Biliary Tract Cancers

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In the United States, an estimated 20,000 new cases of liver and biliary tract cancer are diagnosed annually.1 Biliary tract cancer is the second most common primary hepatobiliary cancer, after hepatocellular cancer. Approximately 7500 new cases of biliary tract cancer are diagnosed per year; about 5000 of these are gallbladder cancer, and between 2000 and 3000 are bile-duct cancers.1 Biliary tract cancers have traditionally been divided into cancers of the gallbladder, the extrahepatic bile ducts, and the ampulla of Vater, whereas intrahepatic bile-duct cancers have been classified as primary liver cancers.2 The term “cholangiocarcinoma” was originally intended to refer only to primary tumors of the intrahepatic bile ducts and was not used for tumors of the extrahepatic bile ducts.3 Lately, however, the term has been used to include intrahepatic, perihilar, and distal extrahepatic tumors of the bile ducts.4 Perihilar tumors involving the bifurcation of the hepatic duct are also called Klatskin tumors, from Klatskin’s original description in 1965.5 In this review, the term “cholangiocarcinoma” is used for primary tumors of the bile ducts, including intrahepatic, perihilar, and distal extrahepatic tumors (Fig. 1).

The perihilar bile-duct tumors were further classified by Bismuth et al. as tumors below the confluence of the left and right hepatic ducts (type I), tumors reaching the confluence (type II), tumors occluding the common hepatic duct and either the right or the left hepatic duct (types IIIa and IIIb, respectively), and tumors that are multicentric or that involve the confluence and both the right and left hepatic ducts (type IV).6 Even more detailed classifications have been proposed, but they are not used in daily practice.7 Most cholangiocarcinomas involve the perihilar and distal extrahepatic bile ducts.

Although the numbers vary among countries and regions, about two thirds of all cases of cholangiocarcinoma are perihilar tumors, about one fourth are distal extrahepatic tumors, and the remainder are intrahepatic.8 Except for embryonal rhabdomyosarcoma, the frequency of all types of biliary tract cancers increases with age. Gallbladder cancers are more frequent in women,8 and cholangiocarcinomas are slightly more common in men.9 These sex differences are probably related to the higher incidence of gallstones in women and of primary sclerosing cholangitis in men. These are known risk factors for gallbladder cancer and cholangiocarcinoma, respectively.

PATHOLOGICAL FEATURES

As with most tumors of the digestive system, the large majority of primary tumors are carcinomas.10,11 There are several histologic types, the most common of which are adenocarcinoma, papillary carcinoma, and mucinous carcinoma. The histologic grade varies from well differentiated to undifferentiated. With the exception of a rare cystadenocarcinoma, the tumors consist of clusters of cells, sometimes surrounded by desmoplastic stroma (Fig. 2A). The desmoplastic reaction of a cholangiocarcinoma can be so extensive that the specimen consists mainly of fibrous tissue with sporadic clumps of malignant cells. This feature, especially in patients with cholangitis, intraductal gallstones, or bile-duct stents, makes it very difficult to distinguish between reactive tissue and well differentiated cholangiocarcinoma. Because normal and malignant bile-duct epithelial cells are not known to express a protein unique to bile-duct tissue, there is no pathognomonic immunohistochemical test to confirm the cell type of origin. However, several types of immunohistochemical staining support the diagnosis of malignant biliary tract tissue. The most frequently used stains are immunohistochemical stains for cytokeratins, carcinoembryonic antigen, and mucins (Fig. 2B and 2C). Other tumor types, which occur in less than 5 percent of cases, include squamous-cell carcinoma, small-cell carcinoma, and mesenchymal tumors. In patients with the acquired immunodeficiency syndrome (AIDS), Kaposi’s sarcoma and lymphoma of the biliary tract have been reported.12,13 Finally, many other types of tumor can obstruct the biliary tree by direct extension (for example, in the case of tumors of the pancreas, duodenum, stomach, or colon), metastasis (for example, tumors of the ovary, breast, or colon), or lymph-node involvement (for example, lymphoma). These tumors will not be discussed in this review.

