INTRODUCTION TO CHOLANGIOCARCINOMA

An Educational Resource for Patient Organisations

November 2023

AMMF

THE CHOLANGIOCARCINOMA CHARITY

Contents

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About this AMMF Cholangiocarcinoma Educational Resource

This educational resource has been developed by AMMF, the UK's only cholangiocarcinoma charity, with the aim of providing an informative, accurate and full overview of cholangiocarcinoma (CCA) for patient organisations and health care professionals who might need further familiarisation with the disease. The information provided here relies on the most current and evidence-based understanding of CCA, its epidemiology, prognosis, treatment, diagnostic options and patient perspectives.

Despite the latest advances in CCA research, the prognosis of patients with CCA remains poor and unchanged over the last decade.[1] This, together with the global rise in CCA cases and mortality,[1] prompts the urgent need to enable more research to find new treatments and better diagnostic tools. Here, we further highlight several unmet needs that currently exist for patients with CCA. This is done to provide the evidence needed to influence stakeholders towards advancing the science behind CCA and improving patient outcomes.

The information included in this document is not intended to provide treatment or diagnostic guidelines for CCA and it is primarily addressed to those based in the UK and Europe.

This educational resource was developed by AMMF with the kind support of AstraZeneca, Incyte, Taiho Oncology, Servier and Jazz Pharmaceuticals. Please note, the supporters had no editorial control over content in this resource. It has been endorsed by the following CCA experts who are members of AMMF's CCA Medical/Clinical Advisory Board: Professor Juan Valle, Professor John Bridgewater, Mr. Hassan Malik, Professor Shahid A. Khan and Dr. Christopher Wadsworth.

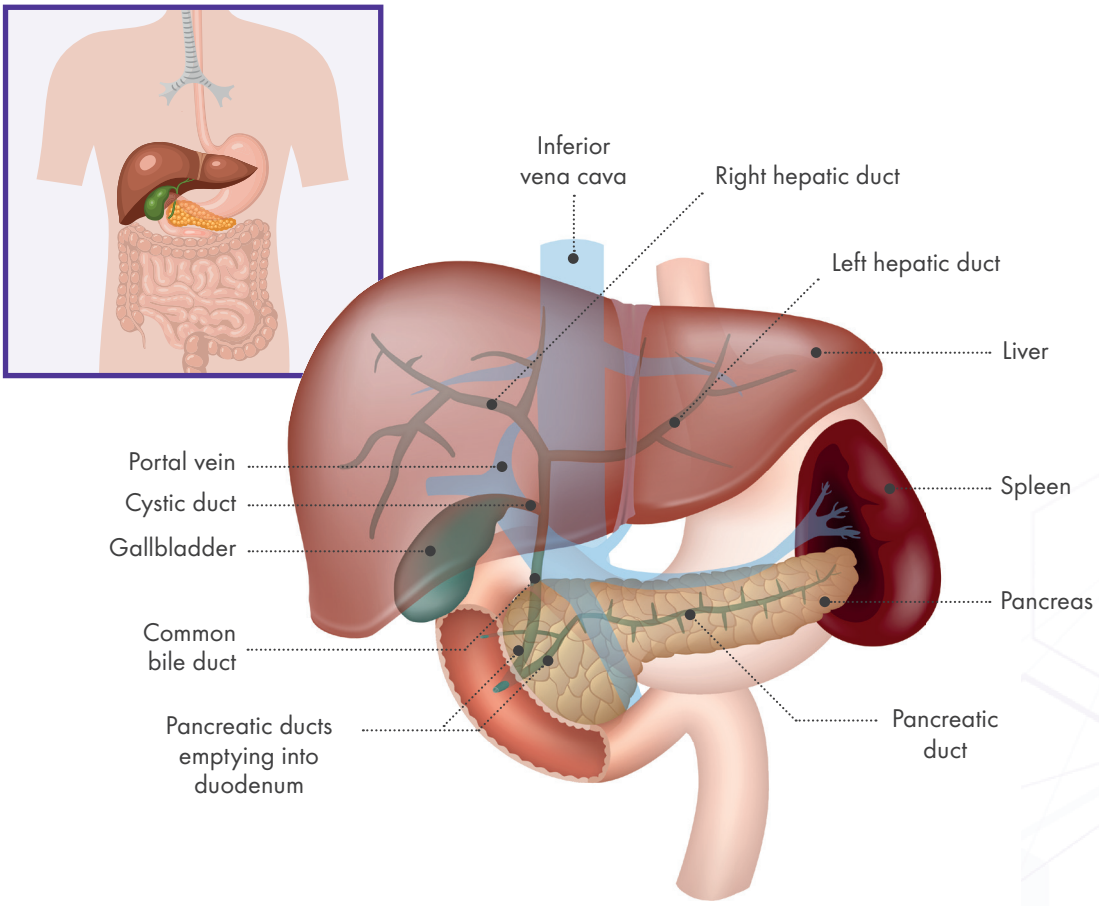


Figure 1. *The biliary system. Illustration © AMMF 2023.*

1 Cholangiocarcinoma Overview

Cholangiocarcinoma (CCA), also referred to as bile duct cancer, is considered a relatively rare cancer that originates in the bile ducts, and can occur in the ducts inside or outside of the liver (see **Figure 1**, see **Section 3**). CCA is a primary liver cancer and is the second most common primary liver cancer after hepatocellular carcinoma.[2] In England alone, approximately 30,000 cases of CCA were reported between 2001–2017.[3] It wasn't until recently that the first and, so far, exclusively pan-European CCA clinical registry was created by the European Network for the Study of CCA (ENS-CCA; 2016). The registry now holds data from more than 2,200 patients with CCA from 11 countries and 26 medical centres.[4] However, it is important to note that the registry includes data from the larger centres and may not be representative of the 'real' CCA experience of most patients/hospitals. ENS-CCA have also recently published the largest observational CCA study to date (February 2022), in which they provide, for the first time, a pan-European overview of the features and management of CCA.[4]

CCA has a very aggressive nature and is difficult to treat.[1] Moreover, the incidence and death rates for CCA have been steadily increasing over the last decades, globally (see **Section 4**).[5–7] The exact causes of CCA remain unclear and it is likely that a combination of different risk factors contribute to the disease. Long term liver damage from any cause increases the risk of CCA. Nevertheless, in the majority of patients no risk factors can be identified (see **Section 5**).[5] CCA causes few or no noticeable symptoms in its early stages, and those there are can usually be non-specific (see **Section 6**).[1,8] As a result, CCA is usually diagnosed late, in advanced stages, when therapeutic options are limited and compromised (see **Sections 7–9**). All that, along with the aggressive nature of the cancer and its potential to resist some current chemotherapy treatments, leads to a poor prognosis. To date, patients with advanced disease who are not eligible for surgery (the only potentially curative option so far) have a median of 11.5–13.0 months to live[1,9,10] and 80–95% of patients will die within 5 years of their diagnosis.[1,7]

The difficulty of an early diagnosis along with the globally rising incidence, poor patient prognosis and limited treatment options, highlight significant unmet needs for patients with CCA, that need to be urgently addressed (see **Section 12**).

Primary and Secondary Liver Cancers

Primary liver cancers are those that originate in the liver or in the bile ducts:

- Hepatocellular carcinoma (HCC) – originates in the liver
- Cholangiocarcinoma (CCA) – originates in the bile ducts inside or outside the liver

Secondary, or metastatic, liver cancers are those that have spread to the liver from primary cancers in other organs of the body.

2 Biliary Tract Cancer

The term biliary tract cancer is frequently used when referring to CCA. However, it should be noted that biliary tract cancer is actually an umbrella term which includes all those cancers occurring in the biliary tract – CCA, gallbladder and ampullary cancer (**Figure 2**).[8] It is important to be aware of this when searching in the wider literature for CCA-specific information.

