INTRODUCTION TO CHOLANGIOCARCINOMA

An Educational Resource for Patient Organisations

AMMF
THE CHOLANGIOCARCINOMA CHARITY

November 2023

About this Educational Resource

- This resource is targeted at small patient groups and pan-cancer organisations across Europe and aims to:
  - Ensure that they have access to credible information and data on cholangiocarcinoma (CCA)
  - Assist them in effectively and knowledgeably addressing CCA-related inquiries from healthcare authorities
  - Assist them in creating strong, robust presentations for local healthcare authorities
  - Ultimately, improve access to CCA treatments across Europe

Endorsed by CCA experts and members of AMMF's Clinical/Medical Advisory Board:
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Cholangiocarcinoma Overview

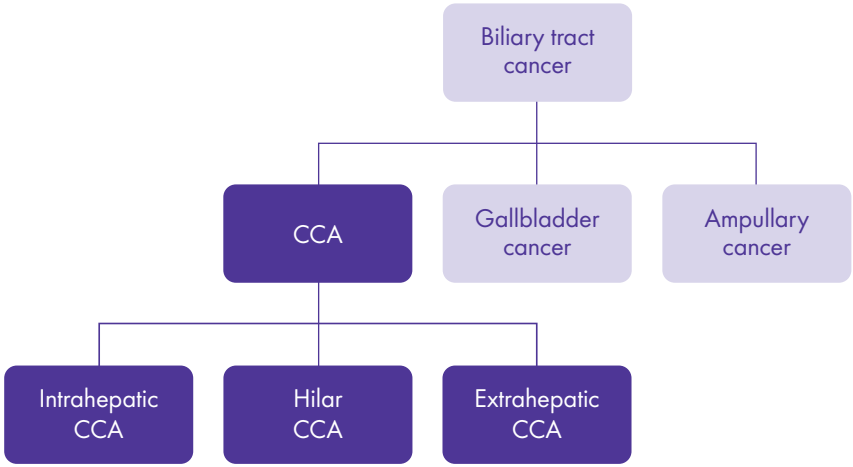
- CCA has a very aggressive nature, is difficult to treat and is invariably fatal[1]
- The incidence and death rates for CCA have been alarmingly increasing over the last decades, globally[1]
- Symptoms of CCA are usually silent in early stages of the disease and, when they do present, they can be non-specific[1,2]
- As a result, it is usually diagnosed late, in advanced stages, when therapeutic options are limited and compromised[1,2]
- Despite latest research advances, patient outcomes and prognosis still have not improved[1] and awareness of CCA remains low with healthcare professionals[3] compared to other cancers
- There is an increasing need to raise the profile of CCA amongst healthcare professionals, to help them better identify the associated signs, symptoms and risk factors, potentially enabling an earlier diagnosis and better patient outcomes[3]

CCA, cholangiocarcinoma

1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol.* 2020;17, 557–588; **2.** ESMO 2019. Biliary Tract Cancer. *ESMO Patient Guide Series* 1–45;
3. AMMF GP Awareness Campaign 2023. Available at: https://ammf.org.uk/gp-awareness-campaign/ [Accessed Jul 2023]

Introduction to Cholangiocarcinoma (Bile Duct Cancer)

- CCA is also known as bile duct cancer, and is one of the biliary tract cancers
- CCA is a primary liver cancer and is the second most common primary liver cancer after hepatocellular carcinoma[1]
- Confusingly, the term biliary tract cancer does not refer to CCA alone, but is an umbrella term that includes cancers of the gallbladder and those of the ampulla of Vater*[2]



Classification of biliary tract cancers.

*Ampulla of Vater is a small opening where the bile duct meets the pancreatic duct as they enter the small intestine

CCA, cholangiocarcinoma

1. Mejia, J.C. & Pasko J. *Surg Clin North Am.* 2020;100(3):535–549; **2.** ESMO 2019. Biliary Tract Cancer. ESMO Patient Guide Series 1–45

Cholangiocarcinoma Subtypes[1]

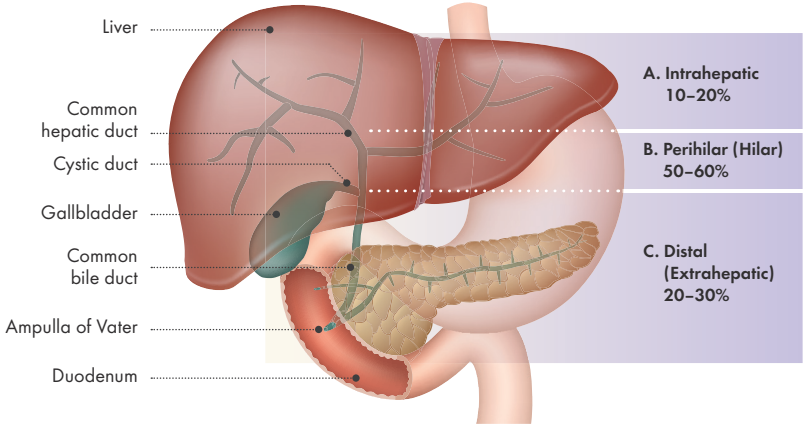
- CCA originates in the bile ducts, and can occur in the ducts inside or outside the liver
- Bile ducts are tubes that carry bile from the liver to the small intestine to aid food digestion and waste product disposal
- Depending on the exact location of the cancer within the bile ducts, CCA is categorised into three distinct subtypes:

A. Intrahepatic – originates in the bile ducts inside the liver

Most common → **B. Perihilar (or hilar)** – originates just outside the liver at the junction of the left and right hepatic ducts

C. Distal/Extrahepatic – originates in the common bile duct outside the liver anywhere from just below the cystic duct

It is crucial to be aware that patients with different subtypes may show differences in symptoms, prognosis, risk factors and diagnosis, as well as treatment strategies



