Cholangiocarcinoma

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Cholangiocarcinoma (CCA) is a rare malignancy arising from the biliary epithelium. Based on the tumor's anatomic origin, CCA can be classified as intrahepatic cholangiocarcinoma (iCCA), perihilar cholangiocarcinoma (pCCA), and distal cholangiocarcinoma (dCCA). While each of these may have various presentations and behave uniquely in comparison to one another, CCA has a poor prognosis. Moreover, diagnosis and surgical resection of CCA can often be technically difficult. In particular, for patients with resectable disease, the operative intervention can be extensive and, depending on the location of the CCA, its extent may involve a liver resection, resection of the extrahepatic biliary tree, or a pancreaticoduodenectomy. Thus, diagnosing and treating CCA in a tropical area with limited resources is quite challenging.

1 Epidemiology

Hepatobiliary malignancies account for 13 % of all cancer-related deaths annually worldwide, with CCA accounting for 10–20 % of deaths from hepatobiliary malignancies [1]. Furthermore, CCA, particularly iCCA, is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC) [2]. However, the worldwide incidence of CCA varies significantly based on geographic location with an incidence of 85 per 100,000 people in northeast Thailand compared with 0.43 per 100,000 in Canada [3]. Most patients present with CCA at a median age greater than 65 years old; younger patients in the age range of 40–50 years can develop CCA, with these patients typically having associated primary sclerosing cholangitis (PSC) [1]. A slight male predominance exists for CCA [1].

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2 Aetiology

Recently, progress has been made in understanding the mechanisms of the pathogenesis of CCA. Traditionally, CCA has been thought to be derived from a chronically inflamed biliary epithelium as a result of various inflammatory processes, such as hepatolithiasis, congenital hepatic fibrosis, choledochal cysts, PSC, and biliary flukes *Clonorchis sinensis* and *Opisthorchis viverrini* endemic to East Asia [1, 2]. These chronic inflammatory insults may result in malignant transformation of cholangiocytes [1]. However, recent evidence indicates that CCA may directly originate from hepatic transdifferentiation of hepatocytes [4, 5]. Supporting this hypothesis, various risk factors associated with iCCA are similar to those for HCC, such as cirrhosis, chronic hepatitis B and C, obesity, diabetes, and alcohol [6]. Cholangiocarcinogenesis is likely a multifactorial process, however, and the majority of CCA cases are sporadic without any of these suspected risk factors present [2].

3 Diagnosis

The majority of CCA cases are clinically silent with symptoms developing only at an advanced stage. However, once symptomatic, clinical presentation is primarily dependent upon tumor location. Given the scant resources in a tropical setting, the clinical presentation is particularly useful as a potential indicator whether the tumor may be a dCCA, pCCA, or iCCA. For instance, painless jaundice is the most common presenting symptom (90 %) in patients with dCCA with 10 % presenting with cholangitis [7]. pCCA can cause unilobar biliary obstruction and ipsilateral vascular compromise resulting in atrophy of the affected hepatic lobe. As a result, the unaffected hepatic lobe often hypertrophies in response [8]. Patients with pCCA typically present with jaundice also, as well as possible constitutional symptoms. Finally, in the case of iCCA, presenting symptoms are typically more constitutional in nature, with patients complaining of abdominal pain, weight loss, night sweats, and generalized fatigue; a palpable mass and jaundice may also be associated with iCCA and typically denotes very advanced disease [1].

Prior to becoming symptomatic, an elevated bilirubin level may be the first indication that the patient may have a biliary obstruction/malignancy. In the setting of abnormal liver function tests or signs and symptoms concerning for a biliary or hepatic lesion, further workup should be initiated with serum tumor markers as well as imaging. While tumor markers such as carbohydrate antigen (CA) 19–9, carcinoembryonic antigen (CEA), and CA-125 are often utilized in the workup of CCA, tumor markers tend to have variable sensitivity and specificity [1, 2, 9]. For instance, CEA and CA-125 can be fairly nonspecific tumor markers that can be elevated in various other gastrointestinal or gynecologic malignancies [1]. CA 19–9 is the most common tumor marker used to detect the presence of CCA. However, CA 19–9 is a more specific, than sensitive, tumor marker for CCA. For instance, a high CA 19–9 may be strongly associated with the diagnosis of CCA and have prognostic significance; in contrast, a low or normal CA 19–9 cannot be used definitively to rule out the diagnosis of CCA [10, 11].

