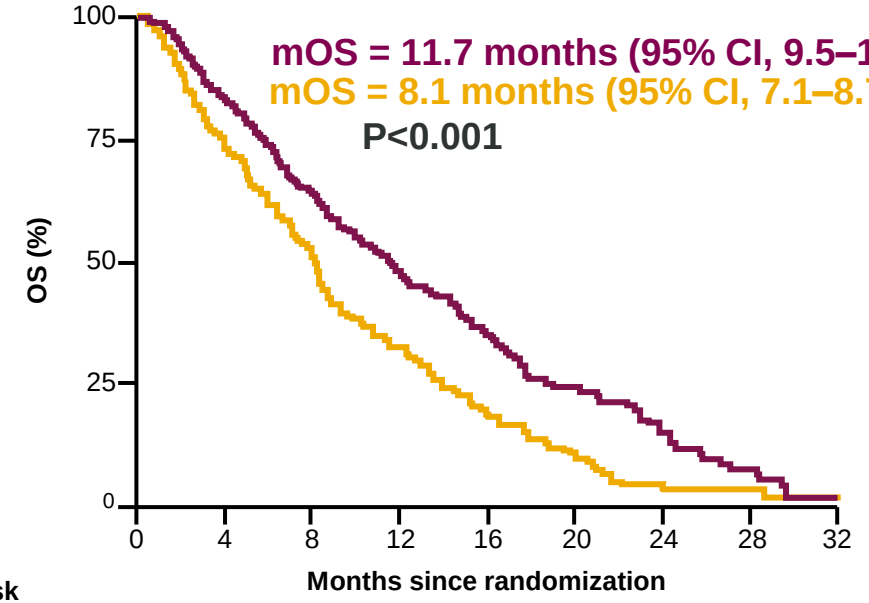
Aggressive biology ?

Cholangiocarcinomas are hypovascular tumors

BTC is an Aggressive Tumor Type with Limited Treatment Options to Address This Unmet Need

ABC-02 demonstrated gemcitabine plus cisplatin superiority over gemcitabine monotherapy, and now IO is under investigation to improve gemcitabine plus cisplatin treatment[1,2]

Kaplan–Meier estimates of overall survival in ABC-02[2]



Number at risk									
Gemcitabine alone	206	151	97	53	28	15	4	3	2
Gemcitabine/cisplatin	204	167	120	76	51	28	17	8	2

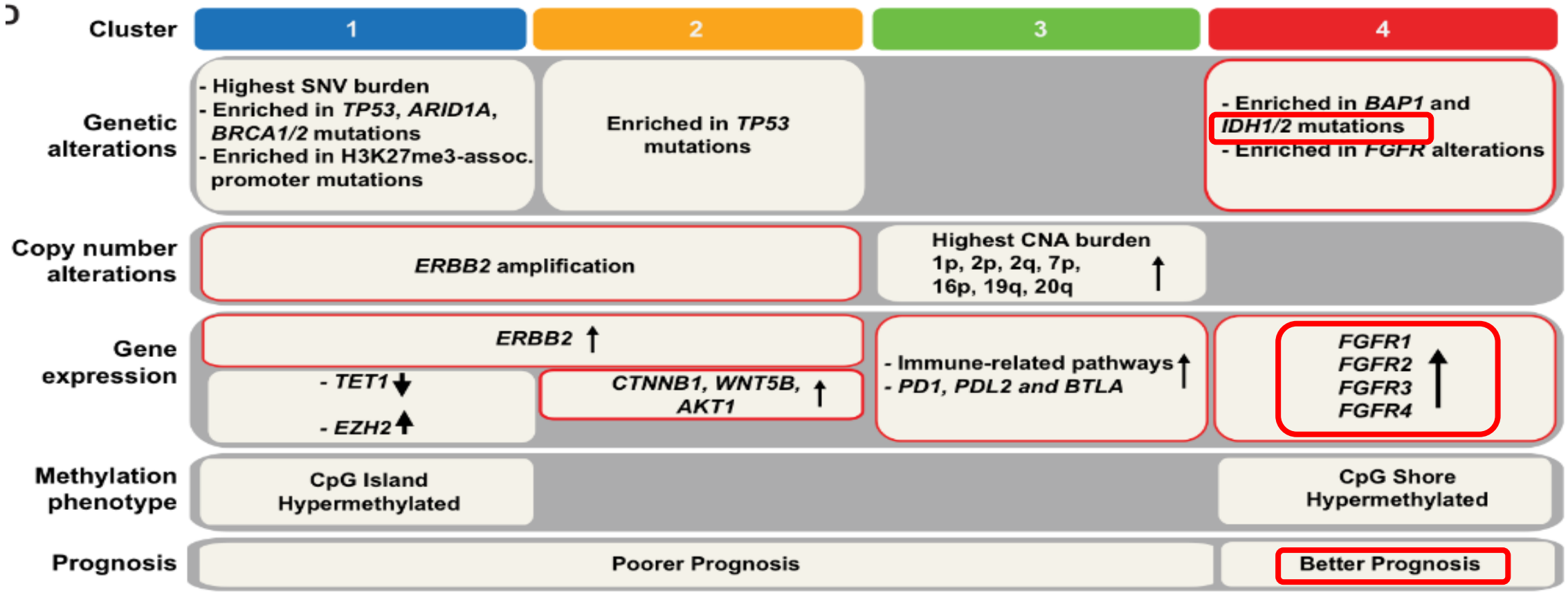
The Phase III ABC-02 trial demonstrated the **superiority of gemcitabine plus cisplatin** vs. gemcitabine monotherapy in BTC,[2] and it became the preferred 1L chemotherapy for patients with advanced BTC[3,4,5]