The stage of cancers of the biliary tract is deter-
Figure 1. Classification of Cancers of the Human Biliary Tract. Panel A shows the overall classification of biliary tract cancers. Panel B shows the Bismuth classification of perihilar cholangiocarcinomas. Yellow areas represent tumor, and green areas normal bile duct.

Figure 2. Cholangiocarcinoma. Tumor cells are shown after staining with hematoxylin and eosin (Panel A, ×62), carcinoembryonic antigen (Panel B, ×62), and MUC-1 (Panel C, ×125). There is extensive desmoplastic stroma surrounding the tubules of the cholangiocarcinoma cells. The specimens in Panels B and C are from the same patient.
RISK FACTORS

Specific risk factors for the development of hepatobiliary cancer have been associated with different parts of the biliary tree. Gallbladder cancer is more frequent in patients with gallstones, especially if the gallstones are symptomatic and large. Other factors associated with gallbladder cancer include female sex, obesity, and high carbohydrate intake, all of which are also associated with gallstone disease. However, the increase in the risk of gallbladder cancer in patients who have cholelithiasis but no symptoms or other risk factors is so low that prophylactic resection of the gallbladder is not recommended. For persons over 50 years of age, the rate of gallbladder cancer is about 0.02 percent per year. Bacterial infection of bile, with or without gallstone disease, occurs in up to 80 percent of patients with gallbladder cancer. Studies from Chile, Bolivia, and India suggest that the combination of chronic infection with Salmonella typhi and cholelithiasis is strongly associated with gallbladder cancer. Polyps, especially when they are more than 1 cm in diameter, and calcification of the gallbladder wall (porcelain gallbladder) are other predisposing factors for cancer. Finally, anomalous pancreaticobiliary ductal junction, a rare anatomical anomaly sometimes associated with a choledochal cyst and found mostly among Asians, is associated with a markedly increased risk of gallbladder cancer. In patients with this condition, prophylactic cholecystectomy with cyst excision is recommended.

Cholangiocarcinoma, both intrahepatic and extrahepatic, is a well-known complication of primary sclerosing cholangitis. Although lifetime risks in excess of 30 percent have been reported among patients with primary sclerosing cholangitis, most studies mention lifetime risks of about 10 percent. The time from the diagnosis of primary sclerosing cholangitis to the development of cholangiocarcinoma ranges from 1 year to more than 25 years, although at least one third of cases of cholangiocarcinoma are diagnosed within 2 years after the diagnosis of primary sclerosing cholangitis. Patients who have ulcerative colitis in the absence of symptomatic primary sclerosing cholangitis or who have long-standing intraductal gallstone disease also have an increased risk. Other, rarer conditions associated with the development of cholangiocarcinoma include bile-duct adenoma, multiple biliary papillomatosis, choledochal cysts, Caroli’s disease (cystic dilatation of intrahepatic bile ducts), and exposure to the radiopaque medium thorium dioxide (Thorotrast). In Southeast Asia, infestation with the parasites Opisthorchis viverrini (in Thailand, Laos, and Malaysia) or Clonorchis sinensis (in Japan, Korea, and Vietnam) is associated with an increase by a factor of 25 to 50 in the risk of cholangiocarcinoma. Case-control studies have shown an increased risk associated with smoking. However, despite all these known risk factors, many cases of cholangiocarcinoma occur in patients without obvious risk factors.

Adenomas of the ampulla of Vater, especially when they are villous, are known to be premalignant lesions. Adenomas are frequently seen in patients with familial adenomatous polyposis, who have a risk of ampullary adenocarcinoma that is 100 times that in the normal population. Other possible, but not well-established, risk factors include cholecystectomy, endoscopic sphincterotomy, and use of tobacco. Finally, AIDS has been associated with cancers throughout the entire biliary tract, including the ampulla of Vater.

