Distal biliary malignancy (cholangiocarcinoma) remains a rare diagnosis with a dismal prognosis. The vast majority of these cancers are adenocarcinomas that preferentially invade adjacent structures and drain to local lymph nodes. Given the small diameter of the common bile duct, early tumor detection with current imaging is not possible. Consequently, these patients typically present with symptoms and most with advanced disease. These cancers tend to grow perpendicularly to, and horizontally along, the bile duct, and therefore tumors that are detected by imaging tend to be underestimated and are often more extensive on surgical exploration. The anatomic relationship of the distal bile duct to the pancreas, duodenum, portal vein, and hepatic artery can also make removal of these tumors technically challenging.

Classification

Cholangiocarcinoma is traditionally classified anatomically as intrahepatic or extrahepatic, with extrahepatic disease further classified as proximal (hilar) or distal. The original report by Klatskin in 1965 [1] described cancer of the perihilar region, which currently accounts for about 60% to 80% of all cholangiocarcinomas. Subsequently, hilar malignancies have been further classified based on the Bismuth-Corlette system, which includes all extrahepatic disease down to the confluence of the cystic and common hepatic ducts [2]. Cholangiocarcinoma of the common bile duct (CBD) down to the level of the ampulla is considered distal disease, and is the...
type discussed in this article. Some of the early studies [3,4] made a distinction between lesions in the middle third (below the cystic duct but not intrapancreatic) and lower third (the intrapancreatic portion) of the bile duct. Because malignancies in the middle third of the extrahepatic bile duct are distinctly rare, more recent reports favor the classification of middle third lesions as distal disease [5].

**Epidemiology**

Cholangiocarcinoma, as a whole, accounts for approximately 3% of all gastrointestinal cancers, with distal bile duct cancer accounting for about 20% to 30% of all cholangiocarcinomas [5,6]. The likelihood of developing distal cholangiocarcinoma increases with age, with a peak in the seventh decade. There also tends to be a slight male predominance for these lesions. The overall incidence of extrahepatic cholangiocarcinoma seems to be declining [6]. The large, population-based statistics are difficult to interpret for two reasons, however. First, hilar and distal cholangiocarcinomas are analyzed together as extrahepatic disease, and second, gallbladder cancer is usually combined with extrahepatic cholangiocarcinoma in these reports [6,7].

**Pathology**

Microscopically, the vast majority (95% to 97%) of bile duct malignancies are adenocarcinomas (Fig. 1). They are typically well-differentiated, mucin-positive lesions that have a propensity to extend submucosally along the bile ducts. Cholangiocarcinomas also tend to have a strong desmoplastic stroma, invasive perineural spread, and, like many adenocarcinomas, they preferentially spread to regional lymph nodes [8,9].

Macroscopically, these lesions are divided into three types: sclerosing, nodular, and papillary. The sclerosing lesions appear as diffusely firm and tend to circumferentially occlude the lumen of the duct. The nodular type appears as a firm mass projecting into the duct lumen with the base continuous with the duct wall. Large, nodular lesions may look circumferential, however, and have features of the sclerosing type (nodular-sclerosing). The papillary subtype grows as a friable, polypoid mass that can have accompanying ductal sclerosis but tends to extend into surrounding structures. In a sentinel paper on the pathology of cholangiocarcinoma [8], 33 gross specimens were evaluated. Of these, 22 were of the sclerosing type and involved the proximal ducts or hilum. There were 8 papillary lesions, 7 of which involved the distal bile duct, and 3 nodular lesions, 1 involving the suprapancreatic CBD and two involving the intra-pancreatic distal CBD.
Risk factors

Like in other carcinomas, cholangiocarcinoma is associated with conditions that directly injure or lead to longstanding inflammation of the bile duct epithelium, which leads to a compensatory increase in the mitotic activity of the cholangiocytes and the consequent increase in the likelihood of...
mutation and error. Although most cases are sporadic and without an identifiable cause, the biliary epithelium can suffer several different forms of injury that may initiate the development of cholangiocarcinoma. Broadly, these injury patterns include acquired (primary sclerosing cholangitis [PSC], chronic stone disease), congenital (choledochal cysts, Caroli disease), infectious (Salmonella typhi, Clonorchis sinensis, Opisthorchis viverrini, hepatitis C) or chemical (smoking, thorotrast, dioxin).

