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Diagnosis and Treatment of Cholangiocarcinoma

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Key Words. *Cholangiocarcinoma · Biliary tract cancer · Bile duct tumor · Biliary obstruction*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the current state-of-the-art treatment of cholangiocarcinoma including the current results of aggressive resection, adjuvant therapies, and neoadjuvant therapies.

2. Outline the criteria for determining resectability.

3. Discuss the roles of chemotherapies and radiation therapies in the palliative care of the patient with unresectable cholangiocarcinoma.

4. Identify the roles of operative bypass and endoscopic or percutaneous stenting in the palliation of cholangiocarcinoma.

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ABSTRACT

Cholangiocarcinoma presents a formidable diagnostic and treatment challenge. The majority of patients present with unresectable disease and have a survival of less than 12 months following diagnosis. Progress has been made by the appropriate selection of patients for treatment options including resection, with the routine use of more aggressive resections in order to achieve margin-negative resections. This has resulted in longer survival times for these patients. Neoadjuvant and adjuvant therapies have, for the most part, not improved survival in patients with this tumor, and new strategies are needed to improve this line of therapy. The prognosis for unresectable patients is poor, and palliative measures should be aimed at increasing quality of life first and increasing survival second. *The Oncologist* 2004;9:43-57

INTRODUCTION

Cholangiocarcinoma is an uncommon malignancy arising from the epithelial cells of the biliary tract. These tumors may arise anywhere along the intrahepatic or extrahepatic biliary tree. Patients with cholangiocarcinoma typically present at advanced stages, and cure rates are low, even with aggressive therapy. The reported incidence of cholangiocarcinoma is one to two cases per 100,000 patients in the U.S.,

and the majority of patients are older than 65 years of age [1]. The peak incidence occurs in the seventh decade of life, and the vast majority of patients with unresectable disease die between 6 months and 1 year following diagnosis [1, 2]. Death usually occurs from liver failure or infectious complications accompanying the advancing biliary obstruction.

The exact cause of cholangiocarcinoma is unknown, and most cases occur sporadically, but there are several well-

defined risk factors. The most common of these is primary sclerosing cholangitis (PSC). The true incidence of cholangiocarcinoma in the setting of PSC is reported as 8%-40%, depending on the type of study. In one study of patients followed over 5 years, 8% eventually developed clinically detectable cancer [3], but occult cholangiocarcinoma in patients with PSC has been reported in 36% of autopsy specimens and 40% of explant specimens [3, 4]. Patients with congenital biliary cysts are also at greater risk of developing cholangiocarcinoma [5]. However, the risk of malignant degeneration is uncommon in patients diagnosed and treated by excision before the age of 20. Patients who are not excised until the third decade of life have a 15%-20% incidence of malignant degeneration [6]. Hepatolithiasis secondary to chronic biliary infection is prevalent in Japan and parts of Southeast Asia, and approximately 10% of patients with this condition develop cholangiocarcinoma [7]. Multiple other risk factors for cholangiocarcinoma have been identified, including dioxin exposure, liver flukes, thorotrast dye, and dietary nitrosamines [4].

The clinical features of cholangiocarcinoma depend on the location of the tumor. Approximately 60%-70% of cholangiocarcinomas occur at the hepatic duct bifurcation, and the remainder occur in the distal common bile duct (20%-30%) or within the liver (5%-15%) [8]. Patients with extrahepatic tumors usually present with painless jaundice from biliary obstruction, and patients with intrahepatic tumors usually present with pain. Common complaints include pruritus (66%), abdominal pain (30%-50%), weight loss (30%-50%), and fever (up to 20%) [9, 10]. When pain occurs, it is generally described as a constant dull ache in the right upper quadrant. Other symptoms related to biliary obstruction include clay-colored stools and dark urine. Physical signs include jaundice (90%), hepatomegaly (25%-40%), and right upper quadrant mass (10%) [10]. A palpable gallbladder, caused by obstruction at or distal to the origin of the cystic duct (Courvoisier law), occurs rarely. Patients with intrahepatic cholangiocarcinomas rarely present with jaundice; most often they present with dull right upper quadrant discomfort and weight loss.

Tumor Biology

A number of different molecular defects have been identified in cholangiocarcinoma. These mutations primarily involve oncogenes and tumor suppressor genes, suggesting that these cancers likely develop due to a series of cellular injuries. In one study, human cholangiocarcinoma cells were shown to escape immune surveillance by either possessing defective Fas receptor signaling or by increasing Fas ligand expression [11]. In another study, the authors demonstrated that overexpression of the proto-oncogene *Bcl*-2 reduced apoptosis in cholangiocarcinoma cell lines [12]. Others have demonstrated increased c-*met* (a receptor for hepatocyte growth factor) expression in cholangiocarcinoma cells, which potentially plays a role in the metastatic transformation of these tumors [13, 14]. Overexpression of K-*ras* and p53 in cholangiocarcinoma have been correlated with a more aggressive phenotype [15-17]. In addition, two studies have suggested that p16[INK4a] promotor point mutations contribute to the initiation and progression of cholangiocarcinoma in the setting of PSC [18, 19].

