Cholangiocarcinoma

Cholangiocarcinomas are tumors that arise from the biliary tract, a part of the digestive system. Although rare, these types of tumors have shown a steady increasing in prevalence and now account for 3% of all gastrointestinal (GI) cancers.[1] These cancers are, however, especially devastating as they are difficult to diagnose, are often found late, and are associated with a high death (mortality) rate.[1]

The following sections can be found on this page:

Anatomy of the liver and gall bladder.

Anatomy and Function

Bile is a mixture of enzymes, modified steroids and breakdown products of hemoglobin. It is produced in the liver, stored in the gall bladder, and helps digest fats in the small intestine. Collectively referred to as the biliary tract (also known as the biliary system or biliary tree), thin tubes (bile ducts) carry bile from the liver and gallbladder to the small intestine.

Bile ducts found inside the liver are called *intra*hepatic bile ducts. They meet outside of the liver (*extra*hepatic bile ducts) to form the common hepatic duct. This larger duct connects with the gallbladder and small intestine.

Types

Cancers can form in any part of the bile ducts. They fall into two broad categories based on the origin of tumor growth: intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma.[1] Intrahepatic cholangiocarcinoma arises from tumors that grow in the small ducts within the liver and extrahepatic cholangiocarcinoma, on the other hand, arises from tumors that grow in the bile ducts outside of the liver.[1] While, extrahepatic and intrahepatic cholangiocarcinoma produce similar symptoms, their risk factors, response to therapies, and origins are different.[1]

Risk factors

Epidemiological case-control studies have identified multiple risk factors that increase an individual's risk cholangiocarcinoma. While specific risk factors are believed to have different effects on an individual's risk for developing ductal or intrahepatic cholangiocarcinoma, research is ongoing in this area. In general, however, the risk factors for cholangiocarcinoma are united by a common mechanism: chronic (long-term) inflammation of the bile ducts.[2]Specifically, inflammation caused by:

- Cirrhosis of the liver[2], [3]
- Alcoholic liver disease[2], [3]
- Hepatitis C virus infection[2] [3]
- Human immunodeficiency (HIV) infection[2], [3]
- Diabetes[2] [3]

- Inflammatory bowel disease[2] [3]
- Parasitic infections[3]
- Bile-duct cysts[3]

Epidemiology studies have also identified other factors that correlate with cholangiocarcinoma.

- Aging: Cholangiocarcinoma rarely occurs in individuals before the age of 40 and is most diagnosed in individuals between 70-80 years old.[3]
- Family history: Bile duct cancers are rare and most are not found in individuals with a family history; however, specific genetic polymorphism may be associated with increased risk of cholangiocarcinoma.[3]

Learn more about chronic inflammation and cancer.

Prevention

Some studies have found that about 4 out of 10 cholangiocarcinoma patients have identifiable risk factors.[2] While some risk factors for bile duct cancer (such as aging and genetic predisposition) can not be changed, there are some things that can be done to lower one's risk. These include maintaining a healthy diet, limiting alcohol consumption, and getting vaccinated against hepatitis B virus.

Symptoms

Symptoms may be nonspecific and usually appear during the late stages of the disease; typically, only after bile ducts have been blocked.[4] Symptoms include:

- Jaundice[4]: Jaundice is a yellowing of the skin and eyes. Bile contains a green/yellow chemical called bilirubin. When the bile ducts become blocked by tumor cells bilirubin enters the bloodstream where it diffuses into the skin and white areas of the eyes.
- Dark urine[4]: When bilirubin levels are high in the blood it can enter urine. Bilirubin makes urine dark.
- Painless itchy skin (pruritis)[4]: Bilirubin in the skin can result in inching.
- Lightcolored stools[4]: Bilirubin contributes to the brown color of stool. When it does not reach the intestine stools may become lighter.
- Fever, nausea, and vomiting[4]: These are not typical symptoms of bile duct cancer but may develop as a result of an infection caused by blockage of the bile duct.
- Weight loss[4]

Detection and Diagnosis

The diagnosis for cholangiocarcinoma is difficult and the disease is often not detected until it has progressed to an advanced state.[4] Cholangiocarcinoma is often first suspected after signs of biliary duct obstruction (via ultrasonography) and/or abnormal liver function.[4] When cancer is suspected, computed tomography (CT) or magnetic resonance imaging (MRI) are often preformed to determine the precise size, number, and location of masses.[4] Unless metastases are observed, however, it is often difficult to differentiate between benign (non-metastatic) and malignant (metastatic) masses using these imaging techniques.[4] A definitive diagnosis of cholangiocarcinoma often requires endoscopic imaging.[4]