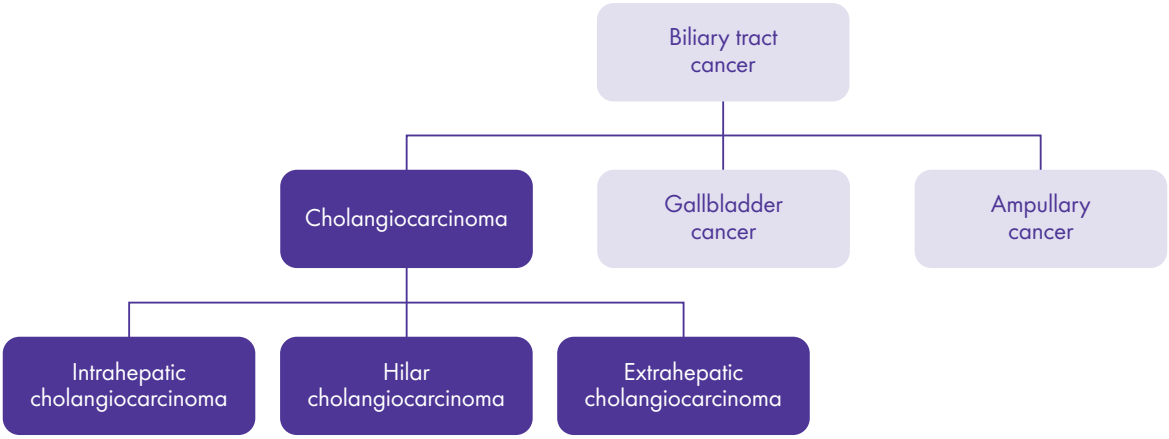


Figure 2. *Classification of biliary tract cancers.*

Gallbladder cancer develops in the gallbladder and, similar to CCA, is an aggressive cancer that is difficult to diagnose early.[11] Ampullary cancer develops in a part of the body called the ampulla of Vater, which is a small opening where the bile duct meets the pancreatic duct as they enter the small intestine. It is the rarest of all three cancers.[8] Interestingly, recent evidence from the UK shows that deaths due to CCA have been steadily increasing over the last 17 years (2001–2017), unlike deaths from gallbladder and ampullary cancers which remained stable.[3,12] This further indicates the importance of raising awareness and improving the research on CCA.

CCA is categorised into three distinct subtypes, which are further explained in the section that follows.

3 Understanding Cholangiocarcinoma and its Subtypes

CCA originates in the bile ducts of the liver, also known as the biliary tract (tree or system). Bile ducts are tubes that carry bile from the liver to the small intestine to aid food digestion and waste product disposal (**Figure 3**). CCA can grow anywhere in this complex network of bile ducts, both inside and outside the liver and, based on the location of origin, it is categorised into three main subtypes:[1,5]

- **Intrahepatic CCA** – This type originates in the bile ducts that are located inside the liver and accounts for 10–20% of the total CCA cases (**Figure 3A**).
- **Perihilar (or Hilar) CCA** – This type originates at the junction of two main ducts, the left and right hepatic ducts. This is the most common CCA subtype, accounting for 50–60% of all cases (**Figure 3B**).
- **Distal/Extrahepatic CCA** – This type originates in the common bile duct outside the liver anywhere from just below the cystic duct, which joins the common bile duct and the gallbladder, down to the small intestine. The common bile duct carries bile from the liver and the gallbladder down to the small intestine. This type accounts for 20–30% of CCA cases (**Figure 3C**).

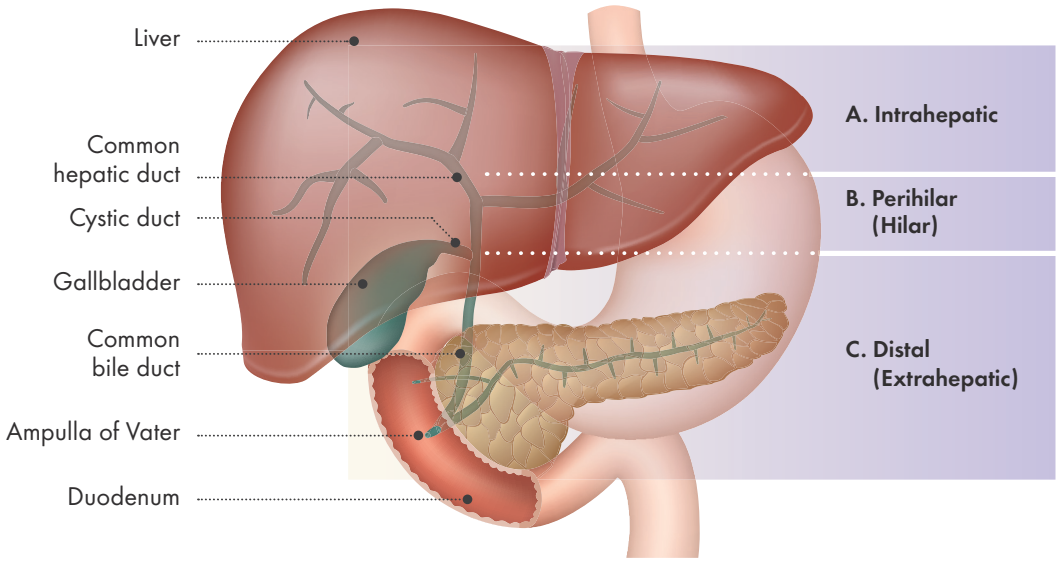


Figure 3. *Schematic of the liver and biliary tract indicating the three main CCA subtypes. CCA can grow anywhere in the bile ducts. Depending on the location of its origin, there are three main CCA subtypes (A) Intrahepatic, (B) Perihilar (or Hilar) and (C) Distal/Extrahepatic. Adapted from ©AMMF 2022.*

In many studies,[13] the perihilar and distal CCA subtypes together are referred to as extrahepatic CCA.

It is crucial for patient organisations and health care professionals to be aware of these subtypes, as patients with different CCA subtypes will show differences in symptoms, prognosis, risk factors and diagnosis, as well as treatment strategies.[1] These differences are explored further under the purple tab entitled 'subtype-specific information' in each of the corresponding sections that follow.

It should be noted that 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, so the three subtypes of CCA are now identifiable: intrahepatic CCA, perihilar CCA and distal/extrahepatic CCA.[14,15] (see **Appendix 1**). This will hopefully facilitate the correct disease coding and recording by health care professionals and create more accurate epidemiological data, as discussed in the section that follows.

4 Epidemiology

The incidence of CCA varies considerably depending on the geographical region (see **Appendix 2**), with Northeast Thailand having the highest number of cases.[1] This is explained by the presence of local, culture-related risk factors which increase the likelihood of developing the disease (see **Section 5**).

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.[5,16] The highest, most recent mortality in Europe has been reported for Ireland, Malta, Portugal, Spain, UK, Belgium, Austria, Germany, Hungary and Lithuania (age-standardised mortality rate >1.5 per 100,000 person-years; data from 2018 for both genders and for all CCA subtypes).[6] In England alone, 2,706 cases of CCA were reported in 2020 and the country's latest incidence rate has been reported as 4.785 per 100,000.[16]

Despite the relatively low case rate of CCA in Europe, evidence from WHO shows that cases and deaths from CCA have been steadily increasing over the last decades in most Western countries.[1] In England, additional data from the country's registry confirm that CCA cases and deaths have almost doubled from 2001 to 2017.[12] Similarly, information from the Dutch health registry show that CCA cases have been exponentially increasing in the last decade.[17,18] Moreover, many experts in the field believe that the true incidence of CCA is much higher, as many primary liver cancers that are classified 'of unknown primary (origin)' could be CCA. In fact, there is recent evidence from England to suggest that this is true for almost one third of those unclassified cancer cases who also show disease in the liver.[19] Thus, epidemiological data need to be interpreted with caution until we can be sure that CCA and its subtypes are properly classified by health care professionals universally.

Subtype-specific information

Recent evidence indicates that deaths from intrahepatic CCA are rising faster than those from extrahepatic CCA (perihilar and distal/extrahepatic) in the majority of Western countries, including England, Germany and France.[6,12,20,21] Unfortunately, information on the incidence of CCA subtypes is currently not fully reliable because until January 2022 and ICD-11 there was no official ICD code to separate perihilar from distal/extrahepatic CCA, leading to miscoding of subtypes. In fact, a recent study in England showed that approximately one third of CCA cases coded by health care professionals as intrahepatic, were actually perihilar CCA.[13] Exactly the same misclassification issue has also been reported in Germany.[20] Future epidemiological studies are needed with the new classification codes adopted universally, in order to correctly examine the trends in CCA subtypes.

5 Causes and Risk Factors

Despite the global rise in cases, what causes CCA remains unclear. Evidence suggests that a combination of risk factors might contribute to the disease. Nevertheless, the existence of a risk factor alone does not necessarily mean that someone will develop the disease. Many people might have several risk factors and never develop the disease, and others with no risk factors might do so.

To date, we know that most cases, particularly in the Western world, are sporadic, meaning that they occur without a known cause or identifiable risk factor.[1,5] Approximately 20–50% of CCA cases can be linked to one of the known risk factors explained below.