Diagnosis and Staging

Cholestasis, abdominal pain, and weight loss together should always raise suspicion of a hepatobiliary or pancreatic malignancy. The differential diagnosis for patients presenting with these symptoms is broad. It includes pancreatic head carcinoma, ampulla of Vater carcinoma, duodenal carcinoma, gallbladder carcinoma, benign biliary strictures (usually postoperative), primary sclerosing cholangitis, choledocholithiasis, and Mirizzi's syndrome, among others. Patients presenting with this triad of symptoms should always be evaluated for the existence of a carcinoma. The diagnosis is aided by both noninvasive and invasive studies, which are discussed below.

Laboratory Tests

Biochemical tests, such as serum alkaline phosphatase and serum bilirubin levels, are of little help in differentiating among the three conditions above, since they all can be associated with jaundice and an elevated alkaline phosphatase level. Certain serum tumor markers, although not specific for cholangiocarcinoma, may be of value, especially in patients with underlying PSC [20]. The most widely studied tumor markers are carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9. Both CEA and CA 19-9 can be elevated in cholangiocarcinoma [21-23]. However, CEA levels alone are neither sensitive nor specific for cholangiocarcinoma [24]. CA 19-9 has a sensitivity of 67%-89% and a specificity of 86%-98% with levels over 100 U/ml. Using combined CEA and CA 19-9 levels may have usefulness. One study showed a 100% sensitivity and specificity using CEA >5.2 ng/ml and CA 19-9 >180 U/ml [24]; however, other investigators did not obtain such outstanding results [25, 26]. In addition, there has been recent interest in the use of CA 242 and CA 125 for the diagnosis of cholangiocarcinoma [27], but early studies have failed to demonstrate sensitivities or specificities greater than those reported above.

Radiological Studies

Radiographic studies are essential in planning management in patients with cholangiocarcinoma. Most jaundiced patients undergo initial transabdominal ultrasound before referral to a hepatobiliary specialist. Ultrasound is operator dependent, but is a sensitive method for visualizing the bile

ducts, confirming ductal dilatation, and ruling out choledo-cholithiasis [28]. An obstructing lesion is suggested by intra- or extrahepatic bile duct dilatation (>6 mm in normal adults) in the absence of stones. In one study of 429 patients who presented with obstructive jaundice over a 10-year period, ultrasound demonstrated ductal obstruction in 89%, and the sensitivity of ultrasound for localizing the site of obstruction was 94% [29]. Ultrasound typically demonstrates intrahepatic bile duct dilatation and normal diameter extrahepatic ducts in patients with proximal (hilar) lesions, or dilation of both intra-hepatic and extrahepatic ducts in more distal lesions [28]. Centers with expertise in duplex ultrasound have found that this method is an accurate predictor of vascular involvement and resectability. *Hann* and colleagues demonstrated, in a small series of patients, that duplex ultrasound was equivalent to computed tomography (CT) portography and angiography for detecting lobar atrophy, the level of biliary obstruction, hepatic parenchymal involvement, and venous invasion [30].

Contrasted CT is sensitive for detecting intrahepatic bile duct tumors, the level of biliary obstruction, and the presence of liver atrophy. In addition, CT may also permit visualization of the pertinent nodal basins [31]. Performance of a triple-phase helical CT will detect essentially all cholangio-carcinomas greater than 1 cm [32, 33]. However, CT may only be able to establish resectability in approximately 60% of patients [34]. Nevertheless, dynamic CT may provide more information regarding resectability than magnetic resonance imaging. While both imaging methods have similar abilities to show tumor enhancement and biliary ductal dilatation, the relationship of the tumor to the vessels and surrounding organs is more easily evaluated using CT [34].

Magnetic resonance cholangiopancreatography (MRCP) is a newer modality that uses magnetic resonance technology to create a three-dimensional image of the biliary tree, liver parenchyma, and vascular structures (Fig. 1). This technique may not be available at all centers, but many studies have demonstrated its utility in evaluating patients with biliary obstruction [35, 36]. MRCP has the capability to evaluate the bile ducts both above and below a stricture, while also identifying any intrahepatic mass lesions. In an early study assessing 126 patients with suspected biliary obstruction, MRCP detected 12 of 14 malignant obstructions, and had a positive predictive value of 86% and a negative predictive value of 98% [37]. In a second series comparing MRCP with endoscopic retrograde cholangiopancreatography (ERCP) in 40 patients with malignant perihilar obstruction, both techniques detected 100% of biliary obstructions, but MRCP was superior in defining the anatomical extent of tumors [38].