However, BTC is an **aggressive** disease and there are **limited treatment options** (for example, gemcitabine plus cisplatin treatment results in a median OS of <1 year)[2]

New treatment strategies are required and thus several IO therapies are under investigation (such as durvalumab) in combination with **existing regimens**

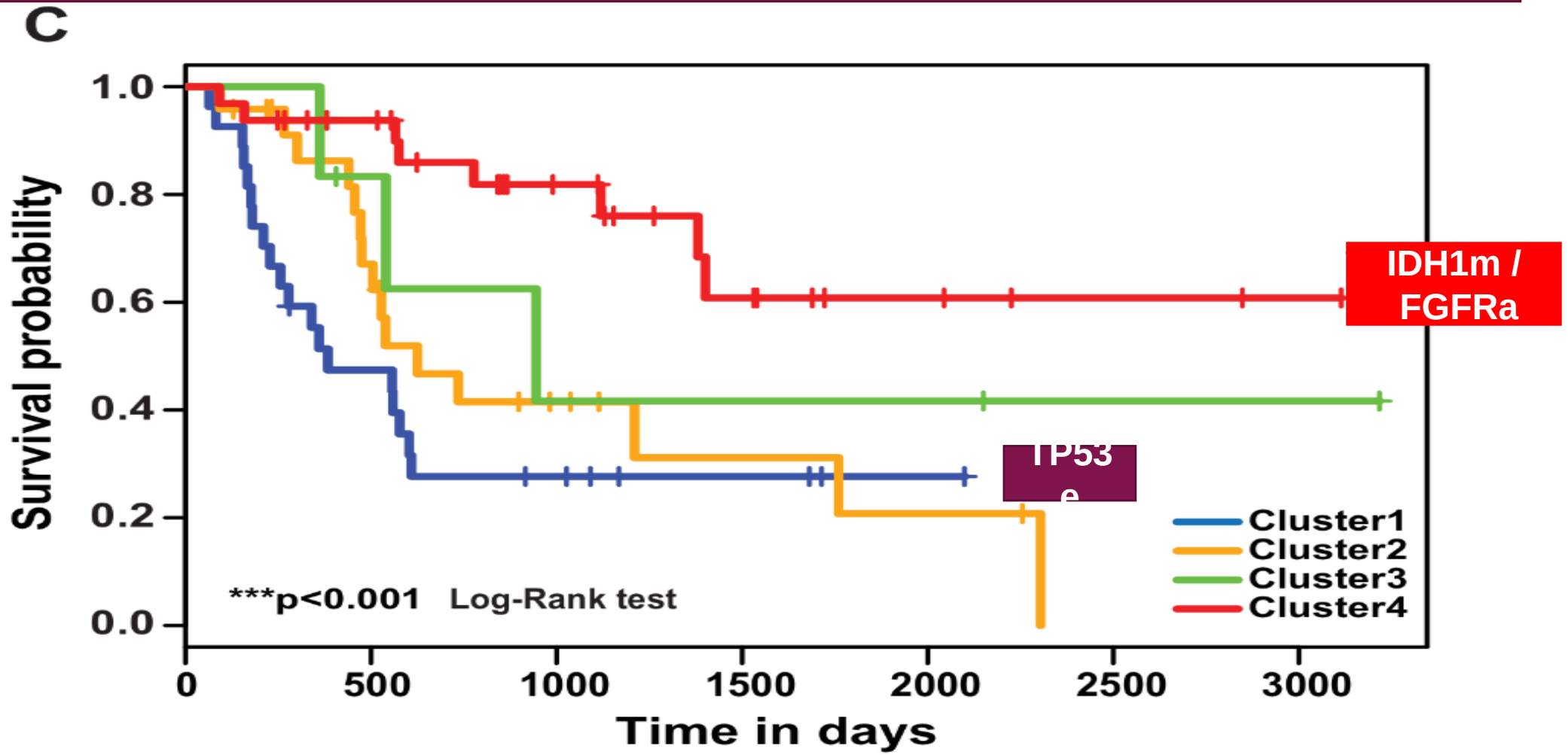
BTC = biliary tract cancer; IO = immuno-oncology; mOS = median overall survival; OS = overall survival.
References in slide notes.