MOLECULAR ASPECTS

Conversion from normal to malignant bile-duct tissue probably requires a number of successive genomic mutations similar to the sequence of events proposed for other gastrointestinal cancers, although our knowledge of biliary tract cancers is less extensive than that of the more common gastrointestinal cancers. A variety of mutations in oncogenes, as well as tumor-suppressor genes, have been described in specimens of biliary tract tumors. These include mutations in the oncogenes K-ras, c-myc, c-neu, c-erb-b2, and c-net and the tumor-suppressor genes p53 and bel-2. These mutations may lead to detectable phenotypic changes; for instance, biliary epithelial cells switch from expressing MUC-1 apomucin before birth to MUC-3 after birth. Malignant transformation can reverse this process, and as mentioned before, many cholangiocarcinomas show staining with antibody to MUC-1. Similarly, core mucin carbohydrate Tn and sialyl-Tn antigens were expressed in many intrahepatic bile-duct cancers. However, as with other tissue types, mutations and phenotypic changes are also seen under nonmalignant conditions, precluding their routine use in clinical practice. Although there is much speculation regarding the factors that induce the various mutations, such as chronic inflammation, ethnic background, diet, and exposure...
to carcinogens, little or nothing is known about how these factors actually cause biliary tract cancer.

**DIAGNOSIS**

The most common presenting symptoms of biliary tract cancer are caused by bile-duct obstruction and include jaundice, clay-colored stools, cola-colored urine, and pruritus. These symptoms tend to occur early if the tumor is located in the common hepatic duct, the common bile duct, or the ampulla of Vater. They develop later in perihilar disease and, when present, are often markers of advanced disease in cancer of the gallbladder and intrahepatic cholangiocarcinoma. Pain in the right upper quadrant is the most frequent presenting symptom in gallbladder cancer but not in cholangiocarcinoma. In general, pain, fatigue, malaise, and weight loss occur in advanced disease. The combination of acute right-upper-quadrant pain, fever, and chills, in association with cholestasis, strongly suggests cholangitis. Cholecystitis in elderly patients is sometimes the first manifestation of gallbladder cancer. Occasionally, pancreatitis is the first manifestation of a peripapillary tumor. The physical examination may reveal jaundice, right-upper-quadrant pain, hepatomegaly, and a palpable gallbladder or mass, depending on the location and stage of the tumor.

Abnormal laboratory-test results in biliary tract cancer can be divided into those due to interference with normal physiologic processes, resulting from inhibition of normal bile flow or tumor invasion, and those due to the secretion of abnormal products. Cholestasis and cholecystitis due to obstruction of bile flow typically result in moderate-to-marked increases in serum levels of alkaline phosphatase, bilirubin, $\gamma$-glutamyltransferase, and bile acids, whereas aminotransferase levels are only mildly elevated or normal. Prolonged obstruction of the common hepatic or common bile duct may lead to deficiency of fat-soluble vitamins and increased prothrombin time. Malignant transformation may result in the secretion of abnormal products into the bile or serum. Indeed, a large number of potential markers of biliary tract cancers have been identified. Many markers, however, are not specific and may also be present under nonmalignant conditions (Table 1). Of these, cancer antigen (CA) 19-9 is currently widely used, in particular for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis (Fig. 3). Serum CA 19-9 levels greater than 100 U per milliliter (the normal level is less than 40 U per milliliter) have been reported to have a sensitivity of 89 percent and a specificity of 86 percent for the detection of cholangiocarcinoma in these patients. A marker consisting of CA 19-9 in combination with carcinoembryonic antigen (according to the formula CA 19-9 + [carcinoembryonic antigen × 40]) had an accuracy of 86 percent. Other serum markers have been studied, but none seem to be as useful as CA 19-9. We also use serum CA 19-9 levels to assess the effect of treatment and to detect recurrence of the disease.