A common feature of most identified CCA risk factors is that they cause long-term inflammation of the bile ducts (cholangitis) and/or impaired bile flow (cholestasis).[1]

The strongest known risk factors in the **Western world** are:[1,4,5,7,22-24]

- **Primary sclerosing cholangitis (PSC)** – a condition that causes long-term inflammation of the bile ducts that in turn leads to the formation of scar tissue and bile duct destruction.
- **Bile duct cysts** – a rare congenital condition where fluid- or bile-filled sacs form in the bile ducts. These can obstruct bile flow leading to bile duct enlargement, infections, inflammation and tissue damage.
- **Caroli disease** – also considered as a type of bile duct cyst, is a rare genetic disorder where the bile ducts inside the liver are abnormally wide (dilated). This can lead to bile duct stone formation and abnormalities in bile flow.[25]
- **Bile duct stones** – stones formed anywhere in the network of bile ducts causing irritation of the lining of the ducts, leading to inflammation and tissue damage.
- **Liver cirrhosis (scarring)** – advanced liver disease (which may be due to a number of causes, such as excess alcohol consumption, damage from viral infections etc.) leads to scarring and damage of the liver and surrounding tissues.
- **Hepatitis B or C infection** – long-term infections with hepatitis B or C viruses lead to liver scarring, inflammation and possibly exert a direct cancerous effect on the surrounding tissues.[5]
- **Other general risk factors** – Type II diabetes, non-alcoholic fatty liver disease, being over 65 years of age[26] and toxins, like asbestos[27,28] or exposure to high concentrations of printing chemicals (e.g., 1,2-dichloropropane and dichloromethane) have been shown to increase the risk of CCA.[29] Smoking, alcohol consumption and obesity have also been reported by some studies as potential risk factors for CCA, but the evidence is still inconsistent.[7,22]

The main risk factor in **Southeast Asia** is:

- **Liver fluke infection *(Opisthorchis viverrini or Clonorchis sinensis)*** – Flukes are parasitic flatworms that infest river fish. Eating traditional raw river fish dishes can then carry the fluke into the body. Once in the liver and/or bile ducts, the flukes cause substantial long-term inflammation and irritation which can lead to CCA. This risk factor is mainly relevant for people in Southeast Asian countries, such as Thailand where, because of the diet of the indigenous people, fluke infestation is very common. In Western countries, this is rare.[1,22]

Subtype-specific information

The Western world risk factors mentioned above are shared by all CCA subtypes with some being equally associated with all subtypes and others having a stronger influence over a specific subtype. For example, bile duct cysts, Caroli disease, bile duct stones and PSC[5] seem to incur the same risk for all subtypes.[1,4,5,24] On the contrary, liver cirrhosis (scarring), hepatitis B/C infections, non-alcoholic fatty liver disease, diabetes[7,30] and asbestos exposure[27,28] seem to be more strongly associated with intrahepatic CCA.[1,4,5,24] It is worth noting that risk factors like diabetes and liver cirrhosis (scarring) are globally increasing and may be contributing to the rising intrahepatic CCA cases in Western countries.[7] Nevertheless, due to miscoding of CCA subtypes in the past (see **Section 4**)[13], new long-term, large-scale studies are needed to confirm such effects and to identify new subtype-specific risk factors.

6 Symptoms

In the early stages of the disease, CCA is usually asymptomatic and, by the time a patient develops symptoms, the disease may be quite advanced. As the disease progresses, patients may experience non-specific symptoms that can resemble other conditions, such as:[1,8,22,31-33]


Feeling generally unwell


Nausea


Unexplained weight loss


Fever


Loss of appetite


Fatigue


Abdominal pain
(usually a constant, dull, right-sided pain just below the ribs)


Skin itching
(pruritis)

Apart from the non-specific symptoms mentioned above, when CCA is 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, like: [1,8,22,31-33]


Jaundice
(yellowing of the eyes and skin, although this may be less obvious in people with darker skin types)


Light coloured stools


Darkening of urine

Subtype-specific information

Interestingly, some of the symptoms mentioned above are more strongly associated with specific CCA subtypes. For example, patients with distal/extrahepatic or perihilar CCA usually present with painless jaundice, itchy skin[22] and changes to the colour of their urine and stools.[1,22,31,33] This is because in these subtypes the cancer physically blocks the free flow of bile from the liver to the small intestine and leads to bile accumulation in the blood and body tissues, like the skin. On the contrary, patients with intrahepatic CCA present more commonly with abdominal pain and non-specific symptoms like weight loss and feeling unwell.[1,22,31,33]

7 Diagnosis and Staging

As discussed above, the lack of symptoms in early disease stages and their non-specific nature, and lack of an accurate diagnostic blood test, makes diagnosing CCA difficult. The majority of patients have no family history of liver disease and, although many presenting with symptoms will be over 65 years of age, interestingly, long-term data in England (2001–2017) suggest that CCA does not occur only at an older age, with 22% of patients diagnosed below the age of 65.[4,34]

When a CCA diagnosis is made it is crucial to identify the precise location of the cancer within the biliary tract and thus diagnose the correct subtype, as every subtype requires a specific clinical approach. To date, there isn't one simple test that can definitively diagnose CCA. For that, a combination approach with multiple tests and examinations is needed. This is further described below.

Initially, upon suspicion of CCA or presence of any of the disease symptoms (see **Section 6**), health care professionals should obtain a full medical history, perform a full physical examination, including checking for abdominal pain and potential liver or gallbladder growths. Alongside those, blood testing is usually performed to assess liver function and the level of cancer proteins in the blood, also known as biomarkers.[30] To date, there is no specific biomarker for CCA but the most widely used one is the carbohydrate antigen 19-9 (CA19-9) and sometimes the carcinoembryonic antigen.[4] Neither of these provide reliable results, while CA19-9 can also be elevated in other conditions or may be completely absent in some patients and it is linked to the patient's blood group.[35–37]

To exclude the possibility of autoimmune inflammation of the bile ducts (cholangitis), the levels of the IgG4 protein may also be tested in the blood.[37] Moreover, the existence of any underlying risk factors, like hepatitis B/C infections, non-alcoholic liver disease, PSC or liver cirrhosis should also be examined at this point.[30] This is important as in fact approximately 20–30% of patients with CCA have a history of PSC.[35]

If any of the above testing is indicative of liver and/or biliary tract problems, patients should be referred to have one or more of the following specialised tests. The choice of test will depend on the country that the patient resides in, their medical team and the suspected location of the cancer:[30,37,38]

A. Imaging scans are tests that try to visualise the affected body organs with the aim of locating the cancer. These do not require patient sedation and include:

Ultrasound – This a painless test that uses high frequency sound waves to recreate an image of the scanned organs and is performed over the abdominal area for patients with suspicion of CCA.

Computed tomography (CT) – This is a painless test that uses a series of X-rays taken at various angles to recreate a three-dimensional image of the organs of interest. Before the CT scan, a special dye, a contrast, may be given as a drink or an injection, to help enhance the area being scanned.

Magnetic resonance imaging (MRI) – This is a painless test that is similar to CT but uses magnetic fields and radio waves to recreate a three-dimensional image of the organs of interest. In some cases, a contrast dye is given to enhance the contrast of the image taken. This test does not involve radiation but may not be possible to perform in all patients (e.g., those with pacemakers).

- **Magnetic resonance cholangiopancreatography (MRCP)** – This is a specialised type of MRI that provides more detailed images of the bile ducts and is usually performed at the same time as a general abdominal MRI.

B. Endoscopy makes use of an endoscope. This is a long, thin tube that can be inserted inside a patient via body openings (e.g., the mouth). This tube has a light source and video-chip built into its tip. An ultrasound probe can be attached to the endoscope, and other tools such as a needle or stent can be introduced down a channel through the endoscope. For patients with suspected liver and biliary tract disease, the endoscope is inserted down the throat to reach the common bile duct at the level of the small intestine. Endoscopic techniques are more invasive than the imaging scans mentioned above and require patient sedation. Although safe, they carry more risks than external scans such as CT and MRI. Rare risks include bleeding and causing a perforation (hole) inside the patient. These endoscopic techniques include: [30,37,38]

- **Endoscopic ultrasound (EUS)** – The endoscope also has a small ultrasound probe on it allowing it to produce an image of the organ in question with the use of sound waves. The operator can introduce a small needle through the endoscope that can be used to take biopsies (a small amount of tissue) from abnormal areas. This process is called EUS-guided fine needle aspiration or fine needle biopsy. Sometimes these are avoided due to the small risk of 'seeding' (spreading) cancer cells in other organs during the procedure.[37]

- **Endoscopic retrograde cholangiopancreatography (ERCP)** – The endoscope has a camera and light at the end of it. Once the endoscope is positioned where the bile duct joins the small intestine, a small tube is passed up into the bile duct. A dye can then be injected at the area of interest to increase the contrast of the image, and X-rays are taken to visualise any pathology in the biliary tract. With this method, it is also possible to obtain a biopsy or cells from the cancer for further assessment.[38] Small tubes called stents can be inserted and left in position to hold open any narrowing in the bile ducts and relieve symptoms, such as jaundice. The commonest risk of ERCP is pancreatitis (inflammation of the pancreas which is an organ that the bile duct passes through), which can be serious. Other risks include cholangitis, cystic duct obstruction, and cholecystitis.[39]

C. Percutaneous transhepatic cholangiography (PTC) is a test that is usually done if, for some reason, ERCP is not appropriate. This is undertaken without an endoscope and is usually performed by a radiologist (X-ray doctor). A long thin needle is inserted through the patient's skin into the liver and bile ducts under careful ultrasound and X-ray guidance. A dye is injected into the bile duct and X-rays are then taken to visualise any disease in the biliary tract. Biopsies from the affected areas can also be taken with this method, and stents can be inserted.