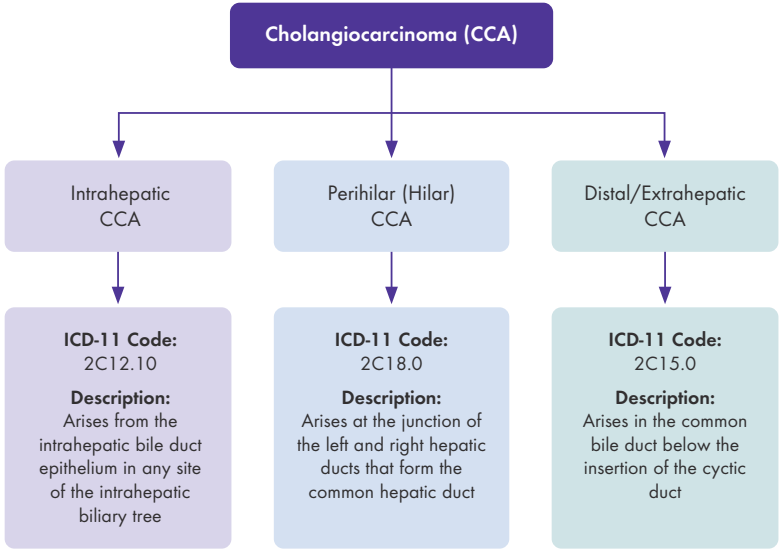
Proportion of cholangiocarcinoma cases attributed to each subtype and their anatomical locations. Illustration adapted from ©AMMF 2022

CCA, cholangiocarcinoma

1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol.* 2020;17, 557–588

Cholangiocarcinoma Subtypes and Miscoding

- Until recently, there was no official WHO classification code to separate perihilar (hilar) CCA from the other subtypes when reported by healthcare professionals (HCPs)[1,2]
- In fact, studies in England and Germany have reported that a substantial number of perihilar CCA cases are miscoded as intrahepatic CCA by HCPs[3,4]
- In January 2022, the WHO published the 11th edition of the International Classification of Disease codes (ICD-11) where, for the first time, a separate code has been assigned to perihilar CCA[1,2]
- ICD-11 will hopefully facilitate the correct subtype coding and recording by HCPs and create more accurate epidemiological data



CCA, cholangiocarcinoma; HCPs, healthcare professionals; ICD-11, International Classification of Disease codes 11th edition; WHO, World Health Organisation

1. Cai, S. & Sivakumar, S. *Hepatobiliary Surg Nutr.* 2022;11, 276–279; **2.** WHO ICD-11. Geneva. License: CC BY-ND 3.0 IGO (2022). Available at: https://icdcdn.who.int/icd11referenceguide/en/html/index.html#copyright-page [Accessed Jul 2023]; **3.** Selvadurai, S. et al. *EJSO.* 2021;*47,* 635–639; **4.** Walter, D. et al. *Liver Inter.* 2019;39, 316–323

Epidemiology

- Evidence from the WHO shows that cases and deaths from CCA have been steadily increasing over the last decades in most Western countries[1]
- Country registry data from England confirm that CCA cases and deaths have almost doubled from 2001 to 2017[2]
- The incidence of CCA varies in different parts of the world. This may be due to regional differences in risk factors and genetic population differences[1]
- Northeast Thailand has the highest number of cases due to the presence of culture-related risk factors that increase the likelihood of developing the disease (e.g., fish infested with liver flatworms)[1]
- In Europe, the incidence is lower than Thailand, with a range of 0.3–4.78 cases per 100,000 people, depending on the country[2,3]
- In most of the Western world, the incidence of intrahepatic CCA seems to be increasing at a faster rate than the extrahepatic subtypes[4] but understanding these trends is not straightforward due to subtype miscoding by healthcare professionals[5,6]

CCA, cholangiocarcinoma; WHO, World Health Organisation

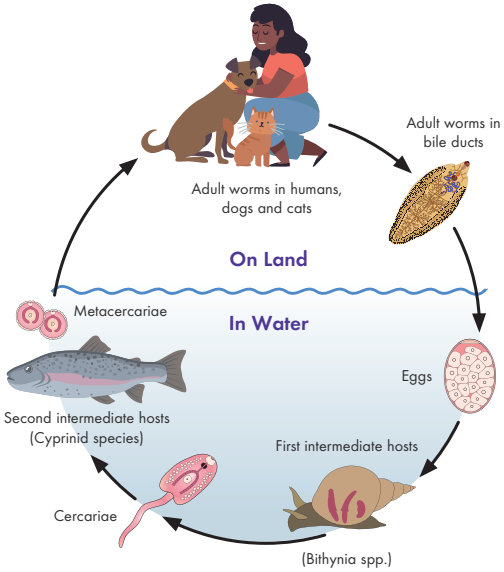
1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol*. 2020;17, 557–588; **2.** Genus, T. et al. ESMO-GI Congress Poster 2019. Available at: https://ammf.org.uk/wp-content/uploads/2020/02/Incidence_Mortality_Poster_ESMO-GI_July_2019.pdf [Accessed Oct 2023]; **3.** Khan, S.A. et al. *Liver Int*. 2019;39 Suppl 1, 19–31; **4.** Vithayathil, M. & Khan, S.A. *J Hepatol*. 2022;77, 1690–1698; **5.** Selvadurai, S. et al. *EJSO*. 2021;47, 635–639; **6.** Walter, D. et al. *Liver Inter*. 2019;39, 316–323

Causes and Risk Factors

- The cause of CCA is still unclear
- A combination of risk factors might contribute to the disease
- The existence of risk factors alone does not mean that someone will develop the disease and conversely people with several risk factors might never develop the disease
- Most cases of CCA occur without an identifiable risk factor, with only 20–50% of them being linked to a known risk factor[1,2]

Liver fluke-related CCA[1,3]

- In **Southeast Asia**, the main risk factor is liver fluke infection (*Opisthorchis viverrini* or *Clonorchis sinensis*)
  - Liver flukes are parasitic flatworms that infest river fish
  - Eating traditional raw fish dishes can carry the fluke inside the body
  - Once in the liver and/or bile ducts the fluke causes severe inflammation that can lead to CCA
  - This risk factor is relevant for people in Southeast Asia due to the locoregional dietary traditions. In Western countries, fluke infestation is very rare



Life cycle of liver fluke infestation that can lead to cholangiocarcinoma[3]

CCA, cholangiocarcinoma

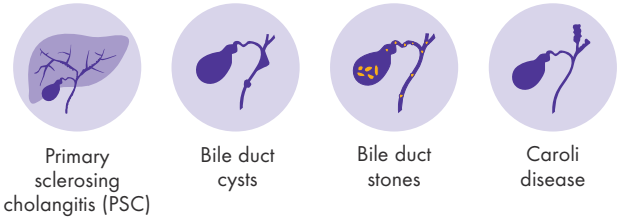
1. Brindley, J.P. et al. *Nat Rev Dis Primers*. 2021;7:1–17; **2.** Khan, S.A. et al. *Liver Int*. 2019;39 Suppl 1, 19–31; **3.** Alsaleh et al. *Int J Gen Med*. 2019;12:13–23

