

Review Article

*Medical Progress***BILIARY TRACT CANCERS**

PIET C. DE GROEN, M.D., GREGORY J. GORES, M.D.,
 NICHOLAS F. LARUSSO, M.D.,
 LEONARD L. GUNDERSON, M.D.,
 AND DAVID M. NAGORNEY, M.D.

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.⁴ 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-

From the Mayo Clinic, Rochester, Minn. Address reprint requests to Dr. de Groen at the Division of Gastroenterology and Hepatology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905.
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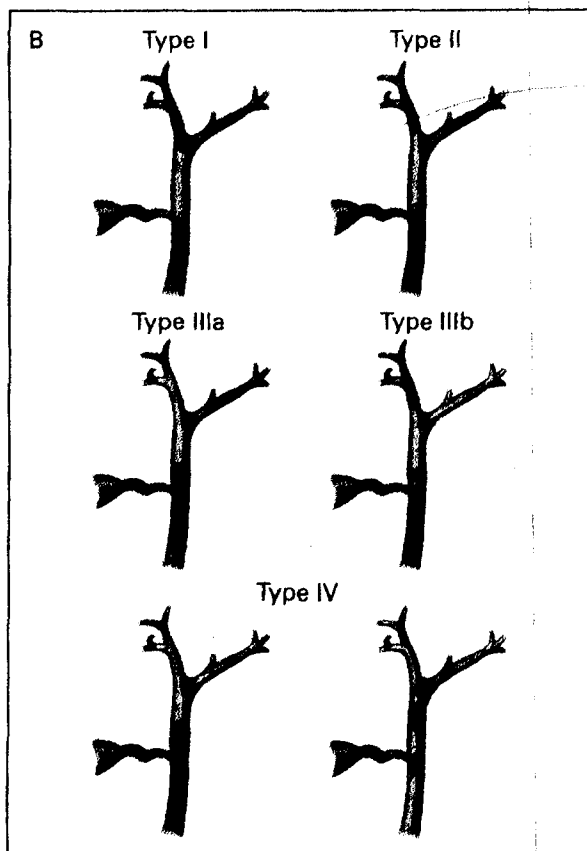
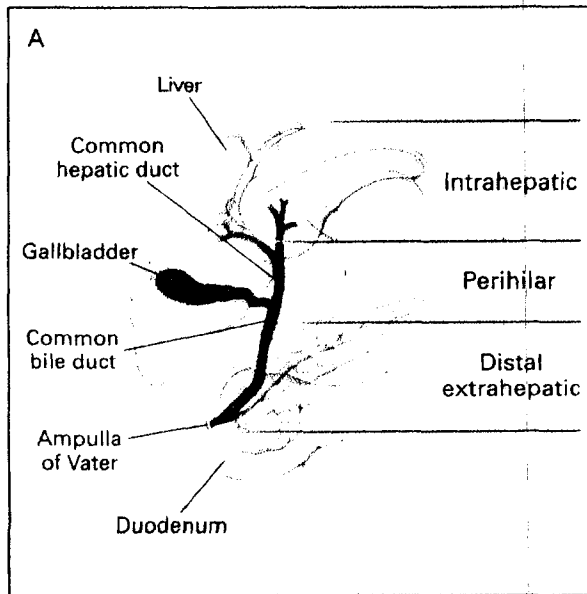
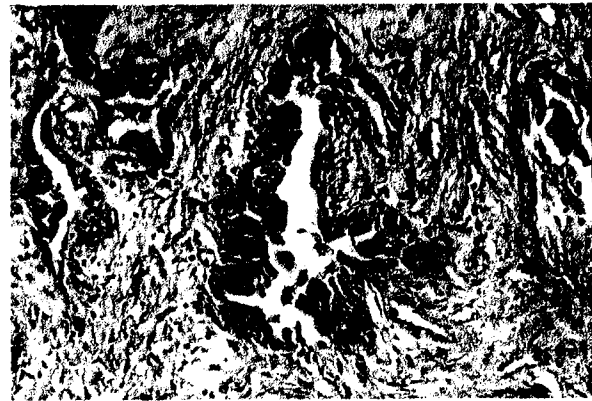
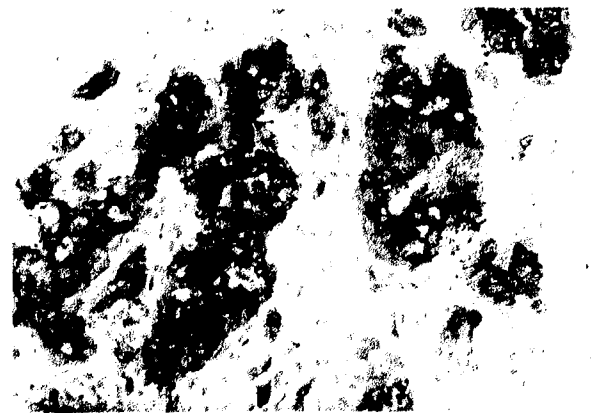


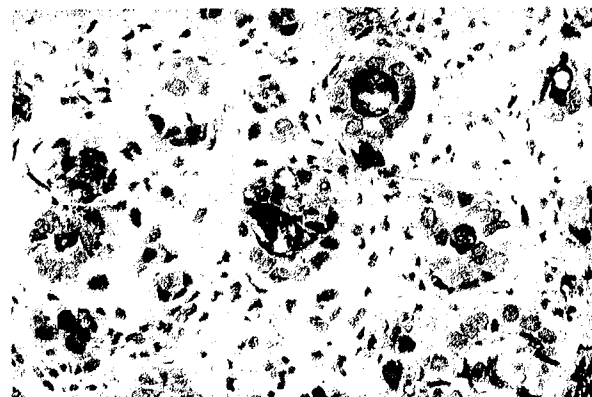
Figure 1. Classification of Cancers of the Human Biliary Tract. Panel A shows the overall classification of biliary tract cancers. Panel B shows the Bismuth classification of perihilar cholangiocarcinomas. Yellow areas represent tumor, and green areas normal bile duct.