Even with all these advanced imaging and endoscopic techniques, it may not be possible to definitively diagnose CCA, unless a biopsy is taken. Biopsies can be taken during an ERCP, an EUS or PTC. Once obtained, the biopsy is sent out for histology, a laboratory process where the cancer tissue is stained with various dyes and looked at closely under the microscope.

The results from histology together with those from the imaging scans and any endoscopy should enable a definitive diagnosis of CCA. Nevertheless, in some cases it is very difficult to obtain a biopsy due to the anatomical location of the cancer, making the need for new, quick and non-invasive diagnostic tools even greater. Currently there is much research into finding biomarkers for CCA that could be easily detected in the blood, urine or bile of the patients that will accurately and non-invasively diagnose the disease.

D. Liquid biopsy is a cutting-edge blood test, currently being studied in the ACCESS program as a potential diagnostic tool to speed up diagnosis of biliary tract cancers. By detecting cancer DNA in the bloodstream, liquid biopsy offers quicker and less invasive detection (see **Section 9**). Encouraging preliminary data from the program have been presented, though challenges remain such as false positive results and cost-effectiveness.[40,41] The ACCESS program has the potential to revolutionise the diagnosis of CCA, greatly improving patient care.[40] With further research and collaboration, liquid biopsies may become a routine and effective diagnostic tool for CCA.

Staging

Once a diagnosis of CCA is made, the stage and extent of the cancer needs to be ascertained, as it will help determine the most appropriate treatment options. For this, a CT of the chest, and sometimes the pelvis, is performed to examine any potential spread of CCA.[30] These scans, together with the CT of the abdomen that patients might already have undergone and the information obtained by the bile duct MRI and MRCP, will help stage the cancer. Currently, the most used staging system for CCA is the TNM system, whereby:[1,30]

- **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 areas of the body

The TNM staging descriptions for each CCA subtype are listed in **Appendix 3**. For perihilar CCA, an additional staging step is usually performed, where the cancer is also subclassified based on the Bismuth-Corlette classification. This is used to describe the exact location of the perihilar CCA along the bile duct system (see **Appendix 4**).[30]

8 Treatment Options

Following the diagnosis and staging of CCA, the treatment options are assessed. These will depend on the position and stage of the disease, the health of the patient and the subtype of CCA. To date, the only potentially curative treatment is surgery. However, not all patients are eligible for surgery, with those with advanced stage disease having limited options. In fact, data from the European CCA Network have reported that only 20–30% of patients with CCA can undergo surgery. The majority of patients (70–80%) are inoperable and their options are limited to chemotherapy and/or clinical trials.[42] Moreover, there seems to be a high risk of the cancer coming back (recurrence) even after apparent complete surgical removal.[30]

In many patients the cancer physically obstructs the bile flow and they require bile duct drainage prior to any further treatment.[4,30] This is usually performed by endoscopically inserting mesh tubes or 'stents' inside the problematic bile ducts to help with restoring the bile flow and thus allowing liver function to improve and which, in turn, makes it possible for patients to receive other treatments.

The decision on the treatment(s) for patients with CCA will depend on the stage of the cancer, the CCA subtype, the country in which the patient resides and their medical team. The options currently available include:

Surgery – Various surgical options are available depending on the stage and location of CCA. These include removal of the affected bile ducts, partial liver removal (a liver resection), bypassing of the blocked bile ducts if cancer removal is not possible, or the Whipple procedure (usually carried out for distal/extrahepatic CCA) where the bile ducts, pancreas, gallbladder, surrounding lymph nodes and parts of the stomach and small intestine are removed, if affected.

Post surgery adjuvant therapies – Because of the high risk of cancer recurrence following surgery, patients are recommended to receive chemotherapy with capecitabine. In the pivotal BILCAP Phase III study, this approach has been shown to significantly improve the survival of patients with CCA.[43]

Radiation or ablation – Local treatments, like radiation or ablation, might be considered as ways to lower the risk of cancer recurrence after surgery but the data supporting this approach is currently limited.[30]

Chemotherapy – For patients with advanced CCA where surgery is not an option, chemotherapy with cisplatin and gemcitabine (CisGem) remains the standard of care first line option, as established by the pivotal ABC-02 trial. If patients progress after CisGem, FOLFOX (folinic acid, fluorouracil and oxaliplatin) is the recommended second-line chemotherapy option with demonstrated improved patient survival.[43,44]

Molecular profiling – This is the classification of samples (e.g., cancer tissue) based on gene expression. Biopsy samples are sent to a laboratory where they undergo tests to analyse tumour DNA and proteins – the results of these tests provide information about the molecular profile of the tumour and can be used to help decide which treatments the cancer is likely to respond to. Molecular profiling may allow patients to benefit from more 'personalised' treatments, or 'precision' medicine (see **Section 9**).

Targeted therapies – A targeted therapy is a treatment that 'targets' a specific mutation or fusion within a cancer, e.g., *FGFR2* or *IDH1*, which may have been found during molecular profiling. Pemigatinib, targeting the gene fusion *FGFR2*, is the first approved targeted therapy in Europe, USA, Scotland and England.[45-48] See more details on targeted therapies in the section that follows (**Section 9**).

Immunotherapies – Immunotherapy uses the immune system to fight cancer by helping it recognise and attack cancer cells. Results from the TOPAZ-1 study showed for the first time that the addition of the immunotherapy, durvalumab, to the standard chemotherapy, CisGem, increased the survival of patients with advanced CCA.[9]

In September 2022, the combination of standard chemotherapy, CisGem, plus durvalumab was approved in USA by the Food and Drug Administration (FDA) as a treatment option for patients with CCA.[49] It is expected that England and Europe will also approve this option. The role of immunotherapy in the treatment of CCA is now being further explored.

Liver transplantation – This is an established treatment in some centres, mainly in USA, with some European centres starting to consider it as a potential treatment option for early CCA too. It has been approved in the UK for intrahepatic CCA under stringent eligibility criteria.[50] Experts in the field urge for more clinical trials on liver transplantation for CCA, with the hopes of improving patient options.[35]

A schematic with the most up-to-date treatment decision pathway based on the 2022 European Society for Medical Oncology (ESMO) guidelines is provided below (**Figure 4**).[30]