Learn more about CT

Learn more about MRI

Learn more about ultrasound

Staging and Pathology Report

Based on previous studies showing a correlation between the extent of invasion and tumor number, the American Joint Committee on Cancer (AJCC) proposed the T classification system (see below) in the 7th edition of the staging manual.[5] The prognostic validity of this system to distinguish between stages of intrahepatic cholangiocarcinoma has been supported by several studies.[5]

- T1: solitary tumor without vascular invasion
- T2a: solidary tumor with vascular invasion

- T2b: multiple tumors with/without vascular invasion
- T3: tumor(s) penetrating or invading the visceral peritoneum
- T4: periductal invasion

Tumor Biology and Genetics

Studies have identified several genes and cellular pathways that are linked to the development and spread of cholangiocarcinomas. Among these are specific tumor suppressor genes and genes that produce proteins that block tumor suppressor activity.

FBW7α

FBW7α (also known as CDC4, AGO and SEL10) works as a tumor suppressor for cholangiocarcinoma progression. When it is produced at high levels, cell division is blocked in the G1 phase. The protein has been shown to inhibit tumor growth in experimental models of cholangiocarcinoma. When FBW7α is present at high levels, it causes the destruction of c-Myc and cyclin E (proteins that promote cholangiocarcinoma growth). Based on this observation, a possible future treatment of cholangiocarcinomas might involve the targeting of the c-Myc gene.

MEN1/miR-24

The gene MEN1 encodes for menin, a tumor suppressor found in neuroendocrine tissue. Menin decreases cell reproduction, angiogenesis, migration, and invasion. Samples of cholangiocarcinoma were found to have less menin, indicating that its absence or inhibition may result in the formation of these tumors. MEN1 has shown to be negatively regulated by a small RNA, miR-24. Levels of miR-24 have been found to be increased in cholangiocarcinoma specimens. Therefore, reduced MEN1 and increased miR-24 are both correlated with the development and progression of cholangiocarcinomas. Note that the association (correlation) does not necessarily mean that they cause the disease. More work is needed to verify the links.

LCN2

Also known as oncogene 24p3, LCN2 is a gene that codes for lipocalin-2. Overexpression of this gene in cholangiocarcinoma cells increased metastatic potential, while it's knockout (silencing) inhibited cholangiocarcinoma cell growth in vitro and in vivo through induction of cell cycle arrest at G0/G1 phases. LCN2 has been shown to negatively regulate tumor suppressor genes like NDRG1 and NDRG2.

Treatment

Treatment options for bile duct cancer are currently very limited; however, depending on the tumor's location, stage of disease, and the health history of the patient, surgical removal can result in a cure.6 New findings suggest that liver transplants in combination with chemoradiotherapy could increase long-term survival.6 For most patients with inoperable tumors, however, chemotherapy and radiotherapy have been largely ineffective.1 Because the main focus of CancerQuest is on the biology of cancer and cancer treatments, we do not list detailed treatment guidelines. Instead, we provide links to organizations in the U.S. that generate treatment guidelines:

Learn about the treatments recommended by the National Comprehensive Cancer Network (NCCN). View NCCN Guidelines for Hepatobilliary Cancers'

Learn about how cancer treatments work at CancerQuest's page on cancer treatments.

For information about clinical trials:

Information about clinical trials from CancerQuest

Information about clinical trials from the National Cancer Institute

Information about clinical trials from Georgia Clinical Trials Online

Information about clinical trials from Winship Cancer Institute of Emory University

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2 [abcdefgh] Shaib YH, El-Serag HB, Davila JA, Morgan R and McGlynn KA. Risk factors of intrahepatic cholangiocarcinoma in the United States: A case-control study. Gastroenterology. 2005;128:620-626.
3 [abcdefghij] Tyson GL and El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology (Baltimore, Md). 2011;54:173-84.
4 [abcdefghijkl] Van Beers BE. Diagnosis of cholangiocarcinoma. HPB : The Official Journal of the International Hepato Pancreato Biliary Association. 2008;10:87-93.
5 [ab] Bartella I and Dufour JF. Clinical Diagnosis and Staging of Intrahepatic Cholangiocarcinoma. Journal of gastrointestinal and liver diseases : JGLD. 2015;24:481-9.
6 [ab] Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y and Ding Y. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. International journal of cancer. 2012;130:2155-63.