A



B



C

Figure 2. Cholangiocarcinoma.

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

mined according to the tumor-node-metastasis system of classification.¹⁴ Because the staging is slightly different for each type of biliary tract cancer, we give only a general description of the stages. Biliary tract cancers are classified from stage 0 to stage IV. Stage 0 is carcinoma in situ; this stage is not defined for intrahepatic cholangiocarcinoma. In stage I, tumor invasion is limited to the mucosa, muscle layer, or ampulla. In stage II, local invasion of tumor is seen. In stage III, tumor invasion is similar to that in stage I or II, but metastasis into regional and hepatoduodenal lymph nodes or invasion of adjacent tissues has occurred. Stage IV cancer is characterized by extensive invasion of the liver; invasion of adjacent structures or organs; metastases in peripancreatic, periduodenal, periportal, celiac, or mesenteric lymph nodes; and distant metastases.

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,¹⁵ especially if the gallstones are symptomatic¹⁶ and large.¹⁷ Other factors associated with gallbladder cancer include female sex, obesity, and high carbohydrate intake, all of which are also associated with gallstone disease.¹⁶ 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.¹⁸ Bacterial infection of bile, with or without gallstone disease, occurs in up to 80 percent of patients with gallbladder cancer.^{19,20} Studies from Chile, Bolivia, and India suggest that the combination of chronic infection with *Salmonella typhi* and cholelithiasis is strongly associated with gallbladder cancer.^{21,22} 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.^{23,24} 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.²⁵ 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.²⁶⁻²⁸ 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.^{27,29} 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.^{27,30} 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).³⁰ In Southeast Asia, infestation with the parasites *Opisthorchis viverrini* (in Thailand, Laos, and Malaysia)³¹ or *Clonorchis sinensis* (in Japan, Korea, and Vietnam)³² 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.^{33,34} 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,³⁵ who have a risk of ampullary adenocarcinoma that is 100 times that in the normal population.³⁶ Other possible, but not well-established, risk factors include cholecystectomy, endoscopic sphincterotomy, and use of tobacco.^{33,37,38} Finally, AIDS has been associated with cancers throughout the entire biliary tract, including the ampulla of Vater.^{12,13,39}

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-met* and the tumor-suppressor genes *p53* and *bcl-2*.⁴⁰⁻⁴³ 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.⁴⁴ 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.^{44,45} 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.^{7,46} 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.⁷ 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.⁴⁷ Occasionally, pancreatitis is the first manifestation of a periampullary 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, γ -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 non-malignant conditions (Table 1).^{59,62} Of these, cancer antigen (CA) 19-9 is currently widely used, in particular for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis (Fig. 3).^{63,64} 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.⁶³ A marker consisting of CA 19-9 in combination with carcinoembryonic antigen (according to the formula $CA\ 19-9 + [carcinoembryonic\ antigen \times 40]$) had an accuracy of 86 percent.⁶⁴ Other serum markers have been studied, but

TABLE 1. POTENTIAL TUMOR MARKERS IN GALLBLADDER CANCER AND CHOLANGIOCARCINOMA.

MARKER	REFERENCE
In bile	
Tumor antigens or products	
Carcinoembryonic antigen	Ker et al. ⁴⁸
CA 19-9	Ker et al. ⁴⁹
CA 125	Ker et al. ⁴⁹
Sialyl-Tn antigen	Sasaki et al. ⁵⁰
Fibronectin	Korner et al. ⁵¹
Oncogene	
K-ras	Rijken et al. ⁴² Voravud et al. ⁴³
Tumor-suppressor gene	
p53	Suto et al. ⁴⁶
Metabolic product	
Lactate	Nishijima et al. ⁵²
In serum	
Tumor antigens or products	
Carcinoembryonic antigen	Kuusela et al. ⁵³
CA 19-9	Kuusela et al. ⁵³ Su et al. ⁵⁴
CA 50	Kuusela et al. ⁵³
CA 125	Su et al. ⁵⁴
CA 195	Bhargava et al. ⁵⁵
CA 242	Kuusela et al. ⁵³
DU-PAN-2	Maeda et al. ⁵⁶
Cytokeratin 19 fragment	Kashihara et al. ⁵⁷
Protein induced by the absence of vitamin K or antagonist II (PIVKA-II)	Nakao et al. ⁵⁸
Cytokine	
Interleukin-6	Goydos et al. ⁵⁹
Proteases	
Trypsinogen-2	Hedstrom et al. ⁶⁰
Trypsin-2- α 1-antitrypsin complex	Hedstrom et al. ⁶⁰
Peptide	
Pancreatic polypeptide	Bruckner et al. ⁶¹

none seem to be as useful as CA 19-9.⁵⁴ 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.⁶⁵ 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 periampullary 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.⁶⁶ 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