The first diagnostic imaging procedure in most patients with cholestasis or right-upper-quadrant pain is ultrasonography of the liver and gallbladder. Gallbladder cancers and intrahepatic cholangiocarcinoma may be detected as mass lesions. The absence of mobile filling defects within the gallbladder that attenuate the sonographic beam with “shadow” essentially excludes the possibility of cholelithiasis. Perihilar, extrahepatic, and peripapillary cancers may not be detected by ultrasonography, especially when they are small. Instead, indirect signs may point toward these diagnoses. The most common indirect sign is ductal dilatation throughout the obstructed liver segments; an abrupt change in ductal diameter may indicate the exact location of the tumor. Color Doppler imaging can detect compression, encasement, or thrombosis of the portal vein as well as encasement or occlusion of the hepatic artery by tumor. The sensitivity and specificity of ultrasonography vary with the type of tumor, the quality of the equipment, and the experience of the operator. Under optimal conditions, gallbladder cancers are detected in at least 50

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**Table 1. Potential Tumor Markers in Gallbladder Cancer and Cholangiocarcinoma.**

<table>
<thead>
<tr>
<th>Marker</th>
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<tr>
<td>Tumor antigens or products</td>
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<tr>
<td>Carcinoembryonic antigen</td>
<td>Ker et al.</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Ker et al.</td>
</tr>
<tr>
<td>CA 125</td>
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<tr>
<td>Sialyl-Tn antigen</td>
<td>Sasaki et al.</td>
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<td>Fibronectin</td>
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<td>Oncogene K-rat</td>
<td>Rijken et al.</td>
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<tr>
<td>Tumor-suppressor gene pS3</td>
<td>Suto et al.</td>
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<tr>
<td>Metabolic product</td>
<td>Nishijima et al.</td>
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<td>Lactate</td>
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<td>CA 195</td>
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<td>CA 242</td>
<td>Maeda et al.</td>
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<tr>
<td>DU-PAN-2</td>
<td></td>
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<td>Protein induced by the absence of vitamin K or antagonist II (PIVKA-II)</td>
<td>Nakao et al.</td>
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<tr>
<td>Cytokine</td>
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<td>Goydos et al.</td>
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<td>Proteases</td>
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<td>Trypsin-2–α1-antitrypsin complex</td>
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<td>Peptide</td>
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<td>Pancreatic polypeptide</td>
<td>Bruckner et al.</td>
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Figure 3. CA 19-9 and Bilirubin Levels in a 75-Year-Old Man with Primary Sclerosing Cholangitis since 1972 and Cirrhosis. CA 19-9 levels gradually increased, although bilirubin levels remained near normal, and ultrasonography and computed tomography (CT) did not reveal a focal abnormality. On endoscopic retrograde cholangiography (ERC), strictures and dilatations of bile ducts typical of primary sclerosing cholangitis were seen, with hilar strictures suggesting cholangiocarcinoma. Brush specimens did not show atypical cells, but mild cytologic atypia was evident in other biopsy specimens. Repeated endoscopic retrograde cholangiography with biopsy five months later revealed a single focus of well-differentiated, invasive adenocarcinoma.

percent of cases, and detection rates as high as 86 percent have been reported for cholangiocarcinoma.67,68

Computed tomographic (CT) scanning may show an intraluminal gallbladder mass, with or without direct invasion of the liver or other adjacent tissues (Fig. 4A).69 Intrahepatic mass lesions (Fig. 4B) and dilated intrahepatic ducts (Fig. 4C) are easily detected, but visualization of perihilar tumors or tumors involving the portal venous or arterial system is best achieved by intravenous bolus-enhanced spiral or helical CT scanning.70 Dilatation of the intrahepatic bile ducts in a single, small hepatic lobe with hypertrophy of the contralateral lobe suggests the atrophy—hypertrophy complex, as seen with tumors chronically obstructing a single lobe and invading the ipsilateral portal vein.71 Bilobate dilated intrahepatic ducts and a normal or collapsed gallbladder and common bile duct suggest a perihilar tumor. A distended gallbladder without dilated intrahepatic or extrahepatic ducts