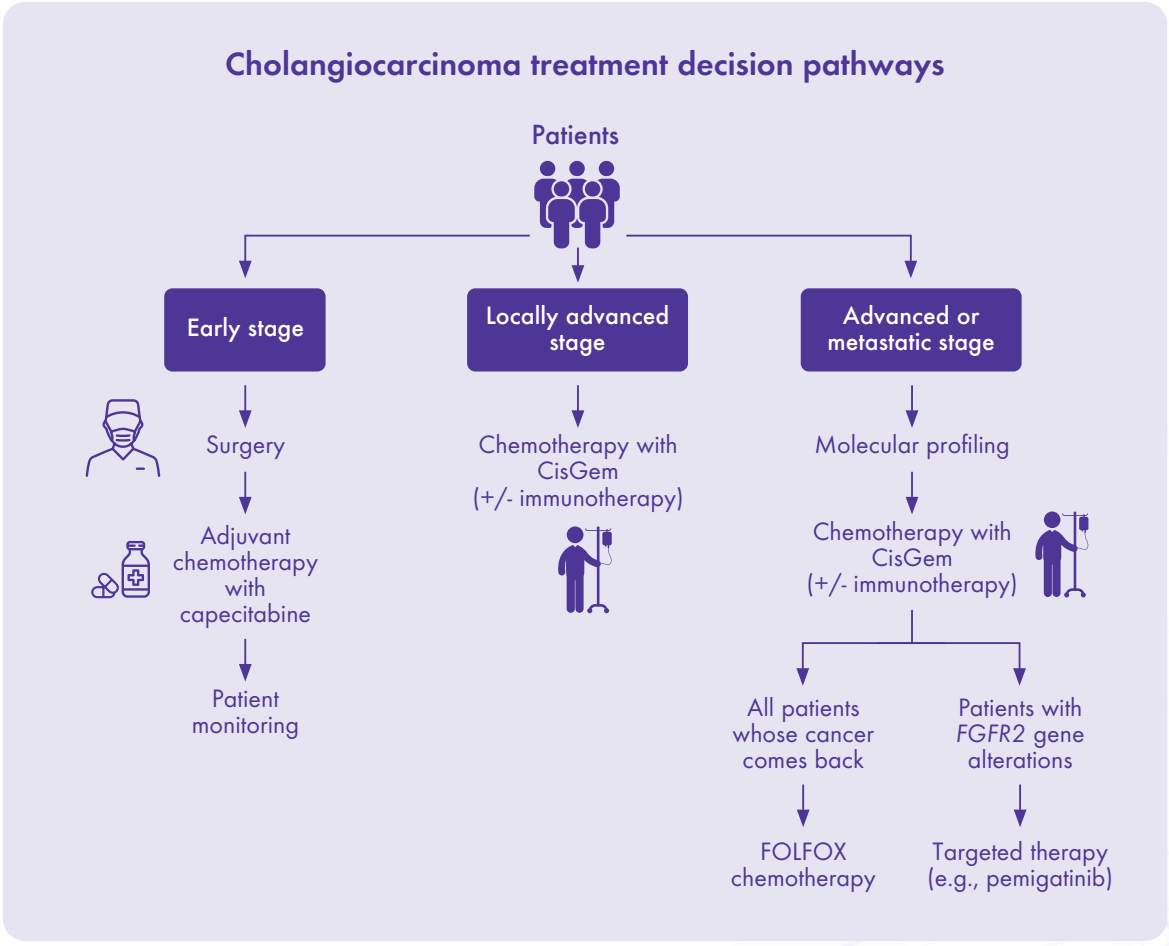


Figure 4. *Treatment decision pathways based on the ESMO 2022 guidelines.*[30]

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

9 Molecular Profiling and Targeted Therapies

We now know that no two cancers are the same, even within the same CCA subtype. That is because each cancer has a different microenvironment surrounding it and expresses different genes and proteins, which make up its unique molecular profile. This molecular profile can be identified in the laboratory from a biopsy (tissue), in a process known as molecular profiling or genetic/genomic testing.

Some molecular profiling tests may use one, two, or a combination of technologies to uncover information about the cancer and identify which genes and proteins the cancer expresses (**Figure 5**). Technologies most often used include next generation sequencing (NGS), and fluorescence *in situ* hybridisation (FISH).[51]

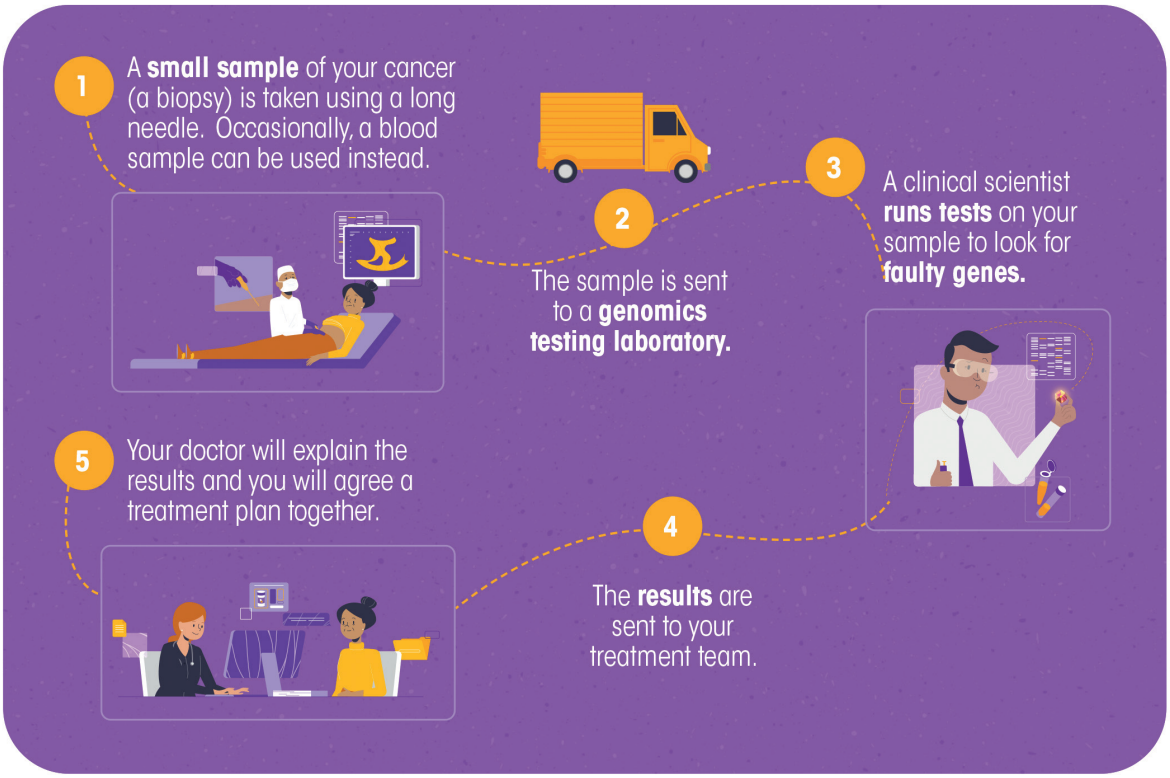


Figure 5. *Summary of steps involved in molecular profiling for patients with CCA. Illustration from © AMMF- Incyte Molecular Profiling Booklet.*

Molecular profiling is a new and exciting field in CCA research that will hopefully allow patients to receive a more personalised treatment depending on the molecular profile of their cancer. A real-life example of this research is the story of the drug pemigatinib that specifically targets a genetic alteration in the *FGFR2* gene (fusion or rearrangement).[47] This genetic alteration was discovered through molecular profiling of cancers in patients with CCA. Pemigatinib is now the first ever targeted treatment to be approved in USA, England, Scotland and Europe for the treatment of CCA patients with an *FGFR2* gene alteration.[45-48] Further targeted therapies are currently under investigation.

Currently, molecular profiling is not available for all patients but is used in clinical trials mainly for those with advanced CCA or whose cancer has returned after surgery or chemotherapy. This is done to assess whether these patients have any genetic alterations that might benefit from targeted treatments (e.g., pemigatinib). It might take several weeks to get the results of molecular profiling, so experts are urging health care professionals to test patients as early as possible.[51] For more information on molecular profiling, please download the AMMF booklet and watch the educational AMMF video **here**.

Liquid biopsy – Targeted therapies can provide promising new treatment options. However, a clear molecular profile is needed to discover which therapy might be best. For those with CCA, there may be insufficient biopsy tissue available for this. An alternative is liquid biopsy, technically a blood sample, which can be tested to detect DNA being shed from the tumour and circulating in the blood. Molecular profiling information can be accessed in this way which may enable a targeted therapy to be identified.[51,52]

Subtype-specific information

Interestingly, different gene alterations have been more commonly associated with perihilar CCA *(ERBB2 [HER2], PIK3CA)* than intrahepatic CCA (*IDH1* and *FGFR2*), making the need for subtype targeting therapies even more important.[51]

10 Nutrition

We know that healthy eating is beneficial for all, including those with cancer. There are no diets that can cure cancer, but some can help alleviate treatment symptoms and improve the quality of life for patients. The nutritional needs and concerns of patients with CCA vary depending on individual needs, disease stage, severity and the type of treatment they are undergoing. Appropriate nutrition is important for patients with CCA, as 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.[53] CCA itself, and also treatments for CCA, can cause various symptoms which affect the nutritional status of patients by reducing their appetite and by causing nausea, diarrhoea, vomiting, sore dry mouth, abdominal pains, lethargy and/or taste changes.[53,54]

In more than half of patients with CCA, and especially those with advanced disease, ongoing muscle loss with or without fat loss will develop. This will eventually make it difficult or even impossible for patients to carry out their daily tasks, and may decrease their chances of survival.[53] This is why it is critical that weight changes are tackled early on and that dietary adjustments are put in place to manage symptoms. Ideally, patients with CCA should work closely with their doctor and a specialist dietician to devise an appropriate treatment and nutritional plan.

Depending on the type of CCA treatment, patients will have distinct nutritional needs that should be managed. The key nutritional considerations for patients with CCA following surgery or during systemic treatment (chemotherapy or radiotherapy) are outlined below.

Key nutritional considerations for patients with CCA following surgery

A. Whipple procedure and pancreatic enzyme replacement therapy (PERT)[53–55]

Patients undergoing a Whipple procedure will have parts of their bile ducts, pancreas, gallbladder, surrounding lymph nodes, stomach and small intestine removed, depending on the extent of the cancer (see **Section 8**). This is a complex and extensive surgery where many parts of the body that aid in food digestion and nutrient absorption are removed. These patients most commonly present with weight loss, diarrhoea, nausea, poor appetite and abdominal discomfort. All these symptoms can have a long-term effect on the nutrition of patients and thus specific dietary adjustments are essential. These usually include early pancreatic enzyme replacement therapy (PERT) and ideally a referral to a specialist dietician to help the patient manage their PERT and diet properly. PERT replaces the enzymes that would normally be produced by the pancreas to digest food. Thus, depending on how much of the pancreas has been surgically removed, PERT might be a necessary life-long treatment. Similarly, because insulin is also produced in the pancreas, depending on the extent of pancreas removal during a Whipple procedure, patients might also need to receive medication for diabetes, either temporarily or for the rest of their lives.