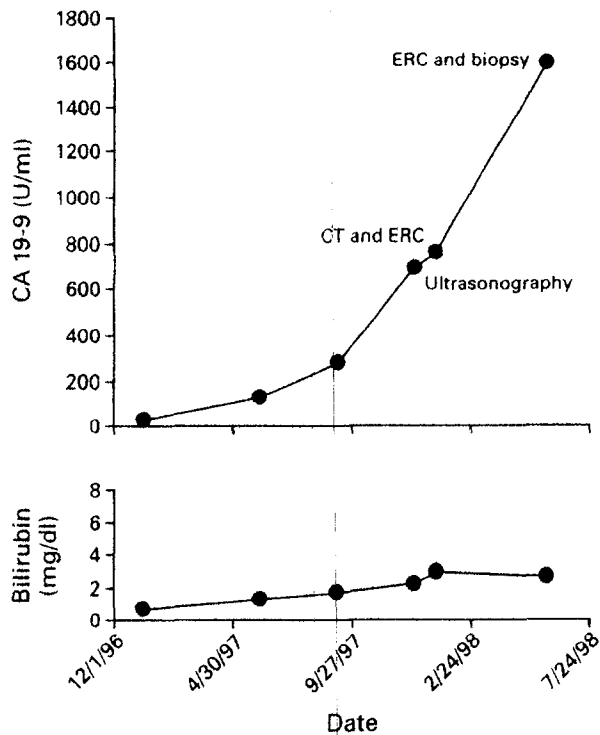


Figure 3. CA 19-9 and Bilirubin Levels in a 75-Year-Old Man with Primary Sclerosing Cholangitis since 1972 and Cirrhosis.

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

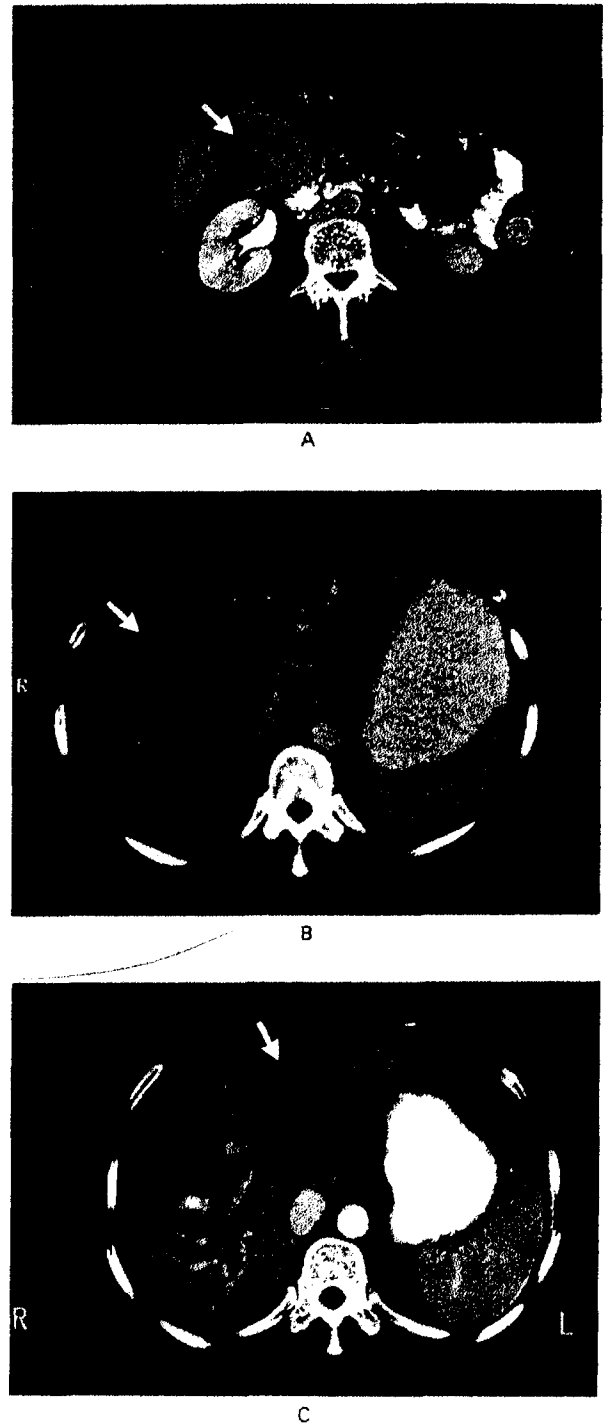


Figure 4. Computed Tomographic Scans of Patients with Gallbladder Cancer and Intrahepatic and Hilar Cholangiocarcinoma. Panel A shows a large gallbladder cancer (arrow) filling part of the distended gallbladder and invading the adjoining intestine. Panel B shows a huge intrahepatic cholangiocarcinoma (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.⁷² Unlike ultrasonography, CT may also show the peripancreatic, periduodenal, periportal, 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.^{73,74} 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. Periapillary 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