Figure 4. Computed Tomographic Scans of Patients with Gallbladder Cancer and Intrahepatic and Hilar Cholangiocarcinoma. Panel A shows a large gallbladder cancer (arrow) filling part of the distended gallbladder and invading the adjoining intestine. Panel B shows a huge intrahepatic cholangiocarcinoma (arrow) limited to the right hepatic lobe. Panel C shows a hilar cholangiocarcinoma causing marked dilatation of the bile ducts in the lateral segments of the left lobe. The left medial segment is atrophied (arrow). The bile ducts in the right hepatic lobe are also dilated.
is seen in patients with cystic duct stones and tumors. On the other hand, a distended gallbladder with dilated intrahepatic and extrahepatic ducts is typical of distal extrahepatic ductal cancers, cancers of the ampulla of Vater, intraductal gallstones, or pancreatic cancers. Tumor emboli from hepatocellular cancer, metastatic colorectal cancer, or intrahepatic cholangiocarcinoma are an unusual cause of perihilar or distal extrahepatic bile-duct obstruction. Unlike ultrasonography, CT may also show the peripancreatic, periduodenal, perirectal, celiac, and mesenteric lymph nodes. Both ultrasonography and CT permit guided fine-needle aspiration or biopsy of suspicious lesions.

Magnetic resonance imaging (MRI) permits excellent visualization of hepatic parenchymal abnormalities, as well as the visualization of the biliary tree and vascular structures. MRI with the use of ferrous oxide and gadolinium yields information similar to that yielded by CT, cholangiography, and angiography combined.72,73 Because MRI is noninvasive and does not involve exposure to radiation, it may replace CT and angiography for the preoperative assessment of biliary tract cancers.

Without doubt, cholangiography is currently the most important radiologic procedure for assessing the resectability of a tumor. Both percutaneous cholangiography and endoscopic retrograde cholangiography are performed; the choice of procedure depends on the suspected location of the tumor and the experience of the operators. In general, more proximal and sclerotic tumors are best assessed by percutaneous transhepatic cholangiography (Fig. 5), whereas distal extrahepatic and simple perihilar lesions are amenable to endoscopic assessment. Periampullary tumors can be directly visualized and biopsies can be performed with a side-viewing endoscope. Both the distal and the proximal extent of tumor growth must be clearly visualized to help the surgeon decide whether an attempt at curative resection is feasible. However, diffuse abnormalities of the biliary system, such as those seen in primary sclerosing cholangitis, sometimes make it impossible to delineate a tumor exactly.

Because many patients with gallbladder carcinoma present with obstructive jaundice, cholangiography is also frequently used in the preoperative assessment of this tumor; typically, a long stricture of the common hepatic duct is found. Once access to the biliary tree has been achieved, bile samples or brush cytologic or biopsy specimens can be obtained. Bile samples, obtained through a percutaneous stent, contain cancerous cells in 30 to 40 percent of cases of cholangiocarcinoma.75,76 The use of brush biopsy and cytologic examination may increase the yield to 40 to 70 percent. Unfortunately, even percutaneous or endoscopic biopsy not infrequently yields nondiagnostic tissue because of the desmoplastic nature of the lesion. The highest diagnostic yield may come from ductal shave biopsies with an atherectomy catheter and percutaneous biopsies at the location of the suspected tumor immediately adjacent to a previously placed biliary stent.77 Placement of percutaneous or endoscopic stents relieves symptoms, improves hepatic function, and allows palpation of the ductal structures at the time of exploration.

Angiography accurately documents vascular encasement and thrombosis of the portal vein and hepatic artery, but in most cases it is not necessary before surgery. When combined with cholangiography, it correctly predicts resectability in the majority of cases.78,79 However, as mentioned before, MRI may replace angiography for the assessment of vascular encasement and patency.

Several new and promising imaging techniques have recently become available. Endoscopic ultrasonogra-
Cholangiocarcinoma cells have a high glucose uptake. 

Both glucose and $[18F]$fluoro-2-deoxy-D-glucose are phosphorylated, but $[18F]$fluoro-2-deoxy-D-glucose is not further metabolized. As a result, cholangiocarcinoma cells accumulate $[18F]$fluoro-2-deoxy-D-glucose, causing "hot spots" on scanning. In addition, hepatocytes have high glucose-6-phosphatase activity and rapidly turn over $[18F]$fluoro-2-deoxy-D-glucose, thereby further increasing the signal-to-background ratio. Several small studies have documented the ability of PET to detect cholangiocarcinomas as small as 1 cm in diameter. Other, less frequently used new diagnostic methods include intraductal ultrasonography, and radiolabeled antibody or ligand imaging.