B. Bile acid malabsorption (BAM)[53–55]

Another issue that might occur in patients with CCA following surgery is bile acid malabsorption (BAM). Bile contains bile acids that are produced in the liver, stored in the gallbladder, and released into the small intestine when food is ingested to help with digestion. Once food digestion is complete, bile acids are reabsorbed in the blood and transported back to the liver. In some patients, bile acids are not properly reabsorbed back in the blood, leading to BAM.[53,54] BAM can cause abdominal discomfort, like bloating, cramps, wind, and pain. In the UK, BAM is thought to affect 1 in 100 people and is often underdiagnosed and neglected.[53] Patients with BAM should work with their dietician and medical team to devise a treatment plan that includes both dietary adjustments (e.g., dietary fat restriction) and medications that can help alleviate symptoms (e.g., bile acid binders, pain relief).[53]

C. Small intestinal bacterial overgrowth (SIBO)[53–55]

Surgery, chemotherapy and radiotherapy can lead to changes in the small intestine which may cause intestinal bacteria to grow to excessive numbers. This condition is called small intestinal bacterial overgrowth (SIBO) and usually causes symptoms of bloating, wind, diarrhoea, as well as weight loss, nutritional deficiencies (vitamin B12) and fragile bones (osteoporosis).[53,54] Depending on the patient, symptoms can range from mild to severe and can be debilitating with a high psychological impact.[53] SIBO is also underdiagnosed and sometimes mistakenly labelled as inflammatory bowel syndrome (IBS). This is why it is important for patients with symptoms of SIBO to seek advice from gastroenterology specialists and specialist dieticians. Treatment for SIBO includes antibiotics and dietary changes to correct for deficiencies, minimise intolerances and help kill off the excessive bacteria (e.g., low-FODMAP diet).[53]

Key nutritional considerations for patients with CCA receiving chemotherapy or radiotherapy[53–55]

It is extremely common for patients undergoing chemotherapy or radiotherapy to develop eating problems during and after treatment. The 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. Moreover, 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).[53,55] SIBO can also occur after chemotherapy or radiotherapy and even months after the treatment is completed.[53]

Additional nutritional resources

More tips and advice on how to manage the nutritional needs of patients with CCA, depending on their symptoms and therapy, are provided by AMMF and a Senior Specialist Dietician **here**.

11 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 properly assessed and offered the right treatment and care. Patients with CCA should ideally be treated in a specialist centre by a multidisciplinary team (MDT) specialising in diseases of the liver and biliary tract (hepatobiliary services). An MDT is a group of doctors and nurses who meet regularly to discuss patient cases and devise the most appropriate treatment plans. Recently, ENS-CCA published the first set of recommendations for how a CCA MDT should run.[56] These recommendations were devised following a large survey completed by surgeons, liver specialists (hepatologists) and oncologists in 34 European and international centres. Amongst those recommendations, ENS-CCA suggests that CCA MDT meetings/sessions occur weekly, with the mandatory presence of a coordinator, and that all new patient cases are discussed. Moreover, the presence of the following medical professionals should be considered mandatory in a CCA MDT, all of whom should have knowledge of diagnosing and treating those with CCA:[56]

- **The doctor responsible for the patient**
- **Oncologist:** *a cancer specialist*
- **Hepatobiliary surgeon:** *a specialist in surgery of liver, bile ducts and pancreas*
- **Radiologist:** *a specialist who can interpret diagnostic images, e.g, X-rays, CT and MRI scans, and has knowledge of interpreting images from patients with CCA*
- **Hepatologist:** *a liver specialist*
- **Pathologist:** *a specialist who examines biopsies, e.g., tissue, blood and other fluids, for diagnostic purposes*
- **Gastroenterologist:** *a specialist in gastrointestinal (stomach and intestines) and hepatological (liver, gallbladder, biliary tree and pancreas) diseases*

In addition to those CCA MDT medical professionals, ENS-CCA recommends the presence of supportive care specialists, nurse specialists, dieticians, psychologists and academic researchers, something that is not currently common practice. Having all these individuals together would provide a more rounded treatment approach and optimise patient care for those with CCA.

In Europe, access to specialist centres and MDT treatment varies by country. A recent study carried out in France revealed that most patients with CCA are treated in non-specialist centres where only one or two patients with CCA are seen per year. This is alarming and highlights the lack of awareness of CCA in such non-specialist centres in France and possibly also in other European countries.[21] In the Netherlands, there are now seven specialist medical centres, known as university medical centres. Nationwide data from the Dutch Hepatocellular and Cholangiocarcinoma Group showed that the survival of patients treated in these university medical centres was significantly longer than those treated in non-specialist centres.[57] The same study also showed that one third of patients with perihilar CCA who had been considered inoperable at the point of referral, were actually surgical candidates following assessment at the specialist centres.[57] Moreover, according to the Dutch guidelines, as of 2022, it is mandatory for all patients with perihilar CCA to be discussed at MDT meetings. In Germany, recent evidence showed that patients with CCA have a lower chance of dying when being treated at centres that have experience with CCA rather than those seeing only very few cases each year.[58]

All these studies indicate that, currently, due to the rarity and aggressiveness of the disease, CCA expertise is concentrated in a few specialist centres in each European country. Patients with CCA do not necessarily live close to such specialist centres, but each one deserves access to the best care regardless of their geographical location. This highlights a major need for raising CCA awareness amongst non-specialist centres and improving MDT and specialist care availability for all patients with CCA in Europe.

12 Clinical Trials

Clinical trials are and have been fundamental in improving the outcomes of patients with CCA. Patient organisations and the public can access registries for information in which clinical trials are currently available, recruiting patients or completed. European patients can search for CCA trials in their countries in the following registries:

- **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 set up)

For convenience, 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**.

When talking about clinical trials, the word 'phase' is important to understand. The table below provides a summary of all the potential phases of a clinical trial and what they mean. If a Phase I trial has positive results then it will most likely pave the way for a Phase II trial on the same treatment and so forth until a Phase III trial is established. Upon completion of a Phase III trial, if the results are positive and the treatment benefits the patients, the approval process will begin with applications to each country's drug authorisation agencies. For countries in the European Union, that is the **European Medicines Agency (EMA)**, for the USA it is the **FDA** and for England it is **The Medicines and Healthcare Products Regulatory Agency (MHRA)**. In addition to EMA, each European Union country has its own authorisation body that works together with the EMA to ensure the authorisation of safe, effective and high-quality medicines. A list of those by country can be found **here**.

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**?

Pivotal clinical trials for CCA

With regards to the fundamental clinical trials that have shaped the treatment landscape of CCA as it is today, the most well-known are the ABC clinical trials conducted in England. Prior to those, there were no reliable, large-scale clinical trials for CCA and there was no standard chemotherapy treatment. The outcomes of the ABC-01 and **ABC-02** clinical trials led to the establishment of the current first-line chemotherapy treatment, CisGem for patients with CCA (see **Section 8**).[59] The **ABC-06** trial established the secondline FOLFOX chemotherapy (see **Section 8**),[60] while the **BILCAP** trial showed for the first time that the best strategy for patients undergoing surgery is to have follow-up chemotherapy with capecitabine.[43] Lastly, the positive results of the Phase II trial **FIGHT-202**, led to the approval of the first targeted treatment, pemigatinib, for those with CCA and the *FGFR2* fusion (see **Section 9**), which is rare prior to the completion of a Phase III trial. The Phase III trial is now underway (**FIGHT-302**). Currently (October 2023), the ClinicalTrials.gov website identifies 194 clinical trials for adults with CCA in Europe, with France, Germany, Italy, Spain and the UK leading the charts.

With the realisation of the importance of molecular profiling and the potential to devise more personalised treatments, many trials are now focusing on targeted treatments (see **Section 9**). Such examples include the SAFIR ABC-10 trial that aims to use molecular profiling to screen patients with advanced CCA and then assess them on different targeted therapies depending on their genetic alterations. This trial is in the late stages of development and is planned to be a joint collaboration between England, France and Belgium, with potentially more European countries joining in.[61]

Another upcoming field of clinical study is that of immunotherapies (see **Section 8**). The efficacy of various immunotherapy agents is currently assessed in multiple clinical trials either alone or in combination with targeted treatments. Currently, in addition to durvalumab (see **Section 8**) a promising immunotherapy agent is pembrolizumab, which has been approved in the USA for use in inoperable, advanced solid cancers (with high microsatellite instability (MSI-H)),[62] including CCA (**KEYNOTE-158** trial) and is further examined in other trials alone or in combination with chemotherapy (e.g., Phase III **KEYNOTE 966** trial – all patients with advanced and/or unresectable biliary tract carcinoma included in this trial, not selective for patients with CCA only).