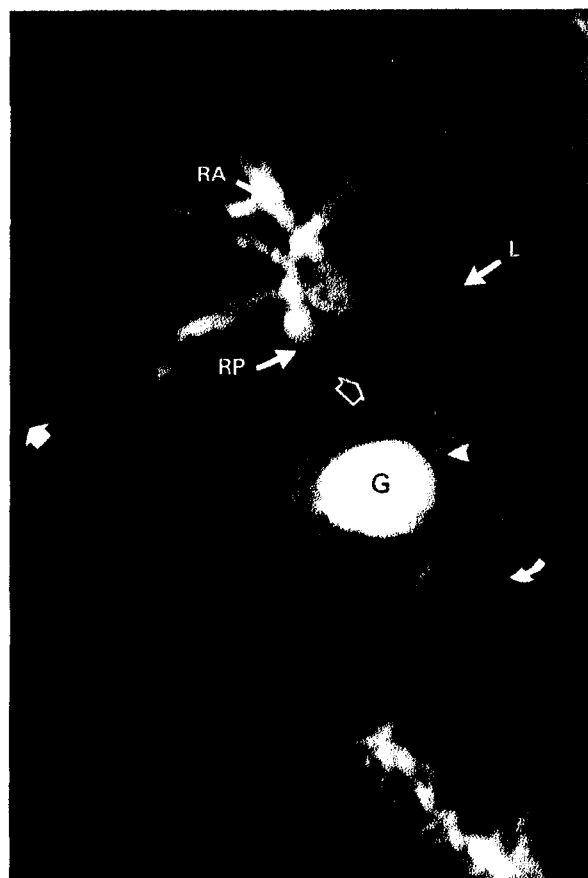


Figure 5. Cholangiogram of a Patient with Cholangiocarcinoma. RA denotes the right anterior ductal system, RP the right posterior ductal system, L the left ductal system, and G the gallbladder. The broad, open arrow points to part of the duct that is narrowed by tumor; the broad, solid arrow to the track of the percutaneous needle used to inject contrast material; the arrowhead to the cystic duct; and the curved arrow to the common hepatic duct.

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-

phy can be used to visualize the distal extrahepatic biliary tree, the gallbladder, and the regional lymph nodes in great detail.⁸⁰ The use of an endoscope equipped with linear ultrasonography allows ultrasound-guided fine-needle aspiration of suspected tumors and abnormal or enlarged lymph nodes.⁸¹ Positron-emission tomography (PET) permits the metabolism of bile-duct epithelial cells to be assessed in vivo by means of a glucose analogue, [¹⁸F]fluoro-2-deoxy-D-glucose.^{82,83} 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.^{82,83} Other, less frequently used new diagnostic methods include intraductal ultrasonography,⁸⁴ endoscopic or percutaneous flexible cholangioscopy,⁸⁵ and radiolabeled antibody or ligand imaging.^{86,87}

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 effec-

tively 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 lobar 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.^{94,95} 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

Patients with unresectable intrahepatic or perihil-

lar cholangiocarcinoma in the absence of extrahepatic disease are potentially treatable with total resection of the liver, bile ducts, and hilar lymph nodes, followed by orthotopic liver transplantation.^{106,107} The results of resection of cholangiocarcinoma in patients with intrahepatic or perihilar cholangiocarcinoma as a complication of primary sclerosing cholangitis are dismal.²⁹ These patients can also potentially be treated by orthotopic liver transplantation. However, the early results of orthotopic liver transplantation in both groups of patients have been disappointing, with rapid 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 explorative 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 choledochojejunostomy 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.^{46,96,104,110}

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 adenomatous 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 beneficial 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. Indeed, several promising novel therapeutic agents, including farnesyl transferase and angiogenesis inhibitors, 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 transformation from normal to malignant biliary tract tissue, genetic repair of the mutations responsible for the malignant phenotype may become possible.