4 Imaging Techniques

While imaging is useful for both diagnosing CCA and determining the resectability of CCA, limited resources in a tropical area may make obtaining advanced imaging difficult. Ultrasound and computed tomography (CT) scan may be the best available imaging modalities for CCA. In the case of preoperative ultrasound, the accuracy of detecting CCA is dependent upon the tumor type, quality of the equipment, and experience of the person performing the ultrasound, making ultrasound fairly nonspecific with low sensitivity for detecting CCA [12, 13]. More useful than ultrasound, CT scan allows for much better delineation of the level of biliary obstruction, potential lymph node involvement, and the tumor's relationship to the vasculature, especially in the arterial and portal venous enhancement phases of the scan [13]. CT scan can also be particularly useful in distinguishing iCCA from HCC as well as distinguishing the various subtypes of CCA. While findings of dCCA and pCCA predominantly are characterized by biliary dilation in the presence or absence of a mass, iCCA characteristically appears as a hepatic mass with irregular borders, peripheral enhancement in the arterial phase, and progressive contrast filling on delayed imaging, attributable to fibrosis enhancement [14]. Magnetic resonance imaging (MRI) can also be very helpful, especially for pCCA; however its availability may be limited in a tropical setting. While ultrasound and cross-sectional imaging are critical in helping to assess resectability of CCA in that they can assist in detecting metastatic disease, vascular involvement, and lymph node involvement, as well as aid in preoperative planning, cholangiography is also typically desirable [13]. Cholangiography in the form of endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), or percutaneous transhepatic cholangiography (PTC) is an important and useful diagnostic modality to assess tumor location and the intraductal extent of CCA among patients with dCCA and, in particular, pCCA [15]. Unfortunately, cholangiography may or may not be readily available in the tropical setting with scant resources.

With limited imaging resources as well as limited resources to obtain a pathological diagnosis of malignancy, a low threshold for surgical intervention and operative exploration should exist. The goals of surgery should be curative intent surgical resection consisting of microscopically negative margins (R0 resection). For those patients with pCCA who require a liver resection, consideration of leaving an adequate future liver remnant is also required. In fact, for patients with pCCA and iCCA, surgical resection can be quite complex requiring extensive hepatic resection as well as biliary resection and reconstruction [2, 16]. In the setting of dCCA, pancreaticoduodenectomy is typically required if the lesion is resectable, which also can be technically difficult. While liver transplantation is not an option for patients with iCCA or dCCA, a subset of patients with unresectable pCCA or primary sclerosing cholangitis-associated pCCA may be candidates for liver transplantation; however, liver transplantation for pCCA may not be an option for patients in a tropical setting with limited resources [17–19].

5 Surgery: Curative Intent

In terms of the technical aspects of surgical resection, the surgeon should be comfortable with hepatopancreaticobiliary anatomy as well as dissecting out the portal structures to proceed forward with abdominal exploration and plan for curative surgical resection in CCA, regardless of subtype. In the operating room, the first step is operative exploration. If the patient is noted to have frankly metastatic disease, biopsies should be taken in the operating room for a pathological diagnosis. When no metastatic disease is present and the surgeon plans to proceed with a curative intent operation, intraoperative ultrasound should be utilized to further define the lesion and its proximity to the major vasculature for intraoperative planning purposes [20]. If the patient appears to be resectable in the operating room and partial hepatectomy is required as in the case of pCCA and iCCA, the portal structures should be dissected out to perform a Pringle maneuver as needed during resection. While dividing the liver parenchyma can be done using various techniques, a crush clamp technique to crush the liver parenchyma thus exposing the vessels and bile ducts for ligation is the most applicable approach in the tropical setting with limited resources. The Pringle maneuver should be implemented as indicated for hemostasis during the resection, and final hemostasis should be obtained with bipolar cautery. For patients with pCCA, in addition to a liver resection, removal of the extrahepatic biliary tree and a hepaticojejunostomy are typically required. For those patients with a dCCA, pancreaticoduodenectomy with removal of the head of the pancreas, duodenum, and distal biliary tree is required.