It is inspiring to see the multitude of clinical trials currently available for patients with CCA, especially when looking back to just over a decade ago when there were no trials or established standard treatment protocols for CCA. Experts are now urging for patient enrolment and participation in these trials, with the hopes of improving the outcomes and quality of life for patients with CCA.

13 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. Unfortunately, patient engagement is still not prioritised in many countries across the globe, and thus systematic efforts from patient organisations are needed to educate both patients and HCPs on the importance of the patient role in developing better and safer health care services. Initially, patient organisations could engage patients by simply collecting their experiences and outcomes of care, through surveys, informal online feedback, interviews or focus group discussions.[63,64] Collating such information and disseminating it to the medical and scientific community could help provide a better understanding of patients' needs and preferences, and ultimately help improve the quality of care.

Many patients have already identified the need for a more responsive, open and transparent healthcare system where they are more directly involved in the planning and decision-making process of their medical care. Patients with CCA have reported that at diagnosis the communication with their treating clinician can be poor (see **Section 11**). This was clear from an online survey devised by AMMF. The survey found that overall, patients did not query treatment decisions but felt confused about the decision-making process at MDT meetings, particularly if the meetings were held at a different hospital to the one in which they were treated. From the survey results, it was recommended that clinicians who know the patient should always attend the MDT meetings and advocate for the patients' wishes.[65]

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.

14 Patient Advocacy and CCA-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. Every year, AMMF hosts a European CCA conference where HCPs and patients can discuss and learn about the latest in treatments, clinical trials and research. AMMF's website provides a wealth of information on all areas of CCA. There is a growing number of **useful resources, some available in a number of European languages.** These resources include dietary/nutrition information, questions to ask the doctor, and information sheets on chemotherapy regimens – what they are, how to manage side effects etc. All resources have been specifically developed to help patients with CCA, but are also useful for HCPs, including clinical nurse specialists. AMMF also provides a **list** of CCA clinical trials currently open and recruiting, and runs a number of private discussion groups for those with CCA.

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. They have compiled a helpful list of CCA-related resources in Italian, **here**. They also organise awareness meetings and campaigns to make citizens and public bodies aware of the possible causes and risk factors of CCA, contributing to a cultural change towards the disease and raising funds to support research on it.

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. The GCA has a wide variety of educational resources addressed at both patients and health care professionals. These can be accessed **here**.

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. It is affiliated with the British Association for the Study of Liver Disease (BASL) and hosts an annual conference to discuss the latest CCA research and promote collaboration in the field.

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.

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 health care professionals is also available **here** in English, French, German, Spanish and Italian.

The European Society for Medical Oncology (ESMO) has created a useful **patient guide** on BTC, 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.

15 The Unmet Needs

CCA is a complex, aggressive and challenging cancer that has become increasingly prevalent globally in the last decades. Patients with CCA face significant challenges, including difficulties in early diagnosis, limited treatment options, and poor prognosis.

One major challenge is the difficulty to diagnose CCA early. This is hindered not only by the asymptomatic nature of the disease in the early stages but also by the difficulty in obtaining high-quality biopsies for accurate diagnosis. Additionally, there is a lack of biomarkers that could indicate the presence of the disease in its early stages in a non-invasive way.

Another major challenge is the poor prognosis associated with CCA. Despite the latest medical advances, the overall survival for patients is still very low, especially for those who are not eligible for surgery. Reasons for this include the lack of understanding of the underlying disease mechanisms, combined with its highly aggressive nature and late diagnosis. We know that CCA is a heterogeneous disease, meaning that it can differ from patient to patient. Due to this heterogeneity, the understanding of the disease and how these cancers can resist treatment is further limited. This is complicated even more by the role of the environment surrounding each cancer, which can influence cancer growth and treatment response differently in each patient. To date, experimental models have not yet been able to fully capture the complexity of CCA, making it harder to understand the disease and how to treat it effectively. Although genetic studies and molecular profiling have identified potential genetic targets for treatment, more research is needed to identify how and for whom personalised treatments can be effective.

Other unmet needs include little understanding of the cause in most of those diagnosed with CCA. There are some known risk factors but, in the Western world, the majority of those diagnosed have no discernible risk factors. Also, this cancer has a high recurrence rate, even after a 'curative' surgical resection has been achieved. There is a need for better understanding of why this happens, and what neoadjuvant therapies may help to prevent this.

In summary, patients with CCA face significant challenges related to diagnosis, treatment options, and overall prognosis. Better and less invasive diagnostic tools and biomarkers are needed to help detect the cancer in its early stages, and more effective treatments are needed to improve patient outcomes. 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.

The Future of Cholangiocarcinoma

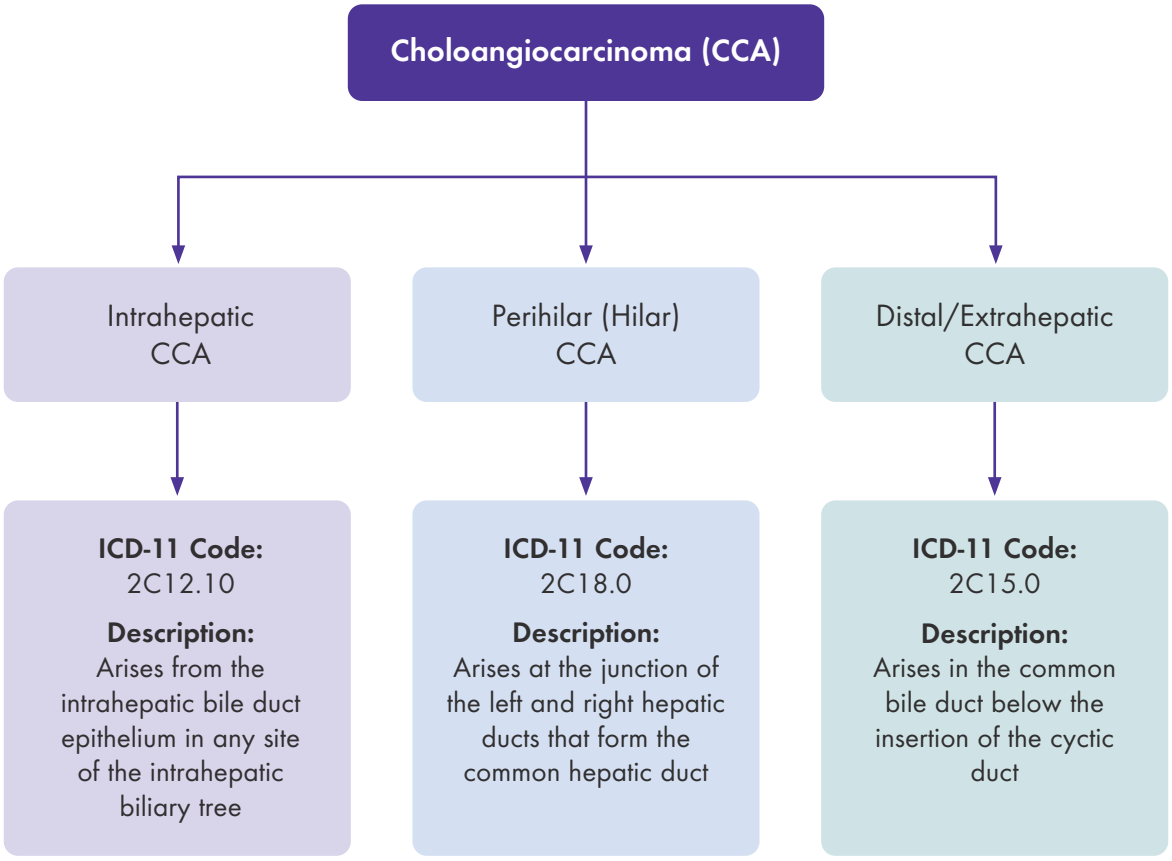
Improving outcomes for patients with CCA is a complex task that requires continuous research and collaboration between researchers, clinicians, patient organisations, patients and their families. To achieve this, a network of dedicated advocates who share the same vision must be grown and nurtured. Patient organisations play a key role in supporting and advocating for patients and their needs, promoting collaboration between researchers and clinicians, and raising awareness of CCA. Despite the extensive collaborative network that AMMF and other patient organisations have set up globally, there is an ongoing need to grow this further and to establish a global voice that will promote and encourage novel research and clinical trials into CCA worldwide.

