CHOLANGIOCARCINOMA FAST FACTS

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AMMF

THE CHOLANGIOCARCINOMA CHARITY

About this AMMF Cholangiocarcinoma Educational Resource

This educational resource has been developed by AMMF, the UK's only cholangiocarcinoma charity, and is a summarised version of the fully referenced document: "Introduction to Cholangiocarcinoma - An Educational Resource for Patient Organisations". The information provided here relies on the most current and evidence-based understanding of cholangiocarcinoma (CCA), its epidemiology, prognosis, treatment, diagnostic options, and patient perspectives.

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.

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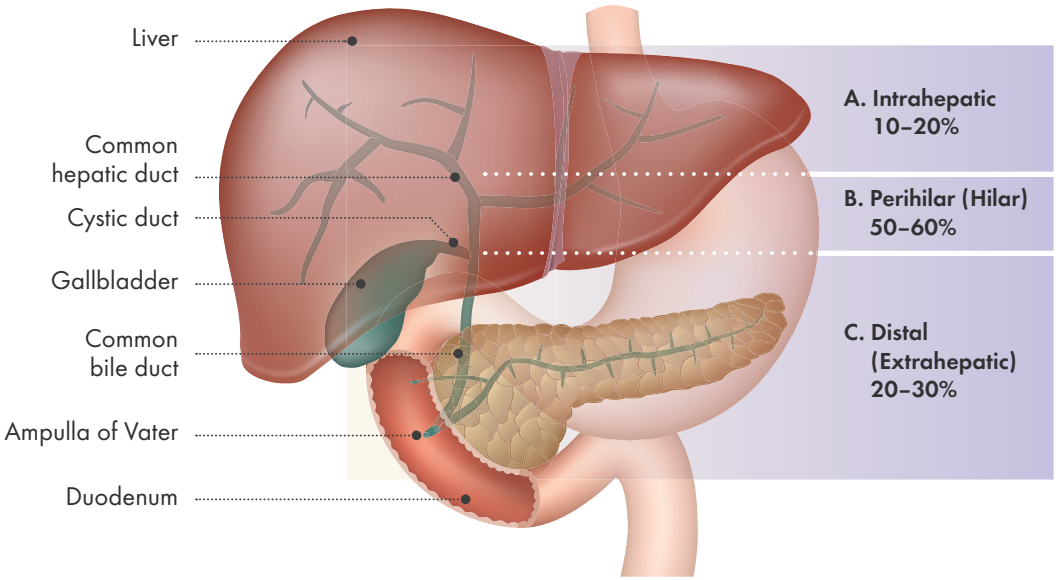
Chapter 1. Cholangiocarcinoma Overview

- Cholangiocarcinoma is a complex and challenging cancer with increasing global incidence and death rates over the last decades
- Cholangiocarcinoma is a primary liver cancer and is the second most common primary liver cancer after hepatocellular carcinoma
- The exact causes of cholangiocarcinoma in the Western world are unclear and it is likely that a combination of different risk factors contribute to the disease
- To date, most cases in the Western world, are sporadic, meaning that they occur without a known cause or identifiable risk factor
- Long term liver damage from any cause increases the risk of cholangiocarcinoma
- Cholangiocarcinoma has a very aggressive nature and is difficult to treat
- Cholangiocarcinoma causes few or no noticeable symptoms in its early stages, and any noticeable symptoms are usually non-specific
- Cholangiocarcinoma is usually diagnosed late, in advanced stages, when therapeutic options are limited and compromised
- The first and, so far, exclusive pan-European cholangiocarcinoma clinical registry was created by the European Network for the Study of Cholangiocarcinoma (ENS-CCA) in 2016. The registry now holds data from more than 2,200 patients with cholangiocarcinoma from 11 countries and 26 medical centres (2023)

Chapter 2. Biliary Tract Cancer

- Biliary tract cancer is actually an umbrella term which includes all cancers occurring in the biliary tract: cholangiocarcinoma, gallbladder and ampullary cancer
- Studies from England show that deaths due to cholangiocarcinoma have been steadily increasing over the last decades unlike those from the other biliary tract cancers (gallbladder and ampullary cancers) that remained stable