Invasive cholangiography may provide diagnostic data in the form of "brush cytology" and may be required preoperatively for therapeutic biliary drainage. It can be performed

Figure 1. Magnetic resonance cholangiopancreatography image. *The arrow indicates the location of an obstruction at the confluence of the left and right hepatic ducts.*

by ERCP (Fig. 2) or by a percutaneous transhepatic cholangiography (PTC) (Fig. 3). The choice depends in part upon the level of endoscopic or radiological expertise available to the clinician. In general, ERCP is preferred in patients with PSC, since the marked stricturing of the intrahepatic biliary tree makes a percutaneous approach difficult. Conversely, PTC provides information about the intrahepatic ducts more reliably and is the preferred study in most centers [4, 39].

Positron emission tomography (PET) using the radionucleotide tracer 18-fluorodeoxyglucose (FDG) has evolved into a useful staging technique in many neoplastic disorders. PET scans can reliably detect cholangiocarcinomas as small as 1 cm [40-42]. We have recently demonstrated that preoperative staging using FDG PET detected distant metastatic disease that was not suspected based on other radiological studies in 30% of patients [42]. Our study also demonstrated that FDG PET may be useful for detecting primary cholangiocarcinoma in patients with PSC; this has also been suggested by *Kluge* and colleagues [40]. Although the cost-effectiveness of PET use for cholangiocarcinoma staging has yet to be evaluated, this modality can be a useful tool when a nuclear radiologist with extensive experience with PET is available.

In summary, making a definitive tissue diagnosis of cholangiocarcinoma is difficult. However, if cholangiocarcinoma is clinically suspected, neither assessment for resectability nor
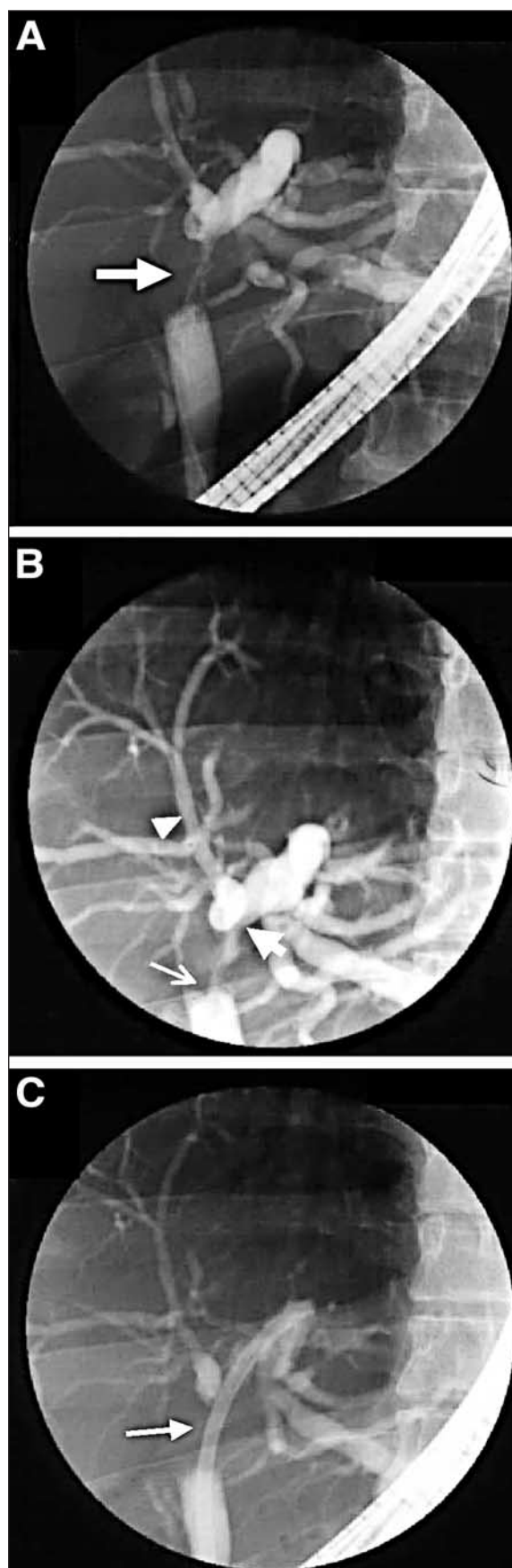
Figure 2. A) Endoscopic retrograde cholangiopancreatography (ERCP) image. The arrow denotes the presence of a tumor. The left-sided ducts are visualized and a diminutive right system is seen. B) On further injection, the right ducts fill more clearly; there is obvious dilation of the central ducts. The thin arrow marks the lower border of the tumor; the thick arrow demarcates the upper border. The solitary arrowhead points to the right ductal system that is more clearly visualized than in A. C) An ERCP stent is placed across the lesion into the left ductal system. Drainage of the left system in this instance is preferred, as it provides drainage of the future remnant liver that will be left following resection.