**Primary sclerosing cholangitis**

PSC is a chronic, autoimmune inflammatory disease that results in multifocal strictures and fibrosis of the intrahepatic and extrahepatic biliary tree. Roughly 80% of patients who have PSC have associated inflammatory bowel disease (usually ulcerative colitis); however, few patients who have inflammatory bowel disease go on to develop PSC [10,11]. Although the natural history of PSC is variable, it is clear that these patients have an increased risk for cholangiocarcinoma. Although colectomy in the setting of ulcerative colitis does remove the risk for colon cancer, it does not affect the incidence or severity of sclerosing cholangitis [12,13]. The true overall risk for the development of cholangiocarcinoma in the setting of PSC is difficult to define because a large percentage of patients die of their disease and do not undergo autopsy. From the available natural history data, roughly 6% to 14% of patients who have PSC will have a cholangiocarcinoma diagnosed during their lifetime [10,12,14], although the true incidence (including autopsy diagnosed) of cholangiocarcinoma in this population is estimated to be as high as 30% to 40%. Although cholangiocarcinoma of the distal bile duct is uncommon in the setting of PSC, it does occur. In one report, it accounted for 13% of all PSC-associated cholangiocarcinomas [15].

Nearly half of these cholangiocarcinomas are diagnosed within 1 year of the initial diagnosis of PSC, suggesting subclinical inflammation and subsequent malignant degeneration, typically heralded by abdominal pain and jaundice. Furthermore, given the multifocal nature of PSC, the diagnosis of cholangiocarcinoma may be delayed, resulting in a higher percentage of unresectable tumors [10,12,14].

**Choledochal cystic disease**

There is a well-described 10% to 15% lifetime risk for cholangiocarcinoma in patients who have choledochal cysts. The development of these cysts is likely a consequence of pancreaticobiliary ductal malunion, in which the pancreatic duct joins the common bile duct proximal to the sphincter complex. It is believed that this abnormal junction of the pancreatic duct allows reflux of pancreatic enzymes proximally up the bile duct. This reflux not only injures the biliary epithelium but also increases the intraductal flow, and
consequently pressure, leading to dilation (cyst formation) of the bile ducts. Once formed, there is biliary stasis and chronic inflammation within the cyst [16,17]. If excised early in life, the risk for malignant degeneration is minimal. If allowed to persist into adulthood, however, the lifetime risk for cholangiocarcinoma in these patients can be as high as 30% [18].

Liver fluke infection

The ingestion of undercooked fish can result in infection with the hepatobiliary flukes *O viverrini* and *C sinensis*. These parasites are particularly common in Thailand, which has the highest incidence of cholangiocarcinoma in the world. The flukes gain entry to the biliary tree through the ampulla of Vater, and the subsequent infestation leads to a localized chronic inflammatory state that is strongly associated with the development of cholangiocarcinoma. The chronic inflammation results in not only biliary ductal hyperplasia but also increased production of nitric oxide and N-nitroso compounds that cause DNA damage [19].

Hepatolithiasis

Cholelithiasis is seen in up to 30% of patients who have cholangiocarcinoma. Although it is clear that gallstones increase the likelihood of gallbladder adenocarcinoma, the incidence of gallstones in patients who have cholangiocarcinoma approaches that of the general population [11]. It has been suggested in a case report [20] that cholelithiasis with associated choledocholithiasis increases the risk for distal bile duct adenocarcinoma; however, this relationship has not been proved. In contrast, the presence of chronic biliary stone disease (hepatolithiasis, Oriental cholangiohepatitis, or recurrent pyogenic cholangiohepatitis) significantly increases the risk for biliary ductal malignancy [21,22]. The consequences of biliary stones are obstruction of the intrahepatic ducts, recurrent cholangitis, stricture formation, and bile stasis, all of which contribute to chronic inflammation and subsequent malignancy.

Toxins

The prototype chemical associated with cholangiocarcinoma is thorotrast. This radiologic contrast agent was banned in the 1950s when its carcinogenic potential was realized. The development of cholangiocarcinoma is greatly increased in patients who received thorotrast, and these malignancies typically develop decades (up to 48 years in one report) after exposure [23]. Other chemical exposures implicated in cholangiocarcinoma development are alcohol, dioxin, nitrosamines, and smoking [24].