Cancers of the gallbladder and of the perihilar and distal extrahepatic bile ducts may spread directly into adjacent organs or the abdominal cavity, where they can be detected by ultrasonography, CT, MRI, or endoscopic ultrasonography. The exact extent of invasion, however, may be difficult to discern. In gallbladder cancer, metastatic disease is rather common and occurs early. In perihilar and distal extrahepatic bile-duct cancers, distant metastases are relatively infrequent and occur late in the course of the disease. The lungs and bones are most commonly involved. The metastases can be detected by chest radiography, CT, or bone scanning.

**TREATMENT AND SURVIVAL**

**Surgery**

At present, only surgical excision of all detectable tumor is associated with improvement in five-year survival.4,8,9,46 Multiple factors related to both the patient and the tumor need to be evaluated when assessing resectability.7 Poor performance status, major cardiopulmonary disease, and preexisting cirrhosis are the most common patient-related factors precluding surgical exploration. Poor nutritional status, sepsis, and severe cholestasis also predict a poor outcome, but these factors can sometimes be reversed preoperatively. Distant metastases, extensive regional lymphadenopathy, and regional vascular encasement or invasion preclude resection. Although laparoscopic ultrasonography in some cases may alter either the diagnosis or the staging of the tumor while obviating the need for open laparotomy,88,89 its value is not fully known.

Stage 0 and stage I gallbladder cancers are effectively treated with laparoscopic cholecystectomy. Although curative resection of stage II disease may also be achieved by laparoscopic cholecystectomy, the survival rates are higher when more extensive, open resections are performed.90 For most stage II, III, and IV gallbladder cancers, extended or radical cholecystectomy is preferred.91 In addition to the gallbladder, the adjacent liver tissue and regional lymph nodes are removed. Depending on the extent of liver invasion, subsegmental, bisegmental, lobar, or extended lobec resection is performed. Japanese investigators found a five-year survival rate of 75 to 80 percent in patients with disease limited to the mucosa, muscularis, or subserosa who were treated by extended cholecystectomy.92 Even more aggressive surgery has been performed in patients with extension of tumor into the duodenum, pancreas, colon, or kidney fossa.93 As expected, mortality and morbidity have been high, and the outcome in general has been disappointing. The overall survival, except for patients with stage 0 or I tumors, is dismal. Most patients present with advanced disease, and the combined five-year survival for all stages of gallbladder cancer is between 5 and 10 percent.

Intrahepatic cholangiocarcinoma is generally treated by hepatic resection alone.4,94 The surgical treatment of perihilar cholangiocarcinoma depends on the Bismuth class.6 Most authors report that about one third of patients can undergo curative resection, but some suggest that up to two thirds of patients should undergo resection with curative intent.4 En bloc resection of the extrahepatic bile ducts and gallbladder, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy are recommended for type I and II tumors, and that treatment plus hepatic lobectomy is recommended for type III tumors.88,96,97 The intent is to achieve a tumor-free proximal margin of at least 5 mm.98 Because type II and III tumors often involve the ducts of the caudate lobe, caudate lobectomy is recommended to improve local control and survival for patients with type II or III tumors.88,99,100 In distal extrahepatic tumors and cancers of the ampulla of Vater, pancreatoduodenectomy is the therapy of choice. Commonly, a pylorus-preserving Whipple procedure is performed. Survival is directly related to the stage of disease. The median survival for patients with intrahepatic cholangiocarcinoma without involvement of the hilum varies among centers from 18 to 30 months. The median survival for patients with perihilar cholangiocarcinoma is slightly less, varying from 12 to 24 months.96,101 The five-year survival for both groups of patients varies between 10 percent and 45 percent, with the best results reported from Japan.88,100,102 Finally, five-year survival rates of 15 to 25 percent in patients with distal extrahepatic cholangiocarcinoma and of 50 to 60 percent in patients with periampullary cancers have been reported.103-105
In the treatment of patients with extrahepatic bile duct cancer, surgery is the only potentially curative option. However, despite advances in surgical techniques and perioperative care, survival remains poor, with a median survival of 6 to 12 months, and most patients experience recurrence of disease.108,109 At the Mayo Clinic, patients undergoing orthotopic liver transplantation for cholangiocarcinoma are selected according to very strict criteria and undergo preoperative external-beam and internal transcatheter radiation, continuous intravenous chemotherapy, and pretransplantation exploratory laparotomy. According to preliminary data, all patients treated so far have had prolonged tumor-free survival.