Chapter 3. Understanding Cholangiocarcinoma and its Subtypes



- Cholangiocarcinoma originates in the bile ducts of the liver. Bile ducts are tubes that carry bile from the liver to the small intestine to aid food digestion and waste product disposal
- Cholangiocarcinoma can grow anywhere in the network of bile ducts, both inside and outside the liver and, based on the location of origin, it is categorised into three subtypes: intrahepatic, perihilar (or hilar) and extrahepatic/distal
- Intrahepatic cholangiocarcinoma originates in the bile ducts located inside the liver and accounts for 10–20% of all cholangiocarcinoma cases
- The perihilar (or hilar) cholangiocarcinoma subtype originates just outside the liver at the junction of two main ducts, the left and right hepatic ducts
- Perihilar (or hilar) cholangiocarcinoma is the most common subtype and accounts for approximately half of all cases
- Distal/extrahepatic cholangiocarcinoma originates in the common bile duct outside the liver and accounts for 20–30% of all cholangiocarcinoma cases
- Patients with different cholangiocarcinoma subtypes can show differences in symptoms, prognosis, risk factors and diagnosis, as well as treatment strategies
- Confusingly, the perihilar and distal cholangiocarcinoma subtypes are commonly referred to together as extrahepatic cholangiocarcinoma
- Since January 2022, there are official WHO classification codes for every cholangiocarcinoma subtype (ICD-11) to facilitate health care professionals with accurate recording/coding of each disease subtype

Chapter 4. Epidemiology

- The incidence of cholangiocarcinoma varies considerably depending on the geographical region, with Northeast Thailand having the highest number of cases
- 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
- Evidence from WHO shows that cases and deaths from cholangiocarcinoma have been steadily increasing over the last decades in most Western countries
- The true incidence of cholangiocarcinoma may be much higher, as almost one third of primary liver cancers that are classified 'of unknown primary (origin)' and have concomitant disease in the liver are actually cholangiocarcinoma
- Studies from England and Germany have reported that a significant number of cholangiocarcinoma cases are miscoded by health care professionals as the wrong subtype
- Epidemiological data for cholangiocarcinoma subtypes is not yet fully reliable because, until January 2022, there was no official classification code to separate perihilar from distal/extrahepatic cholangiocarcinoma by health care professionals

Chapter 5. Causes and Risk Factors

- The causes of cholangiocarcinoma in the Western world remain unclear. A combination of risk factors might contribute to the disease, but then again patients might have several risk factors and never develop cholangiocarcinoma and others with no risk factors might do so
- To date, most cases in the Western world, are sporadic, meaning that they occur without a known cause or identifiable risk factor
- A common feature of most identified cholangiocarcinoma risk factors is that they cause long-term inflammation of the bile ducts (cholangitis) and/or impaired bile flow (cholestasis)
- Some of the strongest known risk factors for cholangiocarcinoma in the Western world are primary sclerosing cholangitis (PSC), bile duct cysts or stones, Caroli disease, advanced liver disease, hepatitis B/C infection, diabetes, non-alcoholic fatty liver disease, older age (>65) and toxins (e.g., asbestos)
- The main risk factor for cholangiocarcinoma in Southeast Asia is liver fluke infestation, a parasitic flatworm that gets carried into the body through the consumption of infested raw river fish
- Advanced liver disease, hepatitis B/C infection, non-alcoholic fatty liver disease, diabetes, and asbestos exposure are risk factors that seem to be more strongly associated with intrahepatic cholangiocarcinoma than any other subtype

Chapter 6. Symptoms

- Cholangiocarcinoma is usually asymptomatic in its early stages
- By the time a patient develops symptoms, cholangiocarcinoma may be in quite advanced stages
- Symptoms of cholangiocarcinoma are usually non-specific, meaning they can resemble other conditions
- Common non-specific symptoms of cholangiocarcinoma include, feeling generally unwell, unexplained weight loss, nausea, fever, loss of appetite, fatigue, skin itching and abdominal pain
- Symptoms that are more specific to cholangiocarcinoma appear when the disease is in more advanced stages and may include, yellowing of the skin and eyes (jaundice), darkening of urine and light-coloured stools
- Patients with distal/extrahepatic or perihilar cholangiocarcinoma are more likely to present with symptoms caused by physical blockage of the bile flow by the cancer (yellowing of skin/eyes, itchy skin, colour changes to urine/stools)
- Patients with intrahepatic cholangiocarcinoma are more likely to present with abdominal pain and non-specific symptoms like weight loss and feeling unwell

