Transplantation for Cholangiocarcinoma

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KEYWORDS

• Cholangiocarcinoma • Klatskin tumor • Liver transplantation
• Living donor liver transplantation • Neoadjuvant therapy
• Biliary stricture • Biliary stenting • Acute cholangitis

Cholangiocarcinoma (CCA) is a primary hepatic neoplasm that arises from the malignant transformation of cholangiocytes, the epithelial cells that line the biliary tree. Most tumors are classified as adenocarcinoma. CCA is the second most common primary hepatic malignancy and it is increasing in incidence globally.[1–4] Nevertheless, CCA remains a rare malignancy with 3500 to 5000 cases diagnosed annually in the United States and an incidence of approximately 0.85 per 100,000.[5]

RISK FACTORS

Although most cases of CCA arise in patients without an identifiable risk factor (ie, de novo CCA), several risk factors for the development of CCA have been identified, with chronic biliary inflammation being a common feature shared by many of them. Primary sclerosing cholangitis (PSC) is the most common identifiable risk factor in Western countries. The incidence of CCA in patients with PSC is 0.6% to 1.5% per year.[6,7] The lifetime risk of developing CCA in patients with PSC is between 7% and 17%, depending on the series.[6–9] Interestingly, the risk of developing CCA is not associated with the duration or severity of PSC or the presence of inflammatory bowel disease.[10] Chronic infection with the Asian liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis* are risk factors for the development of CCA.[11] The high prevalence of *O viverrini* infection in Northeast Thailand is likely responsible for the highest incidence of CCA in the world (96/100,000 in men and 38/100,000 in women).[12] Patients who received Thorotrast, a radiograph contrast agent used in the 1930s to 1950s that contains the radioactive compound thorium dioxide, are at an increased risk for the development of several cancers, including CCA, decades after exposure. CCA is one of the cancers that occur at an increased frequency in patients with Lynch syndrome.[13] Biliary papillomatosis, a condition characterized by multiple papillary

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adenomas in the biliary tree, carries a significant risk for the development of papillary adenocarcinoma and mucinous carcinoma forms of CCA.[14] Choledochal cysts carry a significant risk for the development of CCA by adulthood.[15,16] Cirrhosis from common causes, such as chronic hepatitis C and steatohepatitis, also carries an increased risk for CCA.[17]

PATHOPHYSIOLOGY AND CLASSIFICATION

Greater than 90% of CCAs are adenocarcinomas.[18] Typically CCA is a well-differentiated to moderately differentiated adenocarcinoma with a prominent, dense, desmoplastic stroma (**Fig. 1**). This stroma leads to annular thickening of the bile duct caused by the infiltration and fibrosis of the periductal tissues. The large amount of fibrous stroma greatly increases the difficulty in confirming CCA by cytology and biopsy. Uncommon histologic variants include papillary adenocarcinoma, squamous cell, mucinous, lymphoepitheliomalike, and anaplastic carcinoma.[18,19] Tumor cells are frequently positive for the immunohistochemical markers cytokeratins-7 and -20, alpha-v beta-6 integrin, cytoplasmic carcinoembryonic antigen, mucins, and epidermal growth factor receptor (EGFR).[20–22]

CCA is classified as either intrahepatic or extrahepatic based on its location in the biliary tree. This classification is relevant given the typically different presentations and management of intrahepatic versus extrahepatic CCA.

Intrahepatic CCA originates in a bile duct within the hepatic parenchyma. Intrahepatic CCA is typically a mass-forming neoplasm and is often confused with metastatic

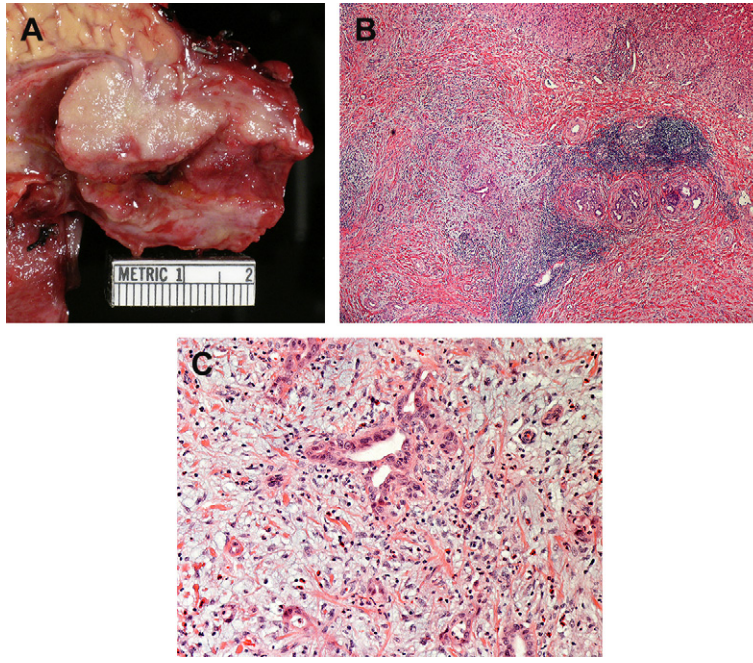

Fig. 1. Gross and microscopic pathology of CCA. (*A*) Gross pathology of CCA present in the distal common bile duct. (*B*) Microscopic pathology of CCA. CCA is present on the left portion of the image, benign peribiliary glands are located on the right, and normal liver tissue is in the upper portion of the image. (*C*) Higher power view of CCA. (*Courtesy of* Dr Thomas C. Smyrk, Mayo Clinic.)