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REFERENCES

- Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1998. *CA Cancer J Clin* 1998;48:6-29. [Errata, *CA Cancer J Clin* 1998;48:192, 329.]
- Percy C, Van Holten V, Muir C, eds. International classification of diseases for oncology. 2nd ed. Geneva: World Health Organization, 1990.
- Albores-Saavedra J, Henson DE, Sobin LH. Histological typing of tumours of the gallbladder and extrahepatic bile ducts. 2nd ed. Berlin, Germany: Springer-Verlag, 1991.
- Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma: a spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996;224:463-75.
- Klarskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatis: an unusual tumor with distinctive clinical and pathological features. *Am J Med* 1965;38:241-56.
- Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg* 1992;215:31-8.
- Pitt HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary tree. *Curr Probl Surg* 1995;32:1-90.
- Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder: histologic types, stage of disease, grade, and survival rates. *Cancer* 1992;70:1493-7.
- Idem. Carcinoma of the extrahepatic bile ducts: histologic types, stage of disease, grade, and survival rates. *Cancer* 1992;70:1498-501.
- Tumors of the gallbladder and extrahepatic bile ducts. In: Albores-Saavedra J, Henson DE. Atlas of tumor pathology. 2nd series. Fascicle 22. Washington, D.C.: Armed Forces Institute of Pathology, 1986.
- Tumors of the liver and intrahepatic bile ducts. In: Craig JR, Peters RL, Edmondson HA. Atlas of tumor pathology. 2nd series. Fascicle 26. Washington, D.C.: Armed Forces Institute of Pathology, 1989.
- Segarra P, Abril V, Gil M, Ortega E, Bailester JE, Traves V. Sarcoma de Kaposi de la vía biliar sin afectación cutánea en paciente con SIDA. *Rev Esp Enferm Dig* 1996;88:637-9.
- O'Boyle MK. Gallbladder wall mass on sonography representing large-cell non-Hodgkin's lymphoma in an AIDS patient. *J Ultrasound Med* 1994;13:67-8.
- Fleming ID, Cooper JS, Henson DE, et al., eds. AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven, 1997.
- Adson MA. Carcinoma of the gallbladder. *Surg Clin North Am* 1973;53:1203-16.
- Zatonski WA, Lowenfels AB, Boyle P, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997;89:1132-8.
- Lowenfels AB, Walker AM, Althaus DP, Townsend G, Domellof L. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. *Int J Epidemiol* 1989;18:50-4.
- Ransohoff DF, Gracie WA. Treatment of gallstones. *Ann Intern Med* 1993;119:606-19.
- Csendes A, Becerra M, Burdiles P, Demian I, Bancalari K, Csendes P. Bacteriological studies of bile from the gallbladder in patients with carcinoma of the gallbladder, cholelithiasis, common bile duct stones and no gallstones disease. *Eur J Surg* 1994;160:363-7.
- Nath G, Singh H, Shukla VK. Chronic typhoid carriage and carcinoma of the gallbladder. *Eur J Cancer Prev* 1997;6:557-9.
- Strom BL, Soloway RD, Rios-Dalenz JL, et al. Risk factors for gallbladder cancer: an international collaborative case-control study. *Cancer* 1995;76:1747-56.
- Dutta U, Garg PK, Kumar R, Tandon RK. Chronic salmonella typhi carrier state and cholelithiasis: cofactors in the pathogenesis of carcinoma of the gallbladder. *Digestion* 1998;59:Suppl 3:576. abstract.
- Chijiwa K, Tanaka M. Polypoid lesion of the gallbladder: indications of carcinoma and outcome after surgery for malignant polypoid lesion. *Int Surg* 1994;79:106-9.
- Polk HC Jr. Carcinoma and the calcified gall bladder. *Gastroenterology* 1966;50:582-5.
- Chijiwa K, Kimura H, Tanaka M. Malignant potential of the gallbladder in patients with anomalous pancreaticobiliary ductal junction: the difference in risk between patients with and without choledochal cyst. *Int Surg* 1995;80:61-4.
- Kornfeld D, Ekblom A, Ihre T. Survival and risk of cholangiocarcinoma in patients with primary sclerosing cholangitis: a population-based study. *Scand J Gastroenterol* 1997;32:1042-5.
- Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut* 1996;38:610-5.
- Farges O, Malassagne B, Sebag M, Bismuth H. Primary sclerosing cholangitis: liver transplantation or biliary surgery. *Surgery* 1995;117:146-55.
- Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ Jr, LaRusso NF. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991;213:21-5.
- Callea F, Sergi C, Fabbretti G, Brisigotti M, Cozzutto C, Medicina D. Precancerous lesions of the biliary tree. *J Surg Oncol Suppl* 1993;3:131-3.
- Watanapa P. Cholangiocarcinoma in patients with opisthorchiasis. *Br J Surg* 1996;83:1062-4.
- Shin HR, Lee CU, Park HJ, et al. Hepatitis B and C virus, Clonorchis sinensis for the risk of liver cancer: a case-control study in Pusan, Korea. *Int J Epidemiol* 1996;25:933-40.
- Chow WH, McLaughlin JK, Menck HR, Mack TM. Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). *Cancer Causes Control* 1994;5:267-72.
- Bergquist A, Glaumann H, Persson B, Broome U. Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: a case-control study. *Hepatology* 1998;27:311-6.
- Sanabria JR, Croxford R, Berk TC, Cohen Z, Bapat BV, Gallinger S. Familial segregation in the occurrence and severity of periampullary neoplasms in familial adenomatous polyposis. *Am J Surg* 1996;171:136-41.
- Offerhaus GJ, Giardiello FM, Krush AJ, et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. *Gastroenterology* 1992;102:1980-2.
- Ekblom A, Yuen J, Karlsson BM, McLaughlin JK, Adami HO. Risk of pancreatic and periampullary cancer following cholecystectomy: a population-based cohort study. *Dig Dis Sci* 1996;41:387-91.
- 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 pancreaticobiliary diseases. *Digestion* 1998;59:Suppl 3:577. abstract.
- Seitz JF, Giovannini M, Wartelle C, Monges G, Dhiver C, Gastaut JA. Association d'un sarcome de Kaposi de l'ampoule de Vater et d'une cholangite scléreuse à *Cryptosporidium* chez un patient porteur d'un SIDA. *Gastroenterol Clin Biol* 1990;14:889-91.
- Suto T, Sugai T, Nakamura S, et al. Assessment of the expression of p53, MIB-1 (Ki-67 antigen), and argyrophilic nucleolar organizer regions in carcinoma of the extrahepatic bile duct. *Cancer* 1998;82:86-95.
- Terada T, Nakanuma Y, Sirica AE. Immunohistochemical demonstration of MET overexpression in human intrahepatic cholangiocarcinoma and in hepatolithiasis. *Hum Pathol* 1998;29:175-80.
- Rijken AM, van Gulik TM, Polak MM, Sturm PD, Gouna DJ, Offerhaus 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.
- Voravud N, Foster CS, Gilbertson JA, Sikora K, Waxman J. Oncogene expression in cholangiocarcinoma and in normal hepatic development. *Hum Pathol* 1989;20:1163-8.
- Sasaki M, Nakanuma Y, Terada T, Kim YS. Biliary epithelial expression of MUC1, MUC2, MUC3 and MUC5/6 apomucins during intrahepatic bile duct development and maturation: an immunohistochemical study. *Am J Pathol* 1995;147:574-9.
- Yamashita K, Yonezawa S, Tanaka S, et al. Immunohistochemical study of mucin carbohydrates and core proteins in hepatolithiasis and cholangiocarcinoma. *Int J Cancer* 1993;55:82-91.
- Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin Proc* 1995;70:425-9.
- Liu KJ, Richter HM, Cho MJ, Jarad J, Nadimpalli V, Donahue PE. Carcinoma involving the gallbladder in elderly patients presenting with acute cholecystitis. *Surgery* 1997;122:748-56.