Chapter 7. Diagnosis

- To date, there is not one simple test that can definitively diagnose cholangiocarcinoma
- Cholangiocarcinoma does not occur only at an older age. Studies have shown that one fifth of patients diagnosed are below the age of 65
- A combination of imaging tests (ultrasound, computed tomography or magnetic resonance imaging), endoscopic tests and biopsies may be needed to diagnose cholangiocarcinoma
- Upon a cholangiocarcinoma diagnosis, it is crucial to diagnose the correct subtype, as every subtype requires a specific clinical and treatment approach
- In patients with suspicion of cholangiocarcinoma, an ultrasound over the abdominal area may be performed. This is a painless test that uses high frequency waves to recreate an image of the scanned organs. Alternatively, a computed tomography (CT) scan or a magnetic resonance imaging (MRI) scan can be performed. These are both painless tests that use X-rays or magnetic fields, respectively, to recreate a 3D image of the scanned organs
- Magnetic resonance cholangiopancreatography (MRCP), is a specialised type of MRI scan that provides more detailed images of the bile ducts and is usually performed at the same time as a general abdominal MRI
- To definitively diagnose cholangiocarcinoma, a biopsy is needed from the cancer. These may be taken via endoscopic ultrasound, endoscopic retrograde cholangiopancreatography (ERCP) or through percutaneous transhepatic cholangiography (PTC). PTC may be performed if the other diagnostic techniques are not appropriate. PTC is undertaken without an endoscope and usually by an X-ray doctor
- Liquid biopsy is an innovative blood test, currently being studied as a potential diagnostic tool for cholangiocarcinoma, which works by detecting cancer DNA in the patient's bloodstream

Chapter 8. Treatment Options

- Treatment for cholangiocarcinoma will depend on the stage of the disease, the health of the patient and the disease subtype
- To date, the only potentially curative treatment for cholangiocarcinoma is surgery
- Cholangiocarcinoma can come back even after 'curative' surgery
- The majority of patients (70–80%) are not eligible for curative surgery, leaving their options limited to chemotherapy and/or clinical trials
- For many patients, cholangiocarcinoma physically obstructs the bile flow and they require bile duct drainage prior to any further treatment. This is usually performed by endoscopically inserting mesh tubes or 'stents' inside the problematic bile ducts to help bile flow restoration and improve liver function
- The decision on the treatment(s) for patients with cholangiocarcinoma will depend on the stage of the cancer, the disease subtype, the country in which the patient resides and their medical team
- Depending on the stage and location of cholangiocarcinoma, various surgical options are available. 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 cholangiocarcinoma) where the bile ducts, pancreas, gallbladder, surrounding lymph nodes and parts of the stomach and small intestine are removed, if affected
- Patients who undergo surgery for cholangiocarcinoma, should receive adjuvant chemotherapy with capecitabine to reduce the risk of the cancer coming back
- For patients with advanced cholangiocarcinoma that is inoperable, chemotherapy with cisplatin and gemcitabine (CisGem) is currently the standard of care for first line treatment
- Patients with cholangiocarcinoma that progress after first line chemotherapy with cisplatin and gemcitabine can receive FOLFOX chemotherapy (folinic acid, fluorouracil and oxaliplatin) which has been shown to improve survival
- Ongoing research is exploring the role of immunotherapy in cholangiocarcinoma treatment. In the USA, the immunotherapy, durvalumab, in combination with standard chemotherapy CisGem has been approved for patients with advanced cholangiocarcinoma and is currently under consideration in the UK and Europe
- Liver transplantation is an established treatment for cholangiocarcinoma in the USA, while some European centres are beginning to explore it as a potential option for early-stage cholangiocarcinoma. It has now been approved in the UK for intrahepatic cholangiocarcinoma (iCCA) under stringent eligibility criteria

Chapter 9. Molecular Profiling and Targeted Therapies

- Each cancer, even within the same cholangiocarcinoma subtype, is unique due to variations in its gene expression, and protein composition, resulting in a distinct molecular profile. Molecular profiling or genetic/genomic testing of a cancer biopsy allows identification of this unique profile in the laboratory and thus the treatments that the cancer is likely to respond to (precision medicine)
- Molecular profiling is a new and exciting field in cholangiocarcinoma research that will hopefully allow patients to receive a more personalised treatment depending on the molecular profile of their cancer
- Targeted therapies in cholangiocarcinoma are treatments that specifically focus on mutations or fusions within the cancer, which are identified through molecular profiling
- Currently, molecular profiling is not available for all patients but is used in clinical trials mainly for those with advanced cholangiocarcinoma or whose cancer has returned after surgery or chemotherapy
- Different gene alterations have been more commonly associated with perihilar (*ERBB2 [HER2], PIK3CA*) than intrahepatic (*IDH1* and *FGFR2*) cholangiocarcinoma, making the need for subtype targeting therapies even more important
- Pemigatinib is the first and only approved targeted therapy in Europe, USA, Scotland, and England, targeting the *FGFR2* gene fusion