With regards to the future of the CCA treatment landscape, areas of interest include liver transplantation, targeted therapies for specific mutations, and immunotherapies. Targeted therapies through molecular profiling show promise in paving a new treatment landscape for CCA. This points towards a more personalised approach that takes into consideration each patient's cancer characteristics and genetic differences. Molecular profiling should be carried out for all following an initial diagnosis of CCA, to ensure that if a specific druggable mutation or fusion is present, then the patient can receive the appropriate treatment or be entered into a clinical trial, in a timely way.

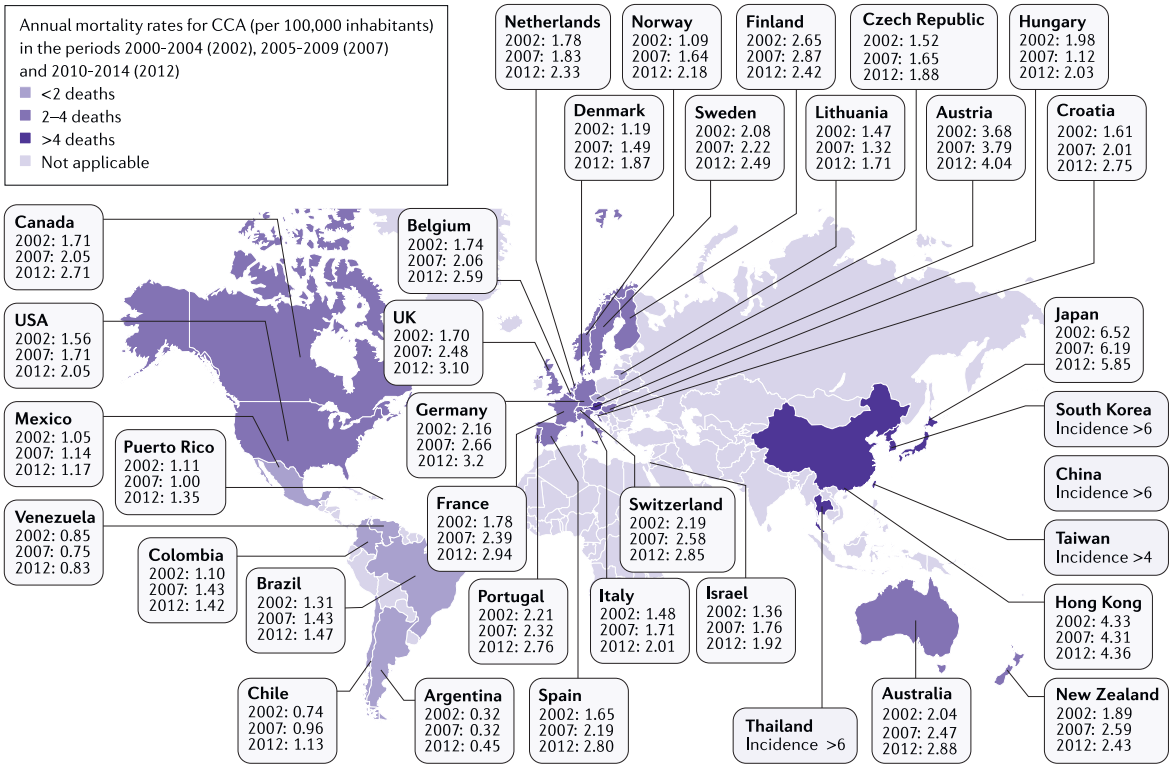
As new insights are gained into the underlying mechanisms of CCA, there is hope that new diagnostic tools and treatments will be developed to help improve the lives of patients and their families affected by this devastating disease. Achieving this requires patient organisations, researchers, clinicians, and patients to work together as a community with a global aim of tackling CCA.

APPENDICES

Appendix 1. WHO Cholangiocarcinoma Subtype Classification Codes[14,15]



Appendix 2. Worldwide Map of CCA Mortality[1]



Global CCA mortality rates defined as deaths per 100,000 inhabitants. The rates include all three subtypes. Data shown as 2002 refer to the period 2000–2004. Data shown as 2007 refer to the period 2005–2009. Data shown as 2012 refer to the period 2010–2014. Figure adapted from Banales et al., 2020.[1]

Appendix 3. TNM Staging Descriptions for CCA Subtypes (8th Edition UICC/AJCC)[30,66]

Perihilar (hilar) CCA – UICC/AJCC classification	
Stage	**Criteria**
T stages	
Tis	The tumour is only within the top layers of cells lining the bile duct
T1	The tumour has grown deeper into the wall of the bile duct
T2a	The tumour has grown through the wall of the bile duct into the fatty tissue around it
T2b	The tumour has grown into the main part of the liver next to the bile duct
T3	The tumour has grown into one of the main blood vessels of the liver (the portal vein or hepatic artery)
T4	The tumour has grown into the right and left hepatic bile ducts or it has grown into more than one of the blood vessels or it has grown into a hepatic bile duct and more than one blood vessel
N stages	
N0	There are no cancer cells in the lymph nodes
N1	There are cancer cells in nearby lymph nodes
N2	There are cancer cells in lymph nodes further away, such as the chest
M stages	
M0	There is no sign of cancer spread
M1	The cancer has spread to other parts of the body away from the bile duct

Intrahepatic CCA – UICC/AJCC classification

Stage	Criteria
T stages	
Tis	The tumour is only within the top layers of cells lining the bile duct
T1	There is one tumour that is contained within the bile duct, but has grown deeper into the wall of the bile duct
T2a	There is one tumour and it has grown through the wall of the bile duct into a nearby blood vessel
T2b	There is more than one tumour which may or may not have grown into a nearby blood vessel
T3	The tumour has either grown into the covering of the liver (the peritoneum) or has grown into nearby structures outside the liver, such as the bowel
T4	The tumour has spread into the liver by growing along the ducts
N stages	
N0	There are no cancer cells in the lymph nodes
N1	There are cancer cells in the lymph nodes
M stages	
M0	There is no sign of cancer spread
M1	The cancer has spread to other parts of the body away from the bile duct

Distal/Extrahepatic CCA – UICC/AJCC classification

Stage	Criteria
T stages	
Tis	The tumour is only within the top layers of cells lining the bile duct
T1	The tumour is entirely inside the bile duct but has grown deeper into the bile duct wall
T2	The tumour has grown through the wall of the bile duct
T3	The tumour has grown into the gallbladder, pancreas, small bowel or other nearby organs
T4	The tumour has grown into the major blood vessel in the abdomen (the aorta) where it joins the main blood vessel of the liver (the hepatic artery)
N stages	
N0	There are no cancer cells in the lymph nodes
N1	There are cancer cells in the lymph nodes
M stages	
M0	There is no sign of cancer spread
M1	The cancer has spread to other parts of the body away from the bile duct

Appendix 4. Bismuth-Corlette Classification Descriptions for Perihilar CCA[30]

Perihilar (hilar) CCA – Bismuth-Corlette classification	
Type	**Criteria**
Type I	The cancer involves the common bile duct
Type II	The cancer involves the bifurcation of the common bile duct
Type IIIa	The cancer involves the right hepatic duct
Type IIIb	The cancer involves the left hepatic duct
Type IV	The cancer involves both the right and left hepatic ducts

GLOSSARY

AJCC, American Joint Committee on Cancer

BAM, bile acid malabsorption

BTC, biliary tract cancer

CA19-9, carbohydrate antigen 19-9 or Lewis A antigen

CCA, cholangiocarcinoma

CisGem, cisplatin plus gemcitabine

CT, computed tomography

DNA, deoxyribonucleic acid

EMA, European Medicines Agency

ENS-CCA, European Network for the Study of Cholangiocarcinoma

ERBB2 [HER2], receptor tyrosine-protein kinase erbB-2

ERCP, endoscopic retrograde cholangiopancreatography

ESMO, European Society for Medical Oncology

EUS, endoscopic ultrasound

FDA, Food and Drug Administration

FGFR2, fibroblast growth factor receptor 2

FOLFOX, folinic acid, fluorouracil and oxaliplatin

HCC, hepatocellular carcinoma

ICD-11, International Classification of Disease eleventh edition

IDH1, isocitrate dehydrogenase 1

MDT, multidisciplinary

MRCP, magnetic resonance cholangiopancreatography

MRI, magnetic resonance imaging

PERT, pancreatic enzyme replacement therapy

PIK3CA, phosphatidylinositol 3-kinase catalytic subunit A

PSC, primary sclerosing cholangitis

PTC, percutaneous transhepatic cholangiography

SIBO, small intestinal bacterial overgrowth

TNM, tumour node metastasis

UICC, Union for International Cancer Control

UK, United Kingdom

USA, United States of America

WHO, World Health Organisation

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