Biliary papillomatosis

Biliary papillomatosis is a rare, premalignant lesion characterized by multiple papillary adenomas distributed along the bile ducts. These tumors
can be mucin or non-mucin secreting and typically present with repeated episodes of right upper quadrant pain, jaundice, or cholangitis. One of the largest published series of biliary papillomatosis [25] reports that 83% of papillary adenomas contain carcinoma.

Other

Other risk factors implicated in the development of cholangiocarcinoma, but with less well-established cause–effect relationships, include hepatitis B, hepatitis C, cirrhosis, HIV infection, and diabetes.

Clinical presentation

The clinical difference between intra- and extrahepatic disease is based on biliary occlusion and local invasion. In general, the more distal the tumor the sooner clinical symptoms suggestive of biliary obstruction are present. Intrahepatic cholangiocarcinoma tends to present later in its course given the multiple drainage options around the tumor and atrophy of the obstructed liver parenchyma. Conversely, extrahepatic disease tends to present much earlier with painless jaundice, pruritus, dark urine, light stools, and fat malabsorption from bile acid deficiency. These patients can also experience abdominal fullness, early satiety, nausea, vague abdominal discomfort, malaise, fevers, night sweats, and weight loss. Given the proximity to the portal vein, hepatic artery, duodenum, and pancreas, distal cholangiocarcinomas quickly become locally invasive and ultimately metastatic. Rarely, distal bile duct malignancy is suspected incidentally when right upper quadrant ultrasound or computed tomographic scans are done for other reasons. Suggestive findings here include biliary ductal dilation, distension of the gallbladder, or a small mass.

All patients suspected of having a cholangiocarcinoma should have routine laboratory tests, including complete blood counts, electrolytes, liver chemistries, and liver function tests. Patients who have distal biliary obstruction are expected to have a direct hyperbilirubinemia and elevated alkaline phosphatase. Depending on the duration and severity of the obstruction, other liver function tests (serum albumin, prothrombin time, transaminases) may be normal. In those patients who have an incidentally discovered elevation in alkaline phosphatase, gamma-glutamyl transferase (GGT) levels should be checked. If the GGT is elevated in the setting of an elevated alkaline phosphatase, biliary etiology is likely and should prompt further investigation.

Molecular pathogenesis

The molecular pathogenesis of biliary malignancy consists of multiple alterations in normal cholangiocyte homeostasis. Although many cases of cholangiocarcinoma have no clear identifiable cause, there is typically
some inciting damage to the biliary epithelium [26]. At the cellular level, malignant transformation proceeds by several mechanisms, including cell-cycle dysregulation/autonomous growth (cyclin D, K-ras, IL-6, COX-2), inactivation of tumor suppressor genes (p53, p16), enhanced antiapoptotic factors (bcl-2, Mcl-1), angiogenesis (VEGF), and invasion/metastases (E-cadherin, α-catenin) [27–29].

In states of chronic inflammation (eg, PSC, liver fluke infection, hepatolithiasis) there is up-regulation of IL-6 and iNOS. The subsequent increase in nitric oxide not only potentiates DNA oxidative damage but also promotes cell growth by inhibiting apoptosis. Biliary inflammation also induces cyclooxygenase-2 (COX-2), which results in cell growth and survival by way of prostaglandin synthesis [27].

The group from Memorial Sloan-Kettering [30] has recently demonstrated a differential expression of various cell-cycle regulatory proteins based on the location of cholangiocarcinoma. Using tissue microarrays, they showed a progressive decline in the expression of p27 from intrahepatic to distal malignancies. Intrahepatic tumors were more likely to have overexpression of cyclin D1 and bcl-2 compared with hilar, gallbladder, and distal tumors. Conversely, distal tumors had overexpression of the tumor suppressor p53 when compared with the more proximal lesions.