Causes and Risk Factors *(continued)*

Non liver fluke-related CCA[1-7]

- The strongest risk factors identified in the **Western world** are:
  - Primary sclerosing cholangitis (PSC)*
  - Bile duct cysts or stones
  - Caroli disease (genetic disease considered a type of bile cyst)
  - Advanced liver disease (cirrhosis)
  - Hepatitis B/C infections
  - Other general risk factors:
    - Type II diabetes
    - Non-alcoholic fatty liver disease
    - Age >65 years
    - Toxins (e.g., asbestos, printing chemicals [1,2-dichloropropane, dichloromethane])

Risk Factors for CCA



General Risk Factors

*This is a condition that causes long-term inflammation of the bile ducts and leads to bile duct destruction

CCA, cholangiocarcinoma

1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol*. 2020;17, 557–588; **2.** Brindley, J.P. et al. *Nat Rev Dis Primers*. 2021;7:1–17; **3.** Khan, S.A. et al. *Liver Int*. 2019;39 Suppl 1, 19–31; **4.** Izquierdo-Sanchez, L. et al. *J Hepatol*. 2021;76:1109–1121; **5.** Clements, O. et al. J Hepatol. 2020;72:95–103; **6.** Alsaleh et al. *Int J Gen Med*. 2019;12:13–23; **7.** Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol*. 2016;13:261–280

Symptoms[1–4]

- In the early stages, CCA is usually asymptomatic, or the symptoms are non-specific and easily attributable to other conditions
- By the time a patient develops symptoms, the disease may be quite advanced
- In more advanced stages, some **disease-specific** symptoms may also appear, which are caused by the cancer obstructing the bile flow from the liver to the small intestine:

Yellowing of the skin and eyes (jaundice)

Light coloured stools

Darkening of urine

The **non-specific** symptoms that patients may experience include:

Feeling unwell

Fatigue

Nausea

Fever

Unexplained weight loss

Loss of appetite

Abdominal pain (usually right-sided dull pain below the ribs)

Skin itching (pruritis)

CCA, cholangiocarcinoma

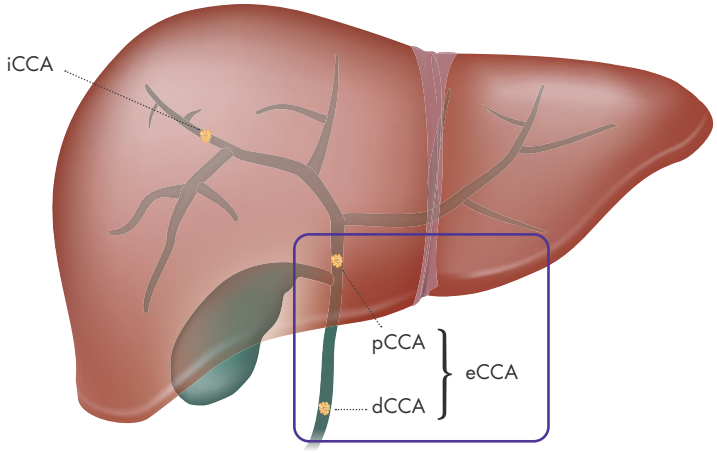
1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol.* 2020;17, 557–588; **2.** ESMO 2019. Biliary Tract Cancer. *ESMO Patient Guide Series* 1–45; **3.** Alsaleh et al. *Int J Gen Med.* 2019;12:13–23; **4.** AMMF. Cholangiocarcinoma symptoms. CCA or bile duct cancer. (2021) Available at: https://ammf.org.uk/symptoms/ [Accessed Jul 2023]

Symptoms *(continued)*

Subtype-specific symptoms[1–4]

Interestingly, some symptoms are more strongly associated with specific CCA subtypes:

- Patients with **distal/extrahepatic or perihilar CCA** usually present with painless jaundice, itchy skin and changes to the colour of their urine and stools
  - This happens because the cancer itself is physically blocking the free flow of bile from the liver to the small intestine, leading to the accumulation of bile in the blood and body tissues, like the skin
- On the contrary, patients with **intrahepatic CCA** more commonly present with abdominal pain and non-specific symptoms (weight loss, generally feeling unwell etc.)



Cholangiocarcinoma subtypes based on their location[5]
eCCA, extrahepatic cholangiocarcinoma; iCCA, intrahepatic cholangiocarcinoma; dCCA, distal cholangiocarcinoma; pCCA, perihilar (or hilar) cholangiocarcinoma

CCA, cholangiocarcinoma

1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol.* 2020;17, 557–588; **2.** ESMO 2019. Biliary Tract Cancer. *ESMO Patient Guide Series* 1–45; **3.** Alsaleh et al. *Int J Gen Med.* 2019;12:13–23; **4.** AMMF. Cholangiocarcinoma symptoms. CCA or bile duct cancer. (2021) Available at: https://ammf.org.uk/symptoms/ [Accessed Jul 2023]

Diagnosis

- CCA is very difficult to diagnose due to:
  - Lack of symptoms or non-specific symptoms in early stages
  - Lack of an accurate diagnostic blood test because of the lack of biomarkers
  - Lack of a simple single test that can diagnose the disease
  - Difficulty to obtain biopsies due to the location of the cancer
- Recent evidence from England, shows that CCA does not only occur in people aged >65 years[1,2]
  - In fact, 22% of patients are diagnosed below the age of 65[1,2]

Step 1. Suspicion of CCA[3]

Healthcare professionals should:

- Obtain full medical history, perform a full physical examination, check for abdominal pain and liver or gallbladder growths
- Perform blood testing to assess liver function and cancer biomarkers (e.g., CA19-9; although not very reliable)
- Do further assessments to identify potential risk factors or underlying disease (e.g., autoimmune bile duct inflammation [cholangitis], primary sclerosing cholangitis [PSC], hepatitis B/C infections, liver disease etc.)