Palliative surgery is used selectively.96,110 Removal of the gallbladder may prevent acute cholecystitis in patients with gallbladder cancer. In all forms of biliary tract cancer, a gastrojejunal bypass for the treatment or prevention of obstruction of the gastric outlet is selectively indicated; intraoperatively, a neurolytic celiac-plexus block can be performed for pain control. Some centers have reported good palliation and quality of life after a segment III or V hepaticojejunostomy.111,112 Finally, adequate relief of cholestasis due to distal extrahepatic tumors can be obtained with choledochojjunostomy or hepaticojejunostomy.

**Radiation**

Biliary tract cancers are difficult to control locally by external-beam radiation therapy alone. However, external irradiation, alone or in combination with fluorouracil, may relieve pain and contribute to biliary decompression.

When external irradiation is used in combination with total resection in patients with microscopically involved margins, or in combination with fluorouracil and supplemental transcatheter brachytherapy, survival appears to be prolonged, and in a few cases long-term survival has been reported.113-115 The median survival increases from 6 to 8 months among patients treated with surgery or palliative stent placement and chemotherapy to 12 to 19 months among those who receive similar treatment combined with external-beam irradiation.114-116 Escalation of the radiation dose may increase survival.113,115 Other investigators have not found a significant survival benefit resulting from the addition of irradiation to surgical resection or stenting.117,118

**Chemotherapy**

Preoperative or postoperative chemotherapy does not significantly improve survival or the quality of life in patients with biliary tract cancers. A large number of agents, including fluorouracil, mitomycin, methotrexate, etoposide, doxorubicin, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, and cisplatin, have been tested as single or combination therapies without appreciable effects. Partial responses lasting from weeks to several months have been observed in approximately 10 to 20 percent of cases.119

**Other Palliative Treatments**

In most patients who are not candidates for surgery, endoscopically or percutaneously placed plastic or metal stents relieve the symptoms associated with cholestasis.120 Plastic stents tend to become occluded and require replacement approximately every three months. Metal stents tend to stay open longer because of their larger diameter. They rarely migrate and are currently widely used.121 According to a recent report, the use of a hematoporphyrin derivative as a sensitizer, followed two days later by intraluminal photoactivation, resulted in prolonged biliary decompression and an improved quality of life.122 Pain is managed by oral and percutaneous narcotics and, if needed, by a celiac-plexus block. Survival is related to the stage of the disease. The median survival varies from 6 to 12 months, with most centers reporting no patients surviving at 5 years.16,96,104,110

**FUTURE DIRECTIONS**

Major improvement in the survival of patients with cancers of the biliary tree will probably not result from more aggressive or advanced surgical techniques or oncologic radiation therapy. Instead, efforts should be directed at prevention, early detection, and novel treatments derived from basic research. The universal benefits of smoking cessation and weight reduction are obvious. Populations at risk — that is, patients with primary sclerosing cholangitis, intraductal stones, cystic diseases of the biliary system, cholelithiasis combined with *S. typhi* infection, liver flukes, or familial adenomatosis polyposis — need to be identified so they can be offered preventive strategies and prophylactic or early treatment.123 For instance, patients with primary sclerosing cholangitis who are found to have cellular atypia on initial brush cytologic examination may benefit from programs of annual surveillance consisting of a serum CA 19-9 measurement and endoscopic retrograde cholangiography. The use of brush cytologic examination or biopsy would be analogous to current surveillance strategies for inflammatory bowel diseases.124

There is a need for new, cost-effective screening methods, including simple assays for tumor markers in the serum, bile,125 or stool.126 A noninvasive radiologic technique that can detect disease at a curable stage may already exist, if the early data from studies of PET scanning are confirmed in larger series. Several promising chemopreventive agents, currently under inves-
tigation for other types of cancer, may also be benefi-
cial to patients with primary sclerosing cholangitis.