**Tumor markers**

The two most widely used serum markers for cholangiocarcinoma are carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA). Much of the literature on the relationship between these tumor markers and cholangiocarcinoma is in patients who had underlying PSC. CA 19-9 is an antibody directed at circulating glycoproteins that are coated with sialylated blood group antigens. The level depends on the blood Lewis phenotype and therefore is undetectable in about 7% of the population [31]. Using a cutoff value of 100 U/mL, the reported sensitivity and specificity of CA 19-9 for detecting cholangiocarcinoma ranges from 53% to 89% and 80% to 91%, respectively [31–35]. The diagnostic accuracy is not improved by using higher cutoff values, for example, 180 U/mL [36]. CA 19-9 levels can be elevated not only in other malignancies (ovarian, stomach, pancreas, and colon) but also in any condition leading to dilation or inflammation of the bile ducts (benign stricture, cholangitis, and cholestasis).

CEA levels are even less accurate than CA 19-9 for diagnosing cholangiocarcinoma. CEA is an oncofetal glycoprotein that is most useful in detecting recurrences of colorectal cancers. It has also been shown to have some diagnostic usefulness in cholangiocarcinoma, however. Using a cutoff value of 5 ng/mL, the reported sensitivity and specificity are 33% to 68% and 82% to 95%, respectively [31,32,36,37]. Because CEA is often monitored together with CA 19-9, a scoring system (the Ramage score) was developed that combines these markers in an attempt to raise the diagnostic accuracy
of each individually. In the original study [38] a score (CA19-9 + [CEA × 40]) of greater than 400 had a reported sensitivity and specificity of 66% and 100%, respectively, in patients who had PSC. In a study performed by Lindberg and colleagues [32], the sensitivity and specificity for the Ramage score in identifying cholangiocarcinoma in patients who had endoscopic retrograde cholangiopancreatography (ERCP)-confirmed strictures was only 43% and 89%, respectively. In those patients who had underlying PSC, however, the sensitivity and specificity went up to 71% and 91%, respectively.

It is clear that CA 19-9 or CEA in isolation are not accurate in making the diagnosis of cholangiocarcinoma. In the appropriate clinical setting and with a high suspicion, however, these tests may aid in the diagnosis. More importantly, these markers should be followed closely in patients after surgical resection and if increasing should prompt aggressive imaging to search for recurrence or metastatic disease.

Other novel molecular tests used for the diagnosis of cholangiocarcinoma include digitized image analysis (DIA) and fluorescent in situ hybridization (FISH). These assays require biliary ductal brushing/aspirate samples collected during ERCP. The DIA allows computer analysis of the cell nucleus and quantification of DNA [39], whereas the FISH assay labels cholangiocyte DNA to detect specific chromosomal abnormalities [26]. In one study, a FISH assay using probes to chromosomes 3, 7, 9, and 17 had a superior sensitivity to routine cytology for the detection of malignancy in patients who had biliary strictures [40].

**Staging**

The most recent staging guidelines for extrahepatic bile duct cancers (6th edition) from the American Joint Committee on Cancer were published in 2002 and are shown in Table 1 [41]. The major difference from the 5th edition (published in 1997) was in the tumor (T) classification. In the earlier edition, a T-3 lesion was defined as tumor invading the liver, pancreas, gallbladder, duodenum, and stomach, whereas in the recent 6th edition, T-3 lesions do not invade the duodenum, stomach, or colon. This change reflects the concept of local invasion following an anatomic pattern and suggests that duodenal invasion portends a worse prognosis than pancreatic invasion alone. Given that these lesions are treated with pancreaticoduodenectomy, some have questioned the idea of duodenal invasion conferring a worse outcome. In a recent study from Japan, 95 patients underwent pancreaticoduodenectomy for distal cholangiocarcinoma. There was no difference in survival between those patients who had T-3 (N = 32) and T-4 lesions (N = 30). There was a clear difference, however, between those who had T-1 or T-2 cancers and those who had T-3 or T-4 cancers [42]. These data suggest that tumor extension outside the wall of the bile duct (whether into the pancreas, duodenum, or both) is a key step in the
natural history of distal cholangiocarcinoma. Furthermore, the likelihood of nodal spread is much higher once tumor has extended beyond the wall of the bile duct, and numerous studies have shown significantly reduced survival in patients who had node-positive disease.

Diagnostic imaging

The ideal diagnostic imaging modality for distal bile duct cancer is one that is easy to perform, is capable of diagnosing disease at an early stage, is without complications, and is able to detect any metastatic disease that may be present. Unfortunately, none of our current imaging modalities are capable of all of these. A combination of multiple complimentary imaging modalities is often required to not only make the correct diagnosis of a distal cholangiocarcinoma but also to adequately stage the patient.