CA 19-9, carbohydrate antigen 19-9; CCA, cholangiocarcinoma

1. Izquierdo-Sanchez, L. et al. *J Hepatol*. 2021;76:1109–1121; **2.** Jose, S. The AMMF CCA Data Project. AMMF 2022 European cholangiocarcinoma conference (2022). Available at: https://www.youtube.com/watch?v=go9EHc22hlk&t=540s [Accessed Jul 2023]; **3.** Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140

Diagnosis – Specialised Tests[1–3]

Step 2. Specialised tests:[1–3]

If Step 1 tests indicate liver/bile duct disease, patients should be referred to have **one or more** of the following specialised tests:

A. Imaging scans – Non-invasive tests to visualise the affected body organs and locate the cancer

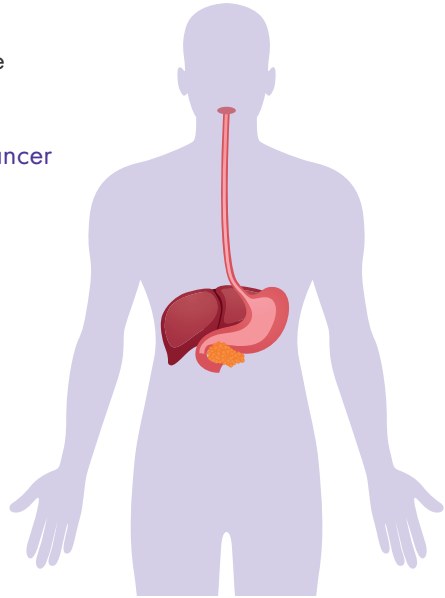
- Ultrasound (US)
- Computed tomography (CT)
- Magnetic resonance imaging (MRI)
  - Magnetic resonance cholangiopancreatography (MRCP)

B. Endoscopy – Requires patient sedation

- Endoscopic ultrasound (EUS)
- Endoscopic retrograde cholangiopancreatography (ERCP)

C. Percutaneous transhepatic cholangiography (PTC) – More invasive and requires patient sedation

D. Liquid biopsy – Technically a blood test (currently under investigation)



1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140; **2.** Khan, S.A. et al. *Gut*. 2012;61(12):1657–1669; **3.** Rizvi, S. et al. *Nat Rev Clin Oncol*. 2018;15, 95–111

Diagnosis – Specialised Tests[1–3] *(continued)*

A. Imaging scans – Non-invasive tests to visualise the affected body organs and locate the cancer

- **Ultrasound (US):**
  - Painless
  - Uses high frequency waves to recreate an image of the scanned organs
  - Performed over the abdominal area

- **Computed tomography (CT)**
  - Painless
  - Uses a series of X-rays taken at various angles to create a 3D image of the scanned organs
  - A contrast dye may be given to help enhance the area being scanned

- **Magnetic resonance imaging (MRI)**
  - Painless
  - Uses magnetic fields and radio waves to create a 3D image of the scanned organs
  - A contrast dye may be given to help enhance the area being scanned
  - Does not involve radiation but may not be possible to perform in all patients (e.g., those with pacemakers)

- **Magnetic resonance cholangiopancreatography (MRCP)**
  - Painless
  - A specialised type of MRI that gives a more detailed image of the bile ducts
  - Usually performed at the same time as the general MRI

3D, three dimensional

1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140; **2.** Khan, S.A. et al. *Gut*. 2012;61(12):1657–1669; **3.** Rizvi, S. et al. *Nat Rev Clin Oncol*. 2018;15, 95–111

Diagnosis – Specialised Tests[1–3] *(continued)*

B. Endoscopy – Uses a long thin tube, called an endoscope, that is inserted inside the patient via body openings (e.g., mouth, nose) and has a light and a video-chip built in. It requires patient sedation. Rare risks include bleeding and intestinal perforation

- **Endoscopic ultrasound (EUS):**
  - The endoscope has an ultrasound probe on it allowing it to recreate images of the organs through sound waves
  - Biopsies can be taken through a small needle at the end of the endoscope (EUS-guided fine needle aspiration [FNA] or fine needle biopsy [FNB])
  - Sometimes FNA and FNB are avoided due to the risk of spreading cancer cells to other organs (seeding)

- **Endoscopic retrograde cholangiopancreatography (ERCP):**
  - The endoscope has a camera on it and can be positioned where the bile duct joins the small intestine. A contrast dye is then injected inside the bile ducts and X-rays are taken to visualise in detail the bile duct network
  - A biopsy or cells from the bile ducts can also be obtained
  - Small mesh tubes, called stents can be inserted and left in position to hold open narrowed bile ducts and relieve symptoms, like jaundice
  - Post ERCP: cholangitis, pancreatitis, cystic duct obstruction and cholecystitis are potential risks[4]

1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140; **2.** Khan, S.A. et al. *Gut*. 2012;61(12):1657–1669; **3.** Rizvi, S. et al. *Nat Rev Clin Oncol*. 2018;15, 95–111;
4. Fugazza, A. et al. *Dig Liver Dis*. 2022;54(4):529–536

Diagnosis – Specialised Tests[1–3] *(continued)*

C. Percutaneous transhepatic cholangiography (PTC) – More invasive and requires patient sedation

- This test is performed if ERCP is not appropriate
- A long thin needle is inserted through the skin into the liver and bile ducts under careful ultrasound and X-ray guidance
- A contrast dye is injected into the bile duct and X-rays are taken to visualise the area
- Biopsies can be taken
- Small mesh tubes, called stents can be inserted and left in position to hold open narrowed bile ducts and relieve symptoms, like jaundice

D. Liquid biopsy – Technically a blood test (currently under investigation)

- This test is basically a blood test that can detect cancer DNA in the bloodstream
- It is currently being studied in the ACCESS program in England[4], as a potential diagnostic tool for CCA
- If effective, it has the potential to revolutionise CCA diagnosis

Even with all these specialised tests, it may not be possible to definitively diagnose cholangiocarcinoma, unless a biopsy is taken and sent to the lab for histology. Biopsies can be taken during an ERCP, an EUS or PTC.