For patients with nonresectable disease, new drugs
that selectively target malignantly transformed cells
without damaging normal tissue are required. In-
deed, several promising novel therapeutic agents,
including farnesyl transferase and angiogenesis inhibi-
tors, as well as immunotherapeutic methods directed
against tumor-specific antigens, may soon be tested
in clinical studies. Finally, once we understand the
complex molecular pathobiology of the transforma-
tion from normal to malignant biliary tract tissue, ge-
etic repair of the mutations responsible for the ma-
lignant phenotype may become possible.

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REFERENCES

2. Percy C, Van Holten V, Muir C, eds. International classification of dis-
3. Albores-Saavedra J, Henson DE, Sobin LH. Histological typing of tu-
mours of the gallbladder and extrahepatic bile ducts. 2nd ed. Berlin, Ger-
5. Klatkin G. Adenocarcinoma of the hepatic duct at its bifurcation in the
porta hepatis: an unusual tumor with distinctive clinical and patho-
6. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation with-
out affecting the common bile duct. Gastroenterology 1969;56:1747-56.
7. Dutta U, Garg PK, Kumar R, Tandon RK. Chronic salmonella typhi
9. Poly HC Jr. Carcinoma and the calcified gall bladder. Gastroenterolo-
y 1966;30:582-5.
10. Chijiwa K, Kimura H, Tanaka M. Malignant potential of the gallblad-
der in patients with anomalous pancreaticobiliary ductal junction: the dif-
11. Kornfeld D, Ekblom A, Ihre T. Survival and risk of cholangiocarcino-
13. Farges O, Malassagne B, Sebagh M, Bismuth H. Primary sclerosing cholangitis: liver transplantation or biliary surgery. Surgery 1995;117:146-
55.
16. Bismuth H, Nakache B, Diamond T. Management strategies in resec-
17. Pitt HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary
18. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallblad-
19. Stauropoulos GD, Scolapio JS. Cholangiocarcinoma of the extrahepatic
20. Santanah AB, Oxford RF, Berk TC, Cohen Z, Bapat BV, Gallinger S.
Familial segregation in the occurrence and severity of peripancreatic neo-
22. Ekblom A, Yuen J, Karlsson BM, McLaughlin JK, Adamo HJ. Risk of
pancreatic and periampullar cancer following cholecystectomy: a popula-
23. Hakamada K, Itoh T, Endoh M, Sasaki M. Late bile duct cancer after
the manipulation of the sphincter of Oddi in the treatment of benign pan-
Association d’un sarcome de Kaposi de l’ampoule de Vater et d’une cho-
langite sclerosante à Cryptosporidium chez un patient porteur d’un SIDA.
p53, MIB-1 (Ki-67 antigen), and argyrophilic nucleolar organizer regions
26. Terada T, Nakamura Y, Sirica AE. Immunohistochemical demonstra-
tion of MET overexpression in human intrahepatic cholangiocarcinoma
27. Bienen AM, van Gulik TM, Polak MM, Sturmd PJ, Gouma DJ, Offer-
haus GJ. Diagnostic and prognostic value of incidence of K-ras codon 12
mutations in resected distal bile duct carcinoma. J Surg Oncol 1998;68:
187-92.
28. Voraveen N, Foster CS, Gilbertson JA, Sikora K, Wxhman J. Oncogene
expression in cholangiocarcinoma and in normal hepatic development.
29. Sasaki M, Nakamura T, Terada T, Kim YS. Biliary epithelial expression
of MUC1, MUC2, MUC3 and MUC5/A apomucins during intrahepatic
bile duct development and maturation: an immunohistochemical study.
of mucin carbohydrates and core proteins in hepatolithiasis and cholangi-
31. Bata N, Gourv S, Foster CS, Gilbertson JA, Sikora K. Malignant transfor-


