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In brief

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This review focuses on the surgical management of biliary cancers from the perspective of a highly specialized and experienced group of surgical oncologists who work together to treat patients with hepatobiliary and pancreatic cancers at a tertiary cancer hospital. We topically combine these cancers because they all appear to arise from biliary epithelial cells. However, despite the apparent common cell of origin, they are remarkably different cancers whose main similarity is the poor outcome seen in the majority of patients. Unquestionably, outcomes have improved in recent decades. Our ability to image these tumors, and perhaps even detect them earlier, is remarkable. It goes without saying that the surgery on the liver, biliary tree and pancreas that is necessary to treat early-stage disease has become much safer. It was not long ago that surgery on the liver and pancreas was considered unsafe at best and unindicated at worst. This is a dramatic step forward and provides hope for cure in properly staged resectable patients. In addition, novel treatments that are informed by unique disease biology, as opposed to organ/cell of origin solely, are beginning to gain traction in this grouping of cancers.

Although there are many differences among biliary cancer types that have implications for various management aspects (tumor biology in particular), from a surgical perspective, anatomic location will always dictate their continued grouping. Thus, our goal in this review is to provide a state-of-the-art description of the surgical treatment of biliary cancers that provides insight into the underlying biology, as well as the surgical and technical issues involved in treating them.

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Whenever discussing disease, it is customary to start by reviewing the epidemiology, as there are often clues about the underlying biology in these data. The epidemiology of biliary cancers is interesting and demonstrative of their disparate qualities. Intrahepatic cholangiocarcinoma typically manifests as a large liver mass, and the associated risk factors are like those of hepatocellular carcinoma. Chronic inflammatory states of the liver, such as viral hepatitis and non-alcoholic fatty liver disease, are associated with both of these malignancies, and indeed intrahepatic cholangiocarcinoma is probably best characterized as a primary liver cancer. Hilar and distal cholangiocarcinoma can be associated with chronic biliary inflammation, such as parasitic hepatobiliary diseases and primary sclerosing cholangitis, but occurs without such risk factors in the majority of patients in the Western world. Gallbladder cancer is associated with chronic inflammation, perhaps related to gallstones. Whether the link to gallstones is causative is difficult to prove, given that the great majority of people with gallstones never develop a gallbladder neoplasm. It is interesting to note that a common link between these cancers may be some form of chronic inflammation; however, enough cases present without preceding inflammatory conditions such that it is clear that we truly do not understand their etiology.

The clinical presentation of patients with biliary cancers also differs. Intrahepatic cholangiocarcinoma typically manifests as a large and often locally advanced liver mass, because in its early stages it is commonly asymptomatic and may not even cause abnormalities in blood tests. Unfortunately, gallbladder cancer is also usually asymptomatic in its earliest and most curable stages. Given the link to gallstones, malignancy of the gallbladder is frequently found due to the symptoms of the stones rather than the tumor. In fact, one of the most common presentations is that of an incidental diagnosis after a cholecystectomy for stone disease. Extrahepatic cholangiocarcinomas, such as perihilar and distal bile duct tumors, present more commonly in early stages because even when small, the tumors occlude the common hepatic/bile duct and cause jaundice.

The surgical challenges inherent to these tumors are also different. Intrahepatic cholangiocarcinoma typically requires a major hepatic resection. In the fortunate cases of small peripheral intrahepatic cholangiocarcinomas (often found incidentally), a minor hepatic resection is adequate. The surgical treatment of localized gallbladder cancer has undergone a fascinating turn of events over the course of decades. Initially, any surgery for gallbladder cancer was felt to be futile due to the poor prognosis found in early studies. However, these early studies were from a time of poor imaging and likely a low rate of early-stage disease. This was followed by studies suggesting that an aggressive surgical approach could be beneficial, and surgeons began performing routine major hepatic resections (extended right hepatectomy) with bile duct resections for almost any stage disease beyond T1 tumors. Ultimately, this was found to be a morbid and unnecessarily extensive operation. Currently, the great majority of early-stage gallbladder cancers are treated with a minor segment IVb/V hepatic resection and portal lymphadenectomy without a bile duct resection, resulting in similar oncologic outcomes and dramatically reduced operative morbidity. Distal bile duct tumors require surgery like any periampullary tumor, with a pancreatoduodenectomy. Perhaps the most complex surgical tumor is hilar cholangiocarcinoma, a small tumor in a difficult location that requires extensive surgery to obtain narrow cancer-free margins. In stark contrast to the evolution of the surgical approach to gallbladder cancer, it has become evident that for the great majority of perihilar cholangiocarcinoma cases extensive surgery is necessary. Early on, these tumors were treated with bile duct resections alone, however margins were frequently positive and outcomes were poor. Due to the proximity of the biliary hilum to the central portion of the liver (it is physically attached to the liver), it has become apparent that in order to obtain negative margins and a chance at long-term survival, a major hepatic resection (left or right) including segment IV and the caudate lobe combined with a biliary resection is essential. In addition, vascular resections are often necessary, making these tumors even more of a surgical challenge. Although these major operations have become feasible – and even somewhat routine in referral centers – they are unfortunately still associated with significant morbidity and mortality.

In this review, we do not address the treatment of unresectable or metastatic disease but do comment on the role of adjuvant (and sometimes neoadjuvant) strategies. Unfortunately,

the development of effective adjuvant systemic therapies for these cancers has largely not been successful. Although the sections that follow provide details and references, the underlying problems with studies of adjuvant therapy on "biliary cancers" ignores that they are different diseases that just happen to start in the biliary tree, with differing epidemiology, clinical presentations and surgical treatments. Most prior adjuvant studies have grouped all biliary cancers together due to the relative rarity of these cancers, making accrual more feasible. Unfortunately, this concept ignores the different underlying biology and outcomes. For example, hilar cholangiocarcinoma is characterized by a high rate of locoregional failure, whereas gallbladder cancer has a similarly high rate of distant failure; studying the same adjuvant strategy in this situation seems counterintuitive. Disease-specific trials on biliary cancers are now currently being developed and are expected to shed light on effective adjuvant strategies, which are desperately needed. In addition, recent advances in the study of tumor biology have highlighted that biologic phenomena beyond organ/cell of origin, such as the underlying somatic genomics, epigenetic modulation, and tumor microenvironment, may be important considerations as we move towards personalized cancer care.

In summary, we provide a comprehensive review of the surgical treatment of early-stage biliary cancers. Although these are different diseases, surgeons, by decree of their specialty, will treat this grouping of tumors and need to understand not only the anatomic and surgical issues but the underlying biology and outcomes. Only with this understanding can we continue to improve the outlook for these patients.