DNA, deoxyribonucleic acid; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; PTC, percutaneous transhepatic cholangiography

1. Vogel, A. et al. Ann Oncol. 2023;34(2):127–140; **2.** Khan, S.A. et al. *Gut.* 2012;61(12):1657–1669; **3.** Rizvi, S. et al. *Nat Rev Clin Oncol.* 2018;15, 95–111; **4.** Starling, N. AMMF 2023 European Cholangiocarcinoma Conference (2023). Available at: https://www.youtube.com/watch?v=qOOxnuOaFpw&list=PLkQcVvFGf0xA5_IYUe5_ohR3LcVA4s5RP&index=31 [Accessed Jul 2023]

Cholangiocarcinoma Staging

- Once CCA is diagnosed, the stage and extent of the cancer needs to be ascertained
- This will help determine the most appropriate treatment options for the patient
- To stage CCA, the following may be needed:[1]
  - CT of the chest and pelvis (to assess for cancer spread)
  - CT of the abdomen (patients might have already done this as part of their diagnostic work-up)
  - MRI of the abdomen and MRCP (patients might have already done this as part of their diagnostic work-up)
- Currently, the most commonly-used staging system for CCA is the **TNM system**, whereby:[1,2]
  - **T** describes the size of the original **tumour**
  - **N** describes whether the cancer has spread to the lymph **nodes**
  - **M** describes whether the cancer has **metastasised** (spread) from its original location to distant body areas
- For **perihilar CCA**, in addition to the TNM, another staging step is usually performed:[1]
  - The **Bismuth-Corlette classification** => this provides a description of the exact location of the perihilar cancer along the bile duct system

CCA, cholangiocarcinoma; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging

1. Banales, J.M. et al. *Nat Rev Gastroenterol Hepatol.* 2020;17, 557–588; **2.** Vogel, A. et al. *Ann Oncol.* 2023;34(2):127–140

Molecular Profiling[1]

- No two cancers are the same, even within the same CCA subtype
- That is because each cancer expresses different genes and proteins, which make up its unique molecular profile
- This molecular profile can be identified in the lab from a biopsy, in a process known as molecular profiling or genetic/genomic testing
- Currently, it is not available for all patients but is used in clinical trials
- It might take several weeks to get the results, so early testing should be planned
- This is a new and exciting field in CCA research that will hopefully allow patients to receive a more personalised treatment plan depending on the molecular profile of their cancer

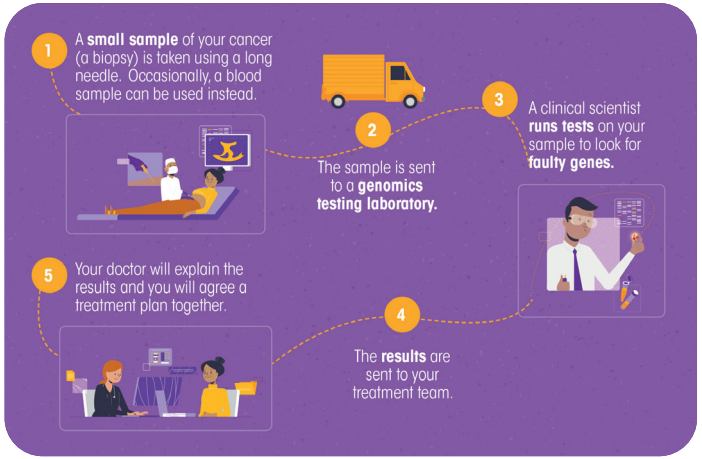


Illustration from AMMF & Incyte Biosciences 2022[1]

FOR MORE INFORMATION CLICK HERE FOR AMMF'S VIDEO AND BOOKLET

CCA, cholangiocarcinoma

1. AMMF & Incyte Biosciences. 2022. Available at: https://ammf.org.uk/wp-content/uploads/2023/07/Molecular-Profiling.pdf [Accessed Jul 2023]

Treatment Options

- Treatment decisions for patients with CCA will depend on the position and stage of the cancer, the subtype, the country in which the patient resides and their medical team
- To date, the only potentially curative treatment is surgery[1]
- However, recent data from the European CCA Network have reported that only 20–30% of patients can undergo surgery with the majority (70–80%) being inoperable, limiting their options to chemotherapy and/or clinical trials[2]
- Also, there is a high risk of the cancer coming back (recurrence) after apparent complete surgical removal[1]
- Currently treatment options for CCA, include:

A. Surgery
- **Post surgery adjuvant therapies**
- **Post surgery radiation or ablation**

B. Chemotherapy

C. Targeted therapies
- **Molecular profiling**

D. Immunotherapies

E. Liver transplantation

CCA, cholangiocarcinoma

1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140; **2.** European Cholangiocarcinoma Network. Available at: https://eurocholangionet.eu/ [Accessed Jul 2023]

Treatment Options *(continued)*

A. Surgery[1] – Depending on the stage and location of the cancer, various surgical options are available:

- Removal of affected bile ducts
- Partial liver removal
- Bypassing of blocked bile ducts (if cancer removal is not possible)
- Whipple procedure (removal of bile ducts, pancreas, gallbladder, local lymph nodes, parts of the stomach and small intestine, as affected)

A1. Post surgery adjuvant therapies[2,3]

- Chemotherapy with capecitabine is recommended as it reduces the risk of recurrence after surgery and improves patient survival (BILCAP study)[2]

A2. Post surgery radiation or ablation[1]

- Local radiation or ablation might be considered to reduce cancer recurrence but the data supporting these are currently limited

B. Chemotherapy[1,3] – Patients with advanced stage CCA where surgery is not possible

- **First line:** cisplatin and gemcitabine (CisGem; ABC-02 study)[4]
- **Second line:** folinic acid, fluorouracil and oxaliplatin (FOLFOX; ABC-06 study)[5] if patients progress after first line

CCA, cholangiocarcinoma

1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140; **2.** Primrose, J.N. et al. *Lancet Oncol.* 2019;20, 663–673; **3.** Vithayathil, M. et al. *J Hepatol*. 2021;75, 981–983; **4.** Valle, J. et al. *NEJM*. 2010;362:1273–1281; **5.** Lamarca, A. et al. *JCO*. 2019;37:15_suppl, 4003

Treatment Options *(continued)*

C. Targeted therapies – Molecular profiling

- A targeted therapy is a treatment that 'targets' a specific mutation or fusion, within a cancer, which has been found through molecular profiling
- Molecular profiling is the classification of the cancer based on the genes and proteins it expresses
- Molecular profiling can be used to decide which treatments the cancer is likely to respond to
- **Pemigatinib** is the first approved targeted therapy for CCA in Europe, USA, Scotland and England (it targets the gene fusion *FGFR2*)[1-3]