6 Palliative Surgery

If the patient is unfortunately not amenable to surgical resection, a surgical palliative bypass should be considered and is dependent upon the subtype of CCA present. In general, a minimum of 30 % of the liver parenchyma or two liver segments must be drained for relief of cholestasis and pruritus [21]. In the case of unresectable dCCA, a hepaticojejunostomy can be performed to alleviate biliary obstruction of the entire liver. In the case of a patient with unresectable pCCA, a proximal hepaticojejunostomy may not be feasible due to the location of the tumor. As such, for unresectable pCCA a segment III cholangiojejunostomy or side-to-side biliary enteric anastomosis at the base of segment IV can be performed intraoperatively for biliary drainage – especially when PTC or ERCP with biliary stent placement is not an available option in a remote tropical setting (Fig. 1) [21–23]. Unfortunately, surgical biliary bypass is not of benefit in the setting of iCCA and patients with massive iCCA causing biliary obstruction an abysmal prognosis.

For patients with advanced disease, systemic therapy should be considered either as definitive therapy (i.e., for patients with unresectable disease) or as adjuvant therapy (i.e., for patients with resected disease and adverse pathological features such as lymph node metastasis). Unfortunately, chemotherapy has minimally proven benefit in CCA and likely would not be administered in a remote tropical area [1]. In addition, radiation or other intra-arterial therapies are not curative in nature, and these therapies are unlikely to be feasible in a remote tropical setting [2].

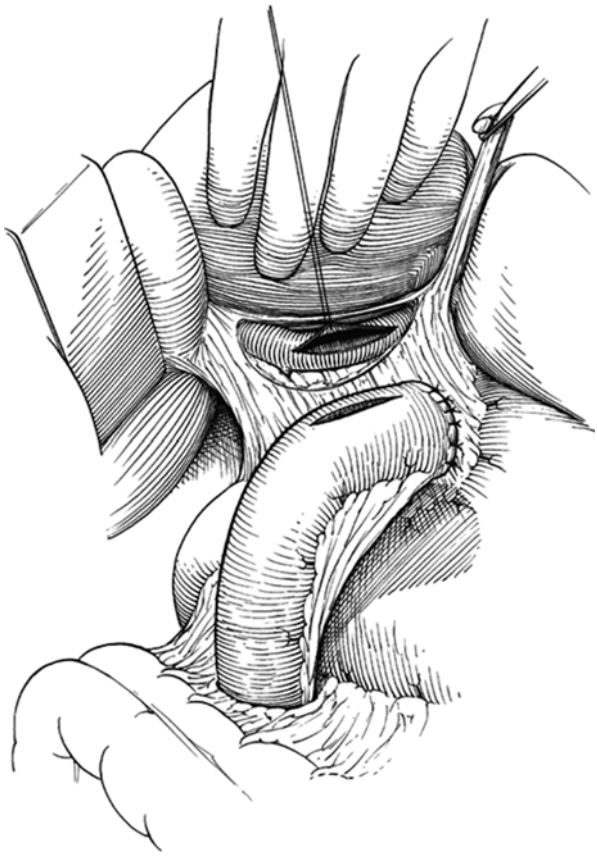

Fig. 1 By incising Glisson's capsule at the base of segment IV, the origin of the main hepatic duct, the bifurcation, and the left main hepatic duct are exposed. By retracting segment IV cephalad and incising the overlying tissue, the proximal extrahepatic biliary system and more specifically the extrahepatic portion of the left main hepatic duct are exposed. A side-to-side biliary enteric anastomosis can be performed at this time for biliary drainage in the setting of unresectable pCCA (Drawing by D. Factor, Mayo Clinic, Rochester, Minnesota, copyright 1995). Used with permission

While cholangiocarcinoma can be managed with scant resources, transferring a patient with a possible diagnosis of CCA to an area with more available resources may be appropriate. In addition, transferring the patient for appropriate surgical resection is also appropriate if the surgeon in the remote setting is not comfortable with the complexity of surgical resection associated with CCA. CCA traditionally requires extensive workup and complex surgical management. As such, both the diagnosis and surgical management of CCA in a tropical setting with limited resources can be quite challenging.

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