Chapter 10. Nutrition

- There are no diets that can cure cholangiocarcinoma, but some can help alleviate treatment symptoms and improve the quality of life for patients
- Malnutrition can negatively affect the prognosis, overall quality of life and the tolerance and response to treatment of patients with cholangiocarcinoma
- Cholangiocarcinoma itself, and treatments for the disease, can cause various symptoms that affect the nutritional status of patients by reducing their appetite and causing nausea, diarrhoea, vomiting, sore dry mouth, abdominal pains, lethargy and/or taste changes
- In more than half of patients with cholangiocarcinoma, and especially those with advanced disease, ongoing muscle loss with or without fat loss will develop
- Ideally, patients with cholangiocarcinoma should work closely with their doctor and a specialist dietician to devise an appropriate treatment and nutritional plan
- Patients with cholangiocarcinoma undergoing a major surgical procedure that involves removal of the pancreas or parts of it (e.g., Whipple procedure) may need early pancreatic replacement therapy (PERT) and potentially diabetes medication
- Bile acid malabsorption (BAM) is a possible issue following surgery in cholangiocarcinoma patients. BAM occurs when bile acids are not adequately reabsorbed in the blood, leading to abdominal discomfort and symptoms like bloating, cramps, and pain. Treatment may involve dietary adjustments and medications like bile acid binders and pain relief to manage symptoms
- Small intestinal bacterial overgrowth (SIBO) can result from treatments like surgery, chemotherapy, and radiotherapy for cholangiocarcinoma, leading to symptoms like bloating, wind, diarrhoea, weight loss, and nutritional deficiencies. It can be mistaken for inflammatory bowel syndrome (IBS) and may have a significant psychological impact. Treatment involves antibiotics and dietary changes to address deficiencies and reduce excessive bacteria. Seeking advice from gastroenterology specialists and dieticians is essential for managing SIBO effectively
- Patients with cholangiocarcinoma undergoing chemotherapy or radiotherapy often face eating difficulties during and after treatment. Nutritional considerations include fortifying and supplementing the diet, focusing on high-protein and high-energy foods, adopting a ‘little and often’ eating approach and timing medications to alleviate symptoms
- SIBO can develop months after the completion of chemotherapy or radiotherapy treatment

Chapter 11. The Importance of Specialist Centres and Multidisciplinary Teams

- It is essential that patients with cholangiocarcinoma are referred to appropriate specialists, so that they can be properly assessed and offered the right treatment and care
- Patients with cholangiocarcinoma should ideally be treated in specialist centres 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
- Recent evidence indicates that, currently, due to the rarity and aggressiveness of cholangiocarcinoma, medical experts in the disease are concentrated in a few specialist centres in each European country
- In Europe, access to specialist centres and MDTs varies by country. A study in France showed that most patients with cholangiocarcinoma are treated in non-specialist centres where only one or two patients with the disease are seen per year
- The first set of recommendations, about how a multidisciplinary meeting should work for patients with cholangiocarcinoma, was recently published by ENS-CCA
- ENS-CCA recommends that the following medical professionals, with prior expertise in the field of cholangiocarcinoma, should be present in an MDT meeting:
  - **The doctor responsible for the patient**
  - **Oncologist:** *a cancer specialist*
  - **Hepatobiliary surgeon:** *a specialist in surgery of the liver, bile ducts and pancreas*
  - **Radiologist:** *a specialist who can interpret diagnostic images, e.g., X-rays, CT and MRI scans*
  - **Hepatologist:** *a liver specialist*
  - **Pathologist:** *a specialist who examines biopsies*
  - **Gastroenterologist:** *a specialist in gastrointestinal (stomach and intestines) and hepatological (liver, gallbladder, biliary tree and pancreas) diseases*
- Including supportive care specialists, nurse specialists, dieticians, psychologists, and academic researchers in the MDT for cholangiocarcinoma cases, will provide a more rounded approach and will enhance patient care
- Recent European studies reveal that patients with cholangiocarcinoma who are treated in specialist centres survive longer than those who are treated in non-specialist centres