48. Ker CG, Wu CC, Chen JS, Hou MF, Lee KT, Sheen PC. A study of CEA, CA 19-9 and CA 125 in biliary tract diseases. *Kao Hsiung I Hsueh Ko Hsueh Tsa Chih* 1989;5:107-13.
49. Ker CG, Chen JS, Lee KT, Sheen PC, Wu CC. Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. *J Gastroenterol Hepatol* 1991;6:505-8.
50. Sasaki M, Morita T, Hosono M, Nakanuma Y, Tanimura H. Carcinoembryonic antigen and blood group-related carbohydrate antigens in glycoproteins in human bile in hepatolithiasis. *Hepatology* 1996;23:258-63.
51. Körner T, Kropf J, Jaspersen D, Schorr W, Hammar C-H, Gressner AM. Fibronectin in menschlicher Galle — ein neuer Parameter zur Diagnostik maligner Gallengangsprozesse? — Eine Pilotstudie. *Z Gastroenterol* 1994;32:87-90.
52. Nishijima T, Nishina M, Fujiwara K. Measurement of lactate levels in serum and bile using proton nuclear magnetic resonance in patients with hepatobiliary diseases. its utility in detection of malignancies. *Jpn J Clin Oncol* 1997;27:13-7.
53. Kuusela P, Haglund C, Roberts PJ. Comparison of a new tumour marker CA 242 with CA 19-9, CA 50 and carcinoembryonic antigen (CEA) in digestive tract diseases. *Br J Cancer* 1991;63:636-40.
54. Su WC, Chan KK, Lin XZ, et al. A clinical study of 130 patients with biliary tract cancers and perampullary tumors. *Oncology* 1996;53:488-93.
55. Bhargava AK, Petrelli NJ, Karna A, et al. Serum levels of cancer-associated antigen CA-195 in gastrointestinal cancers and its comparison with CA19-9. *J Clin Lab Anal* 1989;3:370-7.
56. Maeda I, Ku Y, Iwasaki T, et al. A case of advanced cholangiocellular carcinoma treated successfully by percutaneous isolated liver perfusion with cisplatin. *Gan To Kagaku Ryoho* 1996;23:1607-9. (In Japanese.)
57. Kashiwara T, Ohki A, Kobayashi T, et al. Intrahepatic cholangiocarcinoma with increased serum CYFRA 21-1 level. *J Gastroenterol* 1998;33:447-53.
58. Nakao A, Taniguchi K, Inoue S, et al. Clinical application of a new monoclonal antibody (19B7) against PIVKA-II in the diagnosis of hepatocellular carcinoma and pancreatobiliary malignancies. *Am J Gastroenterol* 1997;92:1031-4.
59. Goydos JS, Brumfield AM, Frezza E, Booth A, Lotze MT, Carty SE. Marked elevation of serum interleukin-6 in patients with cholangiocarcinoma: validation of utility as a clinical marker. *Ann Surg* 1998;227:398-404.
60. Hedstrom J, Haglund C, Haapiainen R, Stenman UH. Serum trypsinogen-2 and trypsin-2-alpha(1)-antitrypsin complex in malignant and benign digestive tract diseases: preferential elevation in patients with cholangiocarcinomas. *Int J Cancer* 1996;66:326-31.
61. Bruckner HW, Chesser MR, Mandeli J, Farber LA, DiGiovanni G. Circulating pancreatic polypeptide in patients with adenocarcinoma of the bile duct. *Acta Oncol* 1993;32:627-9.
62. Nakeeb A, Lipsitt PA, Lillemoe KD, et al. Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. *Am J Surg* 1996;171:147-53.
63. Nichols JC, Gores GJ, LaRusso NF, Wiesner RH, Nagorney DM, Ritts RE Jr. Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. *Mayo Clin Proc* 1993;68:874-9.
64. Ramage JK, Donaghy A, Farrant JM, Iorns R, Williams R. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. *Gastroenterology* 1995;108:865-9.
65. Saini S. Imaging of the hepatobiliary tract. *N Engl J Med* 1997;336:1889-94.
66. Hann LE, Schwartz LH, Panicek DM, Bach AM, Fong Y, Blumgart LH. Tumor involvement in hepatic veins: comparison of MR imaging and US for preoperative assessment. *Radiology* 1998;206:651-6.
67. Bach AM, Loring LA, Hann LE, Illescas FF, Fong Y, Blumgart LH. Gallbladder cancer: can ultrasonography evaluate extent of disease? *J Ultrasound Med* 1998;17:303-9.
68. Frezza EE, Mezgebe H. Gallbladder carcinoma: a 28 year experience. *Int Surg* 1997;82:295-300.
69. Furukawa H, Kosuge T, Shimada K, et al. Small polypoid lesions of the gallbladder: differential diagnosis and surgical indications by helical computed tomography. *Arch Surg* 1998;133:735-9.
70. Tillich M, Mischinger HJ, Preisegger KH, Rabi H, Szolar DH. Multiphasic helical CT in diagnosis and staging of hilar cholangiocarcinoma. *AJR Am J Roentgenol* 1998;171:651-8.
71. Hann LE, Getrajdman GI, Brown KT, et al. Hepatic lobar atrophy: association with ipsilateral portal vein obstruction. *AJR Am J Roentgenol* 1996;167:1017-21.
72. Prinz RA, Ko TC, Maltz SB, Reynes CJ, Marsan RE, Freeark RJ. Common bile duct obstruction by free floating tumor. *HPB Surg* 1993;6:319-23.
73. Fulcher AS, Turner MA. HASTE MR cholangiography in the evaluation of hilar cholangiocarcinoma. *AJR Am J Roentgenol* 1997;169:1501-5.