The initial diagnostic modality for evaluating distal bile duct malignancy is based on the clinical presentation, with essentially two possibilities. First are those who undergo abdominal imaging for some other reason (eg, appendicitis, diverticulitis) and are incidentally found to have either a visible mass or irregularity, or biliary ductal dilation. The second and
much more common group of patients present with symptoms in some way related to the cancer (pain, jaundice). Ultrasound is typically performed in anyone presenting with right upper quadrant pain and jaundice. This modality may be helpful in detecting ductal dilation and, possibly, the level of obstruction. It will rarely visualize a tumor, however. CT is therefore essential if there is concern for the possibility of a distal malignancy (Figs. 2 and 3). A contrast-enhanced CT scan allows visualization of the ductal anatomy and most metastatic disease. More importantly, the arterial and portal-venous phases are separated allowing accurate assessment of the relationship between the cancer and the vascular structures [43], which is essential for proper assessment of resectability.

Computed tomography can provide a large amount of information, but it can underestimate the extent of tumor spread along the ducts and within the peritoneum. Further imaging is typically required before surgical intervention. The most useful tests after CT scan are magnetic resonance cholangiopancreatography (MRCP) and ERCP (Fig. 4). Each modality allows accurate visualization of the biliary tree. ERCP (Fig. 5) has the additional advantage of allowing preoperative biliary drainage and brush cytology to aid in the confirmation of cholangiocarcinoma. Although CT and ERCP are essential for the initial work-up of distal bile duct malignancies, the addition of endoscopic ultrasound (EUS) with fine-needle aspiration can be considered if the diagnosis is still in question (Fig. 6) [44,45].

Management

Surgery remains the mainstay of treatment of cholangiocarcinoma and up to 10% of all pancreaticoduodenectomies done for cancer are performed for distal bile duct malignancy [46–48]. Unfortunately, many patients present with advanced, unresectable disease and can only be offered palliative
Fig. 3. Low (A) and magnified (B) CT images demonstrating a mass in the head of the pancreas. These were taken from a 75-year-old woman who presented with painless jaundice. She underwent pancreaticoduodenectomy and was found to have a T-3 N-1 distal cholangiocarcinoma.

Fig. 4. Coronal MRCP image demonstrating mild dilation of the common bile duct up to the distal portion (A) with a T-2 dark lesion at the level of the transition point (B). Subsequent ERCP demonstrates a stricture in the distal CBD with proximal dilation (C).
Fig. 5. ERCP performed in a 53-year-old male who had nausea, pruritus, and a 20-pound weight loss. The patient initially underwent a CT scan that showed some mild ductal dilatation. Subsequently, this ERCP confirmed a distal bile duct stricture. He underwent pancreaticoduodenectomy and the final histology revealed a T-3 lesion with pancreatic and perineural invasion.

Fig. 6. Coronal reformatted computed tomographic image showing a transition point in the distal CBD (A). Subsequent EUS demonstrated dilation of the CBD (B) and a mass (C). The star indicates the dilated CBD and the arrow points to the mass.
measures. In those who do present with nonmetastatic disease, surgery is the only chance for prolonged survival and, possibly, cure.

In 1975, Dr. Warren [49] at the Lahey clinic published his series on the radical resection for periampullary cancer over the preceding 30 years. Between 1942 and 1971, he performed 348 pancreaticoduodenectomies, 47 of which (13.5%) were for distal bile duct malignancy. The operative mortality for all pancreaticoduodenectomies was 15%, and 21% after Whipple for distal bile duct cancer. This series was the first to analyze long-term outcomes after resection for these cancers. The overall 5-year survival for those patients who underwent resection was 25%, not much different from current reports. Furthermore, there was a distinct difference in the outcomes of patients who did or did not have lymph node metastases.

Over the past 30 years, there have been multiple reports in the literature on outcomes for distal bile duct cancer [3,5,42,49–58]. From these, it is clear that surgery remains the cornerstone of treatment (Table 2). These papers demonstrate that R-0 resection confers a survival advantage and that the prognosis for those who have unresectable disease is dismal. They also show that nodal status is the most important prognostic factor in those who undergo resection. Although the average overall 5-year survival for all patients undergoing resection is 24% (range 0%–44%), this goes up to 39% (range 22%–61%) in those who have R-0 resection and node-negative disease. Conversely, the average 5-year survival after resection with positive nodes is only 8.7% (range 0%–21%) and the median survival for palliated disease is months.