International Cancer Genome Consortium for Cholangiocarcinoma



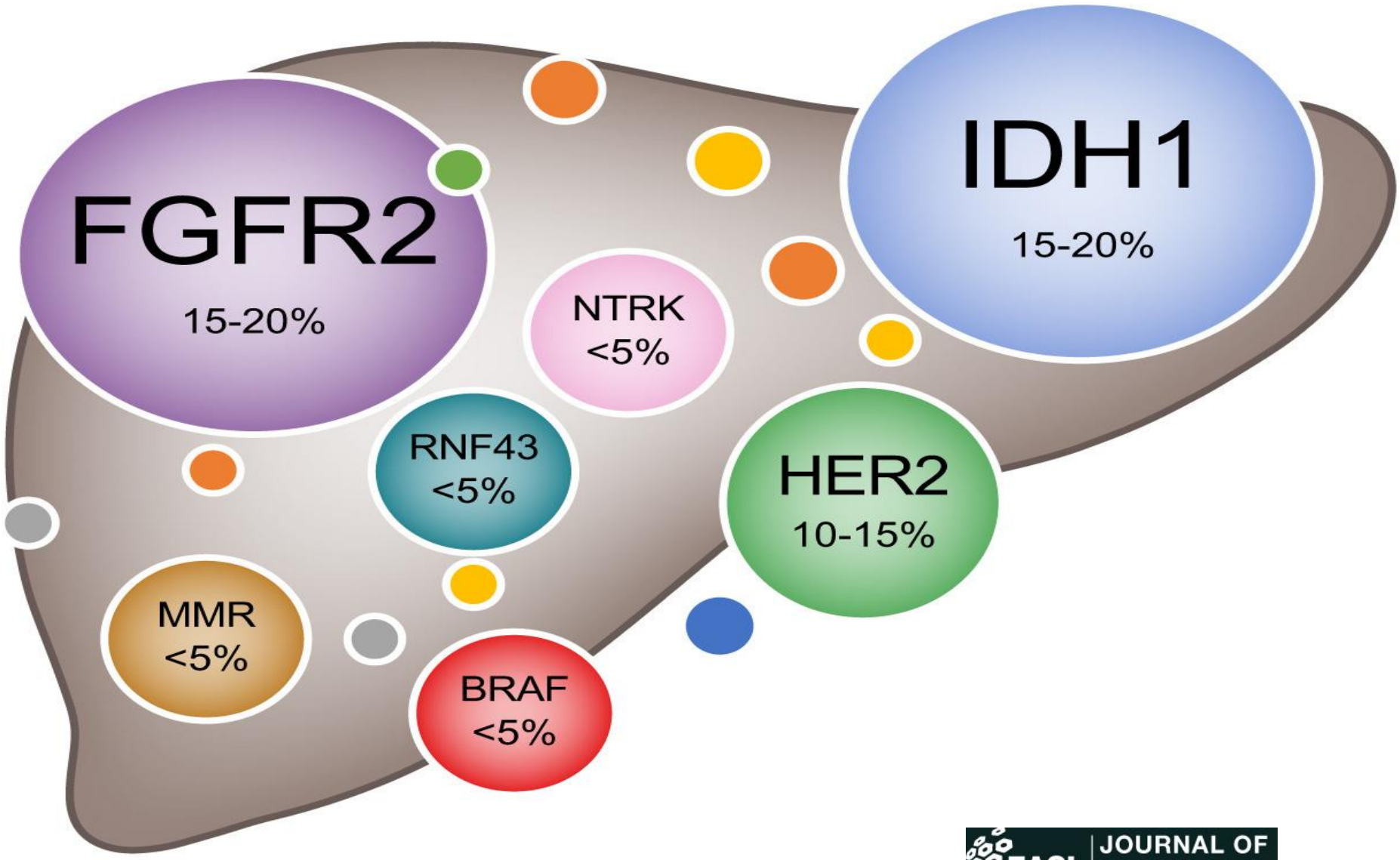
Jasakul, Cancer Discovery 2017

International Cancer Genome Consortium for Cholangiocarcinoma: Prognosis



Genetic Targets in Biliary Tract Cancer

CHOLANGIOCARCINOMA
"TARGET RICH DISEASE"



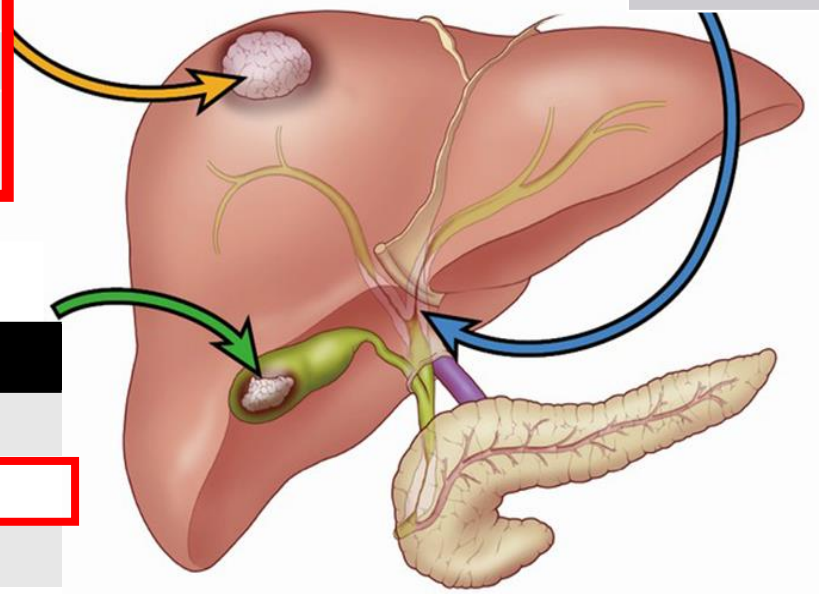
Genetic Targets in BTC

Intrahepatic cholangiocarcinoma

Targetable gene	Prevalence, %
FGFR2 (fusions)	10-20
IDH1/2	22-28
BAP1	15 to 25
BRAF V600 (mutation)[1,2]	5-7

Extrahepatic cholangiocarcinoma

Targetable gene	Prevalence, %
Her2/neu (mutation)	11-20
PRKACA and PRKACB	9
ARID1A	5-12



Gall bladder cancer

Targetable gene	Prevalence, %
EGFR	4-13
HER2/neu (amplification)	9
ERB3	0-12
PTEN	0-4
PIK3CA	6-13

Jain A, Javle M. Molecular profiling of biliary tract cancer: a target rich disease. J Gastrointest Oncol. 2016;7(5):797-803

Treatment-related challenges?

Multiple agents approved.

Availability of treatment.

Cost.

Presentation: **Mostly at advanced stages around 2/3 of cases. (Khan et al Gut 2012)**

Fitness for treatment; a significant proportion of patients are unfit

Aggressive biology: Resistant to systemic treatments.

Cost/availability of novel treatments.

Thank you