Cholangiocarcinoma

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KEYWORDS

• Cholangiocarcinoma • Bile duct • Intrahepatic • Extrahepatic • IDH1 • IDH2

Key points

- Cholangiocarcinomas can be classified according to anatomic location, macroscopic growth pattern, microscopic features, and cell of origin.
- Intrahepatic cholangiocarcinomas have recently been divided into 2 subtypes based histologic features and cell of origin: small duct type/canals of Herring and large duct type/peribiliary glands.
- Intrahepatic cholangiocarcinomas of small duct type can express neural cell adhesion molecule, N-cadherin, and C-reactive protein, and can harbor mutations in *IDH1/2*.
- In intrahepatic cholangiocarcinomas, the main risk factor is chronic liver disease (viral hepatitis).
- Extrahepatic cholangiocarcinomas can express S100P.

ABSTRACT

This article focuses on cholangiocarcinoma, both intrahepatic and extrahepatic. The various classification schemes based on anatomic location, macroscopic growth pattern, microscopic features, and cell of origin are outlined. The clinicopathologic, immunohistochemical and molecular differences between intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma, as well as differences in the 2 subtypes of intrahepatic cholangiocarcinoma, are discussed. Finally, precursor lesions, prognosis, treatment, and promising new potential targeted therapies are reviewed.

OVERVIEW

Cholangiocarcinoma is the most common malignancy of the biliary tree. Gaining a complete understanding of this disease can be challenging for many reasons. Cholangiocarcinoma is a heterogenous disease with different definitions, different classification schemes, newly described subtypes, and an evolving knowledge of the molecular basis of this disease. By its most simple definition, cholangiocarcinoma is cancer of the bile ducts. However, although many people include cancers that involve both intrahepatic and extrahepatic bile ducts in their definition,[1–3] other sources only view cholangiocarcinoma as cancer of the intrahepatic bile ducts and perihilar bile ducts (the American Joint Committee on Cancer [AJCC]/International Union Against Cancer [UICC] does not specifically use the term cholangiocarcinoma for distal tumors)[4] or just the intrahepatic bile duct.[5] For the remaining of this discussion, cholangiocarcinoma is defined as a cancer that arises from either the intrahepatic or extrahepatic bile ducts, excluding the ampulla of Vater and gallbladder.

The incidence of cholangiocarcinoma is low in the United States, with reported rates ranging from 0.72 to 1.67 per 100,000.[1,6,7] The incidence varies widely worldwide and the highest incidence of the disease is in Asia (Northeast Thailand) with a rate of more than 80 per 100,000 population.[1] Interestingly, in the United States, the incidence of intrahepatic cholangiocarcinoma (ICC) from 1992 to 2000 showed a 4% annual increase,

Disclosure Statement: No disclosures.
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Surgical Pathology 11 (2018) 403–429
https://doi.org/10.1016/j.path.2018.02.005

whereas the incidence of extrahepatic cholangiocarcinoma (ECC) remained constant with annual percent changes of 1%.[8] The increasing incidence of ICC in the United States was also supported by another study that showed the rates of both hepatocellular carcinoma and ICC approximately doubled between 1976 and 2000.[9] These trends seem to also be occurring worldwide.[10,11]

Most of the risk factors for the development of cholangiocarcinoma are related to chronic inflammation and irritation (**Box 1**). Some well-established risk factors are similar for both ICC and ECC.[12,13] Because of the differences in the incidence rates between ICC and ECC, studies have shown some differences in risk factors as well. A population-based study in the United States showed liver cirrhosis, thyrotoxicosis, chronic pancreatitis, and possibly duodenal ulcer disease to be related to both ECC and ICC, and hepatitis C virus infection, obesity, chronic nonalcoholic liver disease, and smoking to be significantly more common in ICC; because of the rarity of liver fluke infections and hepatolithiasis in the United States, these entities were not found to be risk factors in this study.[13]

Box 1
Risk factors for cholangiocarcinoma

Risk factors for extrahepatic and intrahepatic cholangiocarcinoma

- Biliary diseases (primary sclerosing cholangitis; primary or secondary biliary cirrhosis)
- Biliary malformations/choledochal cysts
- Cholelithiasis/choledocholithiasis
- Cholecystitis/cholecystectomy
- Liver flukes (clonorchis sinensis should be italicized)
- Cirrhosis
- Alcoholic liver disease
- Type II diabetes
- Thyrotoxicosis
- Chronic pancreatitis

Risk factors for intrahepatic cholangiocarcinoma

- Hepatolithiasis
- Hepatitis C virus infection
- Chronic nonalcoholic liver disease
- Obesity
- Smoking

CLASSIFICATION SCHEMES

Owing to the heterogeneity of cholangiocarcinoma and multiple sites of origin in the biliary tree, many classification schemes have been developed and used in clinical practice, creating some confusion as to the best way to classify these lesions.[14] Cholangiocarcinomas can be classified according to anatomic location, macroscopic growth pattern, microscopic features, and cell of origin.

CLASSIFICATION BY ANATOMIC LOCATION

Cholangiocarcinomas can divided by location into 2 general categories: intrahepatic and extrahepatic. ICCs arise within the second-order bile duct branches and peripheral branches.[4,5,15] Although ECCs are further subdivided by location, the definition varies among different major publications. According to the AJCC/UICC and College of American Pathologists (CAP), ECCs are further divided into perihilar and distal bile duct tumors: Perihilar cholangiocarcinomas arise proximal to the cystic duct origin, distal to the second-order bile ducts, and often involve the hepatic duct bifurcation, whereas distal bile duct tumors arise between the cystic duct origin and the ampulla (AJCC/UICC, CAP).[3,4,16] According to the World Health Organization (WHO), hilar (extrahepatic) tumors arise at or near the junction of the right and left hepatic ducts, whereas perihilar intrahepatic tumors arise in the right and left hepatic ducts away from the junction; and tumors arising in the distal bile duct are not classified as cholangiocarcinoma.[5] According to guidelines published by the European Association for the Study of the Liver, cholangiocarcinoma should be subclassified as intrahepatic, perihilar, or distal, where intrahepatic cholangiocarcinoma arises within the liver parenchyma; use of the term Klatskin is discouraged and the term extrahepatic is felt to not be helpful.[1]

Although there are limitations to this classification scheme, and although more recent molecular and epidemiologic data support using different classification schemes for cholangiocarcinoma (discussed elsewhere in this article), classifying cholangiocarcinomas by anatomic location has been widely used in the literature. Many current treatment regimens are also based on this classification scheme and are