D. Immunotherapies – Use the immune system to fight cancer by helping it recognise and attack cancer cells

- Addition of the immunotherapy durvalumab to standard chemotherapy (CisGem) increases the survival of patients with advanced CCA (TOPAZ-1 study)[4]

E. Liver transplantation[5]

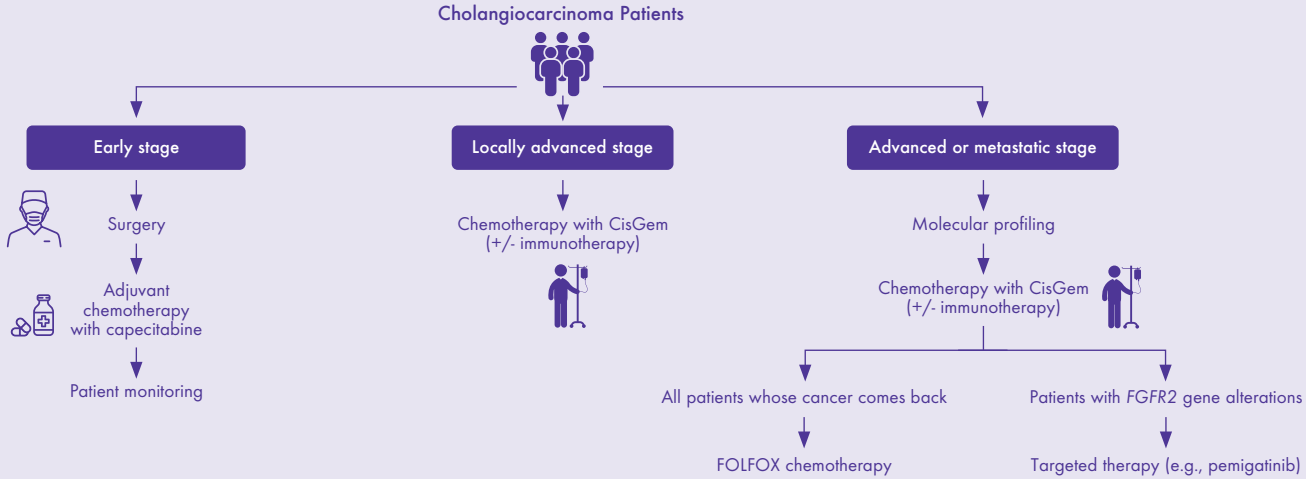
- This is established in some centres, mainly in USA
- Some European centres are starting to consider it for early CCA
- Now available in the UK in some limited circumstances[6]

CCA, cholangiocarcinoma; CisGem, cisplatin and gemcitabine; FGFR2, fibroblast growth factor receptor 2; USA, United States of America

1. AMMF. Pemigatinib. Available at: https://ammf.org.uk/?s=pemigatinib [Accessed Aug 2023]; **2.** EMA. Pemazyre. 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/pemazyre [Accessed Jul 2023]; **3.** SMC. Pemigatinib. 2022. Available at: https://tinyurl.com/3t8bsp3j [Accessed Jul 2023]; **4.** Oh, D.-Y. et al. *NEJM Evidence*. 2022;1(8); **5.** Khan, S.A. AMMF 2022 European Cholangiocarcinoma Conference (2022). Available at: https://tinyurl.com/2kret6zp [Accessed Jul 2023]; **6.** Hakeem, R.A. et al. *Hepatoma Res*. 2023;9:38.

Treatment Options *(continued)*

Simplified treatment decision pathway based on the 2022 ESMO guidelines[1]



CisGem, cisplatin and gemcitabine; FGFR2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin

1. Vogel, A. et al. *Ann Oncol*. 2023;34(2):127–140

Nutrition for the Cholangiocarcinoma Patient

- CCA itself, and the treatments for it, can lead to various symptoms that affect the nutritional status of patients, by causing:[1]
  - Lethargy and reduced appetite
  - Sore dry mouth
  - Nausea and vomiting
  - Abdominal pains
  - Diarrhoea
  - Taste changes
- Evidence indicates that malnutrition can negatively affect patient outcomes, with regards to their tolerance and response to treatment, their prognosis and overall quality of life[1]
- More than half of patients with CCA will develop ongoing muscle loss, making it difficult or even impossible for them to carry out their daily tasks[1]
- Thus, suitable nutrition is key and ideally **patients** should work closely with their **doctor** and a **specialist dietician** to devise an appropriate treatment and nutritional plan
- Depending on the type of treatment for CCA, patients will have different nutritional needs to be considered and managed

CCA, cholangiocarcinoma

1. O'Connor, G. AMMF's Virtual 2021 European Cholangiocarcinoma Conference (2021). Available at: https://www.youtube.com/watch?v=Ey5381ei76o&t=7s [Accessed Jul 2023]

Key Nutritional Considerations After Surgery[1]

Whipple procedure and pancreatic replacement therapy (PERT)

- Patients undergoing the Whipple procedure will have many body parts that aid in food digestion/absorption removed
- It is a complex and intense surgery that can lead to weight loss, diarrhoea, nausea, poor appetite and abdominal pain
- Patients may need PERT, depending on the extent of pancreas removal
- PERT replaces the enzymes that would normally be produced by the pancreas to digest food
- Patients might also need diabetes treatment (insulin), depending on the extent of pancreas removal

Bile acid malabsorption (BAM)

- BAM might occur after surgery
- Bile acids are stored in the gallbladder and released into the small intestine when food is ingested to help digestion. Then they are reabsorbed back into the blood and recycled
- With BAM, bile acids are not properly reabsorbed, causing bloating, cramps, wind and pain
- BAM is often underdiagnosed or neglected
- Suitable dietary adjustments (e.g., dietary fat restriction) and medications that can help alleviate symptoms (e.g., bile acid binders, pain relief) are recommended

BAM, bile acid malabsorption; PERT, pancreatic replacement therapy

1. O'Connor, G. AMMF's Virtual 2021 European Cholangiocarcinoma Conference (2021). Available at: https://www.youtube.com/watch?v=Ey5381ei76o&t=7s [Accessed Jul 2023]

Key Nutritional Considerations After Surgery[1] *(continued)*

Small intestinal bacterial overgrowth (SIBO)