74. Schwartz LH, Coakley FV, Sun Y, Blumgart LH, Fong Y, Panicek DM. Neoplastic pancreaticobiliary duct obstruction: evaluation with breath-hold MR cholangiopancreatography. *AJR Am J Roentgenol* 1998;170:1491-5.
75. Desa LA, Akosa AB, Lazzara S, Domizio P, Krausz T, Benjamin JS. Cytodiagnosis in the management of extrahepatic biliary stricture. *Gut* 1991;32:1188-91.
76. Mansfield JC, Griffin SM, Wadehra V, Matthewson K. A prospective evaluation of cytology from biliary strictures. *Gut* 1997;40:671-7.
77. Schechter MS, Doemeny JM, Johnson JO. Biliary ductal shave biopsy with use of the Simpson atherectomy catheter. *J Vasc Interv Radiol* 1993;4:819-24.
78. Dooley WC, Cameron JL, Pitt HA, Lillemoe KD, Yue NC, Venbrux AC. Is preoperative angiography useful in patients with perampullary tumors? *Ann Surg* 1990;211:649-55.
79. Kuszyk BS, Soyer P, Bluemke DA, Fishman EK. Intrahepatic cholangiocarcinoma: the role of imaging in detection and staging. *Crit Rev Diagn Imaging* 1997;38:59-88.
80. Tio TL, Sic LH, Kallimanis G, et al. Staging of ampullary and pancreatic carcinoma: comparison between endosonography and surgery. *Gastrointest Endosc* 1996;44:706-13.
81. Wiersma MJ, Vilman P, Giovannini M, Chang KJ, Wiersma LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology* 1997;112:1087-95.
82. Delbecq D, Martin WH, Sandler MP, Chapman WC, Wright JK Jr, Pinson CW. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. *Arch Surg* 1998;133:510-6.
83. Keiding S, Hansen SB, Rasmussen HH, et al. Detection of cholangiocarcinoma in primary sclerosing cholangitis by positron emission tomography. *Hepatology* 1998;28:700-6.
84. Itoh A, Goto H, Naitoh Y, Hirooka Y, Furukawa T, Havakawa T. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. *Gastrointest Endosc* 1997;45:251-60.
85. Nimura Y, Kamiya J. Cholangioscopy. *Endoscopy* 1998;30:182-8.
86. Jewkes AJ, Macdonald F, Downing R, Droic Z, Allum WH. Labelled antibody imaging in pancreatic cancer, cholangiocarcinoma, chronic pancreatitis and sclerosing cholangitis. *Eur J Surg Oncol* 1991;17:354-7.
87. Tan CK, Podila PV, Taylor JE, et al. Human cholangiocarcinomas express somatostatin receptors and respond to somatostatin with growth inhibition. *Gastroenterology* 1995;108:1908-16.
88. Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. *Arch Surg* 1995;130:270-6.
89. van Delden OM, de Wit LT, Nieveen van Dijkum EJ, Smits NJ, Gouma DJ, Reekers JW. Value of laparoscopic ultrasonography in staging of proximal bile duct tumors. *J Ultrasound Med* 1997;16:7-12.
90. Fong Y, Heffernan N, Blumgart LH. Gallbladder carcinoma discovered during laparoscopic cholecystectomy: aggressive resection is beneficial. *Cancer* 1998;83:423-7.
91. Donohue JH, Nagorney DM, Grant CS, Tsushima K, Ilstrup DM, Adson MA. Carcinoma of the gallbladder: does radical resection improve outcome? *Arch Surg* 1990;125:237-41.
92. Ogura Y, Mizumoto R, Isaji S, Kusuda T, Matsuda S, Tabata M. Radical operations for carcinoma of the gallbladder: present status in Japan. *World J Surg* 1991;15:337-43.
93. Nakamura S, Nishiyama R, Yokoi Y, et al. Hepatopancreatoduodenectomy for advanced gallbladder carcinoma. *Arch Surg* 1994;129:625-9.
94. Lieser MJ, Barry MK, Rowland C, Ilstrup DM, Nagorney DM. Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience. *J Hepatobiliary Pancreat Surg* 1998;5:41-7.
95. Sasaki A, Aramaki M, Kawano K, et al. Intrahepatic peripheral cholangiocarcinoma: mode of spread and choice of surgical treatment. *Br J Surg* 1998;85:1206-9.
96. Klempnauer J, Ridder GJ, Werner M, Weimann A, Pichlmayr R. What constitutes long-term survival after surgery for hilar cholangiocarcinoma? *Cancer* 1997;79:26-34.
97. Nimura Y, Kamiya J, Nagino M, et al. Aggressive surgical treatment of hilar cholangiocarcinoma. *J Hepatobiliary Pancreat Surg* 1998;5:52-61.
98. Sakamoto E, Nimura Y, Hayakawa N, et al. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. *Ann Surg* 1998;227:405-11.
99. Bartlett D, Fong Y, Blumgart LH. Complete resection of the caudate lobe of the liver: technique and results. *Br J Surg* 1996;83:1076-81.
100. Nagino M, Nimura Y, Kamiya J, et al. Segmental liver resections for hilar cholangiocarcinoma. *Hepatogastroenterology* 1998;45:7-13.
101. Madariaga JR, Iwatsuki S, Todo S, Lee RG, Irish W, Starzl TE. Liver resection for hilar and peripheral cholangiocarcinomas: a study of 62 cases. *Ann Surg* 1998;227:70-9.
102. Reding R, Buard JL, Lebeau G, Launois B. Surgical management of 552 carcinomas of the extrahepatic bile ducts (gallbladder and perampul-