Chapter 12. Clinical Trials

- Prior to the ABC clinical trials in England there were no reliable large-scale clinical trials or standard chemotherapy treatments for cholangiocarcinoma
- The outcomes of the pivotal ABC-01 and ABC-02 trials led to the establishment of the current first-line chemotherapy treatment, CisGem (gemcitabine and cisplatin), the ABC-06 trial established the second-line FOLFOX chemotherapy and the BILCAP trial demonstrated that follow-up chemotherapy with capecitabine is beneficial for patients who underwent surgery
- To date, there are many promising clinical trials currently underway for patients with cholangiocarcinoma
- Personalised, targeted treatments for cholangiocarcinoma based on the molecular profile of each patient is the primary focus of many current clinical trials
- Immunotherapies are a promising treatment for cholangiocarcinoma and are currently being evaluated in multiple trials either alone or combined with targeted treatments

Chapter 13. Patient Perspectives and Engagement

- Engaging with patients and their families is a critical component of high-quality healthcare
- Many patients have 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 cholangiocarcinoma have reported that at diagnosis the communication with their treating clinician can be poor and they feel distanced and confused from the decision-making processes that occur at multidisciplinary team meetings
- Many patients with cholangiocarcinoma feel the need to research their own disease and treatments to self-advocate and request a second and third medical opinion

Chapter 14. Patient Advocacy and CCA-focused Organisations

AMMF is the world's first and the UK's only charity exclusively dedicated to cholangiocarcinoma. It provides information, support, and encourages research to enhance disease diagnosis and treatment.

AMMF hosts an annual European cholangiocarcinoma conference, facilitating discussions among health care professionals and patients on the latest treatments, clinical trials, and research. Their website offers various resources in eight European languages, including dietary guidance, questions for doctors, and information on chemotherapy regimens and side effects management.

https://ammf.org.uk

APiC is a patient organisation in Italy, focused on increasing awareness, supporting research, and providing assistance to cholangiocarcinoma patients and their families during diagnosis and therapy.

APiC offer a comprehensive list of cholangiocarcinoma-related resources in Italian and organise awareness meetings and campaigns to educate the public and public bodies about the potential causes and risk factors of the disease.

https://en.apicinfo.it/la-ricerca-in-italia

The Global Cholangiocarcinoma Alliance (GCA) is an initiative guided by an experienced global Steering Committee to champion international collaborations and partnerships within the community, establishing a global voice for cholangiocarcinoma. They provide a wide range of educational resources both for patients and health care professionals.

https://globalccaalliance.com/en

Cholangiocarcinoma UK is a multidisciplinary group promoting collaborative research, improved patient services, and cholangiocarcinoma awareness. Affiliated with the British Association for the Study of Liver Disease (BASL), they host an annual research conference to foster collaboration in the field.

https://www.basl.org.uk/index.cfm/content/page/cid/28

ENS-CCA is a network of researchers from 13 European countries focused on understanding the biological mechanisms behind cholangiocarcinoma and identifying potential new treatments through basic, translational, and clinical research.

https://eurocholangionet.eu/european-network-for-the-study-of-cholangiocarcinoma-2

Chapter 15. The Unmet Needs

- Patients with cholangiocarcinoma face significant challenges, including difficulties in early diagnosis, limited treatment options, and poor prognosis
- Cholangiocarcinoma poses a major challenge due to its difficulty in early diagnosis, attributed to its asymptomatic nature, challenges in obtaining high-quality biopsies, and the lack of non-invasive biomarkers for early detection
- Cholangiocarcinoma is difficult to detect early due to not showing many symptoms or symptoms being non-specific and because of the challenges in obtaining accurate biopsies
- Prognosis for cholangiocarcinoma is poor, particularly for those that are ineligible for surgery, due to limited understanding of the disease, its aggressive nature, and usually late diagnosis
- Cholangiocarcinoma can come back even after 'curative' surgery
- Cholangiocarcinoma requires better early detection tools and treatments. Continued research and clinical trials are vital to improve patient outcomes and quality of life
- Patients with cholangiocarcinoma may not have easy access to specialised treatment centres due to their geographical location, highlighting a major need for raising disease awareness amongst non-specialist centres and improving access to multidisciplinary teams and specialist care for patients in Europe

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