- Surgery can make intestinal bacterial grow to excessive numbers, leading to SIBO
- SIBO causes bloating, wind, diarrhoea, weight loss, nutritional deficiencies (e.g., vitamin B12) and fragile bones
- SIBO is also underdiagnosed and often mistaken for inflammatory bowel syndrome (IBS)
- Treatment for SIBO includes antibiotics and suitable dietary changes to correct deficiencies and minimise intolerances

SIBO, small intestinal bacterial overgrowth

1. O'Connor, G. AMMF's Virtual 2021 European Cholangiocarcinoma Conference (2021). Available at: https://www.youtube.com/watch?v=Ey5381ei76o&t=7s [Accessed Jul 2023]

Key Nutritional Considerations After Chemotherapy or Radiotherapy[1]

- Patients undergoing chemotherapy or radiotherapy very commonly develop eating problems during and after treatment
- Dietary adjustments in these cases are mainly targeted at making 'every bite count' by fortifying and supplementing the diet but also through practical advice on specific diet changes (e.g., eating foods that are high in protein and energy)
- The 'little and often' approach is recommended with a daily aim of six small meals
- The timings of medications that could alleviate some of the symptoms are also important for maximising food intake (e.g., medication to stop vomiting, nausea, diarrhoea or pain relief)
- SIBO can also occur after chemotherapy or radiotherapy and even months after the treatment is completed

FOR MORE NUTRITIONAL TIPS AND ADVICE FOR CHOLANGIOCARCINOMA CLICK HERE

SIBO, small intestinal bacterial overgrowth

1. O'Connor, G. AMMF's Virtual 2021 European Cholangiocarcinoma Conference (2021). Available at: https://www.youtube.com/watch?v=Ey5381ei76o&t=7s [Accessed Jul 2023]

The Importance of Specialist Centres and Multidisciplinary Teams

- Due to the relative rarity and complexity of CCA, it is essential that patients are referred to specialists so that they can be offered the right treatment and care[1]
- Patients should ideally be treated in specialist centres by a multidisciplinary team (MDT) specialising in diseases of the liver and biliary tract (hepatobiliary services)[1]
- An MDT is a group of doctors and nurses who meet regularly to discuss patient cases and devise the most appropriate treatment plans
- In Europe, access to specialist centres and MDTs varies by country:
  - In **France**, evidence shows that most patients are treated in non-specialist centres that only see 1–2 CCA cases per year[2]
  - In **the Netherlands,** there are now 7 specialist centres. Nationwide data reported significantly longer survival of patients being treated at these specialist centres than those in non-specialist sites[3]
  - Similarly, a study in **Germany** showed that CCA patients are less likely to die if they are being treated in specialist centres[4]
- Currently, CCA expertise is concentrated in a few specialist centres in each European country. Patients do not necessarily live close to such specialist centres, making of high importance the need for improved access to such care

CCA, cholangiocarcinoma

1. Casadio, M. et al. *ESMO Open*. 2022;7,100377; **2.** Neuzillet, C. et al. *Lancet Reg Health Eur*. 2022;15:100324; **3.** Van Keulen, A.M. et al. Liver Inter. 2021;41,1945; **4.** Roderburg, C. et al. *Cancers (Basel)*. 2022;14(16):4038

The Importance of Specialist Centres and Multidisciplinary Teams *(continued)*

- The first European guidelines on how CCA MDTs should run have been recently published by the European Network for the Study of Cholangiocarcinoma (ENS-CCA). These include:[1]
  - Weekly occurrence
  - Mandatory presence of a coordinator
  - All new patient cases to be discussed
  - The mandatory presence of the medical professionals shown here, all of whom should have knowledge of diagnosing and treating CCA
- In addition to the depicted healthcare professionals, ENS-CCA recommends the MDT presence of nurse specialists, dieticians, psychologists, researchers and supportive care specialists to optimise patient care[1]

CCA, cholangiocarcinoma; CNA, certified nursing assistant; ENS-CCA, the European Network for the Study of Cholangiocarcinoma; MDT, multidisciplinary team

1. Casadio, M. et al. *ESMO Open*. 2022;7,100377

Clinical Trials for Cholangiocarcinoma

- Clinical trials have been and continue to be fundamental in improving patient outcomes
- European patients and patient organisations can access these registries for clinical trial availability and information:
  - **ClinicalTrials.gov**
  - **EU Clinical Trials Register**
  - **ISRCTN Registry**
  - **The German Register of Clinical Trials** (Germany only)
  - **The Netherlands Trial Register** (The Netherlands only – currently in the making)
  - A list of the current CCA trials in England have been collated by AMMF **here** and a list of those across Europe is provided by Orphanet **here**

CCA, cholangiocarcinoma

Clinical Trials for Cholangiocarcinoma *(continued)*

- The table below explains what each clinical trial 'phase' investigates and the differences between them

How does a clinical trial work?		
Phase	**Usual number of patients**	**Question**
1	<20 (small study)	Is drug A **safe**?
1b	<20 (small study)	Are drugs A & B **safe when given together**?
2 (single-arm)	<100 (small study)	Does drug A **work**?
2 (randomised)	<100 (small study)	Does drug A **work well enough to progress further**?
3	100-1000 (large study)	Does drug **A work better than the current best drug**?

CCA, cholangiocarcinoma

Fundamental Clinical Trials for Cholangiocarcinoma

- The fundamental clinical trials that have shaped the treatment landscape of CCA are the ABC clinical trials conducted in England and the ones shown below
- Prior to those, there were no reliable, large-scale clinical trials and no standard chemotherapy treatments

Pivotal clinical trials	Outcomes
ABC-01 (phase I/II)[1] & **ABC-02** (phase III)[2]	Established CisGem as first line chemotherapy treatment
ABC-06 (phase III)[3]	Established FOLFOX as second line chemotherapy
BILCAP (phase III)[4]	Established adjuvant chemotherapy with capecitabine following surgery
FIGHT-202 (phase II)[5]	Approval of the first targeted therapy, pemigatinib, for those with *FGFR-2* fusion

CCA, cholangiocarcinoma; CisGem, cisplatin and gemcitabine; FGFR-2, fibroblast growth factor receptor 2; FOLFOX, folinic acid, fluorouracil and oxaliplatin