The largest series in the literature comes from the group at Johns Hopkins. They initially reported their experience with all histologically confirmed cholangiocarcinomas (N = 294) between January 1973 and December 1995 [5]. They subsequently combined this with data collected between January 1995 and March 2004 to give a total of 564 patients [58]. Over the 31-year period, 239 (42%) distal lesions were reported. During the early period, 27% (N = 80) of cholangiocarcinomas were distal cancers, whereas in the later period, 59% (N = 159) were distal cancers. This high proportion of distal lesions during the later period likely reflects referral patterns. In those who underwent surgery for a distal cholangiocarcinoma, 96% were resected (91% in the early period and 98% in the late period). The overall 5-year survival for distal lesions was 23% with a median of 18 months, and patients who had positive margins or nodes had significantly lower survival.

Since Whipple’s [59] description of pancreaticoduodenectomy in 1935, it remains the operation of choice for distal biliary malignancies. Pancreaticoduodenectomy is now a safer procedure, with current operative mortality rates of less than 5% (see Table 2). At our institution, we prefer a standard Whipple (with antrectomy) and we routinely perform a stented end-to-side pancreaticojejunostomy. The surgical outcomes after Whipple are improved when this procedure is performed at experienced centers. Despite great
<table>
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<sup>a</sup> Estimated from survival curve.
improvements in overall operative mortality, morbidity remains high. The most common complication after Whipple procedure is a pancreatic fistula, with leak rates ranging from 11% to 30% depending on the definition [60–63]. Although overall operative mortality may be as low as 1%, the mortality associated with pancreatic fistula after pancreaticoduodenectomy is significant. Moreover, these deaths may not occur within the first 30 days of surgery or during the same hospitalization. Typically, mortality from pancreatic fistula is from bleeding pseudoaneurysms or intra-abdominal sepsis [64].

Palliation

Unfortunately, not all patients who have distal bile duct malignancy present at a resectable stage. The reported resectability rates range from 22% to 89% [3,50,52,53,57]. Because there is no good evidence to support the use of chemotherapy or radiation, palliative measures should be offered. The goals of palliative management for distal cholangiocarcinoma are threefold. First is the alleviation of biliary obstruction. This alleviation can be accomplished surgically (hepaticojejunostomy or choledochojejunostomy) or endoscopically (plastic or metal stenting). Our general approach is to place a plastic stent at the initial ERCP if clinically indicated (complete obstruction with severe hyperbilirubinemia) or if surgical intervention will be delayed. Because most pancreaticoduodenectomies are performed at large academic centers, it is a common scenario for patients to receive a stent at the outside institution to allow time for transfer and appropriate work-up at the tertiary center. Metal stents are placed if it is clear that a patient has unresectable disease or if the patient had a plastic stent placed initially, but is subsequently found to have unresectable disease.

The second goal of palliative care is the relief of duodenal obstruction. Although this represents a premorbid state, obstruction of the duodenum must be treated in a way to minimize time in the hospital. Endoscopic duodenal stenting offers a relatively easy method of relieving obstruction with minimal risk for postprocedure complications.

Finally, all patients should have adequate pain control. Because these tumors have a tendency for perineural invasion, they can become painful. If pain is uncontrollable with oral narcotics, patients should be offered hospice care with intravenous narcotics, antiemetics, and other medications as needed.

Other biliary malignancies

Aside from cholangiocarcinoma, some other malignant neoplasms of the distal bile duct include carcinoid, other neuroendocrine tumors, lymphoma, squamous cell carcinoma, and undifferentiated tumors. These malignancies
are rare, however, representing less than 3% to 5% of tumors in this location [11,58], with most descriptions of these tumors in case reports [65–67].

Summary

Cancer of the distal bile duct remains a diagnosis with a dismal outlook. Despite great advances in diagnostic imaging, molecular pathogenesis, and surgical outcomes, the 5-year overall survival remains poor. A pancreaticoduodenectomy with an R-0 resection gives the best likelihood of prolonged survival.

References