- lary tumors excluded): results of the French Surgical Association Survey. *Ann Surg* 1991;213:236-41.
103. Monson JR, Donohue JH, McEntee GP, et al. Radical resection for carcinoma of the ampulla of Vater. *Arch Surg* 1991;126:353-7.
104. Fong Y, Blumgart LH, Lin E, Fortner JG, Brennan ME. Outcome of treatment for distal bile duct cancer. *Br J Surg* 1996;83:1712-5.
105. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periapillary adenocarcinoma: analysis of 5-year survivors. *Ann Surg* 1998;227:821-31.
106. Iwatsuki S, Todo S, Marsh JW, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg* 1998;187:358-64.
107. Urege M, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 1999;44:121-6.
108. Goldstein RM, Stone M, Tillery GW, et al. Is liver transplantation indicated for cholangiocarcinoma? *Am J Surg* 1993;166:768-72.
109. Goss JA, Shackleton CR, Farmer DG, et al. Orthotopic liver transplantation for primary sclerosing cholangitis: a 12-year single center experience. *Ann Surg* 1997;225:472-83.
110. Nordback IH, Pitt HA, Coleman J, et al. Unresectable hilar cholangiocarcinoma: percutaneous versus operative palliation. *Surgery* 1994;115:597-603.
111. Taschieri AM, Elli M, Danelli PG, Cristaldi M, Montecamozzo G, Porretta T. Third segment cholangio-jejunostomy in the treatment of unresectable Klatskin tumors. *Hepatogastroenterology* 1995;42:597-600.
112. Jarnagin WR, Burke E, Powers C, Fong Y, Blumgart LH. Intrahepatic biliary enteric bypass provides effective palliation in selected patients with malignant obstruction at the hepatic duct confluence. *Am J Surg* 1998;175:453-60.
113. Foo ML, Gunderson LL, Bender CE, Buskirk SJ. External radiation therapy and transected iridium in the treatment of extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1997;39:929-35.
114. Gonzalez Gonzalez D, Gerard JP, Maners AW, et al. Results of radiation therapy in carcinoma of the proximal bile duct (Klatskin tumor). *Semin Liver Dis* 1990;10:131-41.
115. Alden ME, Mohiuddin M. The impact of radiation dose in combined external beam and intraluminal Ir-192 brachytherapy for bile duct cancer. *Int J Radiat Oncol Biol Phys* 1994;28:945-51.
116. Kuvshinov BW, Armstrong JG, Fong Y, et al. Palliation of irresectable hilar cholangiocarcinoma with biliary drainage and radiotherapy. *Br J Surg* 1995;82:1522-5.
117. Pitt HA, Nakeeb A, Abrams RA, et al. Perihilar cholangiocarcinoma: postoperative radiotherapy does not improve survival. *Ann Surg* 1995;221:788-98.
118. Bowling TE, Galbraith SM, Hattfield AR, Solano J, Spittle ME. A retrospective comparison of endoscopic stenting alone with stenting and radiotherapy in non-resectable cholangiocarcinoma. *Gut* 1996;39:852-5.
119. Sanz-Altamira PM, Ferrante K, Jenkins RL, Lewis WD, Huberman MS, Stuart KE. A phase II trial of 5-fluorouracil, leucovorin, and carboplatin in patients with unresectable biliary tree carcinoma. *Cancer* 1998;82:2321-5.
120. Prat F, Chaput O, Ducot B, et al. Predictive factors for survival of patients with inoperable malignant distal biliary strictures: a practical management guideline. *Gut* 1998;42:76-80.
121. Schima W, Prokesh R, Osterreicher C, et al. Biliary Wallstent endoprosthesis in malignant hilar obstruction: long-term results with regard to the type of obstruction. *Clin Radiol* 1997;52:213-9.
122. Ortner MA, Liebetruht J, Schreiber S, et al. Photodynamic therapy of nonresectable cholangiocarcinoma. *Gastroenterology* 1998;114:536-42.
123. de Groen PC, Barry JA, Schaller WJ. Applying World Wide Web technology to the study of patients with rare diseases. *Ann Intern Med* 1998;129:107-13.
124. Johlin FC, Voigt M, Wu YM. Surveillance cytology (SC) in the detection of asymptomatic progression to cholangiocarcinoma (CCC) in patients with primary sclerosing cholangitis. *Hepatology* 1998;28:Suppl: 393A. abstract.
125. Ito R, Tamura K, Ashida H, et al. Usefulness of K-ras gene mutation at codon 12 in bile for diagnosing biliary strictures. *Int J Oncol* 1998;12:1019-23.
126. Caldas C, Hahn SA, Hruban RH, Redston MS, Yeo CJ, Kern SE. Detection of K-ras mutations in the stool of patients with pancreatic adenocarcinoma and pancreatic ductal hyperplasia. *Cancer Res* 1994;54:3568-73.