1. Valle J. et al. *Br J Cancer*. 2009;101:621–627; **2.** Valle, J. et al. *NEJM*. 2010;362:1273–1281; **3.** Lamarca, A. et al. *JCO*. 2019;37:15_suppl, 4003; **4.** Primrose, J.N. et al. *Lancet Oncol. 2019*;20, 663–673; **5.** Ghassan, K.A et al. *Lancet Oncol*. 2020;21(5):671–684

Patient Perspectives and Engagement

- Engaging with patients and their families is a critical component of high-quality healthcare
- Engaged patients are more informed and better able to make decisions about their treatment and care
- Systematic efforts from patient organisations are needed to educate both patients and healthcare professionals on the importance of actively involving patients in their care planning and decision making
- Patient survey results have shown that those with CCA can feel distanced and confused by the decision making processes that occur at the multidisciplinary team meetings, and communication with their treating doctor can be poor[1]
- When reading through patient experiences, it is apparent that many feel the need to research their own disease and treatments to self-advocate and request a second and third medical opinion
- Patient perspective engagement is essential to gain a deeper understanding of the experiences and needs of individuals with CCA. By actively listening to patients and advocating for their wishes, we can truly be their voice and improve the support and care they receive

CCA, cholangiocarcinoma

1. Morement, H. et al. *Int J Gen Med*. 2017;10:305

Patient Advocacy and Cholangiocarcinoma-focused Organisations

AMMF is the world's first charity dedicated solely to CCA and remains the UK's only CCA charity. AMMF provides information and support to those who need it and encourages research to improve the diagnosis and treatment of CCA. AMMF's website provides a wealth of information on all areas of CCA. There is a growing number of useful resources, some available in multiple European languages.
Moreover, the **AMMF European Cholangiocarcinoma website** provides resources and information for patients and carers across Europe, in eight languages.

APiC is a patient organisation, based in Italy, dedicated to raising awareness and enabling research in CCA, as well as supporting patients and their families through their diagnosis and therapy.

CCA, cholangiocarcinoma

Patient Advocacy and Cholangiocarcinoma-focused Organisations *(continued)*

The **Global Cholangiocarcinoma Alliance** (GCA) has a highly experienced global Steering Committee who meet regularly to guide the initiative. Their aim is to champion international collaborations and partnerships within the CCA community and to establish a global voice for CCA.

Cholangiocarcinoma UK is a multidisciplinary group of clinicians, researchers and patient advocates that aims to facilitate collaborative research, improve services for patients, and raise CCA awareness.

The European Society for Medical Oncology (ESMO) has created a useful **patient guide** on biliary tract cancer, which includes CCA. The guide runs through symptoms, causes, diagnosis, treatment, clinical trials, side effects from treatments and support groups. The patient guide is also available in Italian and Greek.

CCA, cholangiocarcinoma

Patient Advocacy and Cholangiocarcinoma-focused Organisations *(continued)*

Cholangiocarcinoma-EU is a website for European and English residents created by Incyte to support patients with CCA and their carers. There are multiple educational resources that can be found **here**. The website and the resources are also available in French **here**. The equivalent website for healthcare professionals is also available **here** in English, French, German and Italian.

The European Network for the Study of Cholangiocarcinoma (ENS-CCA) is a network of researchers from 13 European countries that aim to better understand the biological mechanisms involved in the development and onset of CCA. Using basic, translational and clinical research, they hope to identify potential new treatments for CCA.

CCA, cholangiocarcinoma

The Unmet Needs of Cholangiocarcinoma

- CCA is a complex and aggressive cancer with increasing global prevalence
- Challenges faced by patients include difficulties in early diagnosis, limited treatment options, and poor prognosis
- Early diagnosis is hindered by the asymptomatic or non-specific nature of the disease in early stages
- Lack of non-invasive biomarkers further complicates early disease detection
- There is limited understanding of CCA's underlying disease mechanism, with experimental models failing to fully capture its complexity and thus impeding treatment development
- Obtaining robust epidemiological subtype data has been hindered by the previous lack of proper classification codes and miscoding incidences. It is paramount that healthcare professionals are made aware of and follow the new ICD-11 classification
- Continued research and clinical trials are essential to better understand CCA and develop new treatments and supportive care strategies that can improve patient longevity and quality of life

CCA, cholangiocarcinoma

The Future of Cholangiocarcinoma

- Future CCA treatment areas of interest include liver transplantation, targeted therapies for specific mutations, and immunotherapies
- Targeted therapies based on molecular profiling offer promise for a personalised treatment approach tailored to each patient's cancer characteristics and genetic differences
- Molecular profiling should be carried out for all patients after diagnosis to identify appropriate treatment or clinical trial enrolment opportunities
- Advancements in understanding CCA's underlying mechanisms are also needed in order to develop new diagnostic tools and treatments to improve patient lives
- For the above to happen, and for tackling CCA, strong collaborations among patient organisations, researchers, clinicians, and patients are vital
- Patient organisations play a key role in establishing such collaborative networks and are essential for growing the global CCA voice and fueling novel research and clinical trials worldwide

CCA, cholangiocarcinoma

About AMMF

- Founded in 2002, AMMF was the world's first charity dedicated solely to CCA. Today, AMMF remains the UK's only CCA charity, extending its reach nationally and across Europe, while fostering global collaborations
- AMMF provides information and support to those who need it, runs campaigns to raise awareness of this devastating disease, and encourages and supports specialised research teams in their work towards better diagnostic techniques and treatments and, ultimately, a cure

AMMF VISION:

- A world where CCA no longer poses a life-threatening risk, granting people the freedom to live their lives

AMMF MISSION:

- Enhancing the lives of CCA patients by facilitating the exchange of knowledge within the research community and amongst affected families worldwide

AMMF OBJECTIVES:

- Elevate CCA awareness among medical professionals, researchers, and those impacted by the disease
- Provide information to those who need it, either individually or via the website
- Encourage and support research, particularly focused on early detection methods and effective therapies
- Advocate for patients' perspectives in national and global forums
- Operate efficiently, deliver exceptional services, and be adequately and sustainably resourced

CCA, cholangiocarcinoma

Thank you

AMMF
THE CHOLANGIOCARCINOMA CHARITY

www.ammf.org.uk www.ammf-eu.org

AstraZeneca Incyte SOLVE ON. TAIHO ONCOLOGY SERVIER moved by you Jazz Pharmaceuticals