the resection should be delayed by the absence of a tissue diagnosis. To determine resectability, all of the available clinical and radiological data are needed. Currently, there is no system that stratifies patients into subgroups based on their potential for resection. The current American Joint Commission on Cancer staging system (Table 1) is based on pathological data and can convey information pertaining to the patient's prognosis. This staging system, however, cannot predict the likelihood of resection for stage I-III patients [2, 43]. The Bismuth-Corlette system (Table 2) can reliably stratify patients based on the location and extent of the tumor in the biliary tree [44]. Although this system is useful for description of tumors, it is not predictive for resectability or survival.

Operative Therapy

Assessment

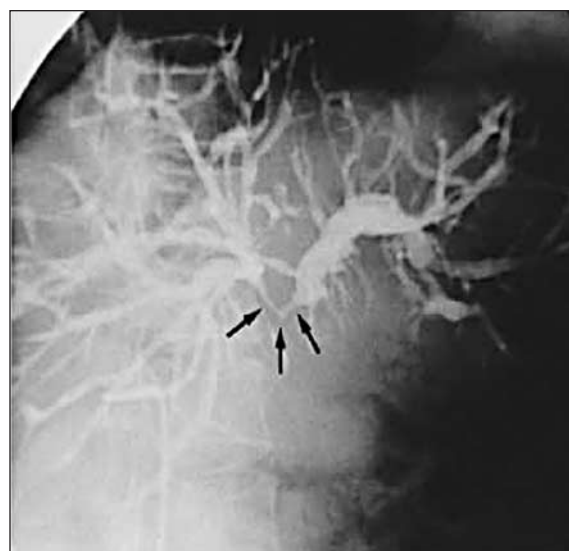Patients with cholangiocarcinoma have extremely poor prognoses, with an average 5-year survival rate of 5%-10%.

Figure 3. Percutaneous transhepatic cholangiogram. The arrows demarcate tumor at the confluence of the left and right hepatic ducts. The left main and right main ducts are both involved.

Table 1. Current American Joint Commission on Cancer staging system for cholangiocarcinoma

Stage 0	T_{is}	N_0	M_0
Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III	T_1 or T_2	N_1 or N_2	M_0
Stage IVA	T_3	Any N	M_0
Stage IVB	Any T	Any N	M_1

T_{is} = carcinoma in situ; T_1 = tumor invades the subepithelial connective tissue; T_2 = tumor invades perifibromuscular connective tissue; T_3 = tumor invades adjacent organs.

N_0 = no regional lymph node metastases; N_1 = metastasis to hepatoduodenal ligament lymph nodes; N_2 = metastasis to peripancreatic, periduodenal, periportal, celiac, and/or superior mesenteric artery lymph nodes.

M_0 = no distant metastasis; M_1 = distant metastasis.

Table 2. The Bismuth-Corlette classification scheme of biliary strictures

Type I	Tumor involves the common hepatic duct
Type II	Tumor involves the bifurcation of the common hepatic duct
Type IIIa	Tumor involves the right hepatic duct
Type IIIb	Tumor involves the left hepatic duct
Type IV	Tumor involves both the right and left hepatic ducts

Table 3. Radiological criteria that suggest unresectability

Bilateral hepatic duct involvement up to secondary radicals.

Bilateral hepatic artery involvement.

Encasement of the portal vein proximal to its bifurcation.

Atrophy of one hepatic lobe with contralateral portal vein encasement.

Atrophy of one hepatic lobe with contralateral biliary radical involvement.

Distant metastasis.

Surgery remains the only intervention offering the possibility of a cure. The main treatment goal should be complete excision with negative margins. All patients should be fully evaluated for resectability before any type of intervention is performed because stent-associated inflammation or infection often renders assessment more difficult.

Patients being evaluated for resectability must first be physiologically suitable for a potential operative resection that may include a partial hepatectomy. There are four traditional determinants of resectability; these are the extent of tumor within the biliary tree, vascular invasion, hepatic lobar atrophy, and metastatic disease. However, in a recent review of 90 patients, main portal vein involvement was found to be the only independent predictor of unresectability by multivariate analysis [2]. Hepatic lobar atrophy and hepatic ductal extension predict the need for hepatectomy in order to achieve a margin-negative resection [2]. All available data must be used to distinguish resectability from unresectability. Radiographic criteria that suggest unresectability of perihilar tumors include bilateral hepatic duct involvement up to secondary radicals, encasement or occlusion of the portal vein proximal to its bifurcation, atrophy of one liver lobe with encasement of the contralateral portal vein branch, involvement of bilateral hepatic arteries, and atrophy of one liver lobe with contralateral secondary biliary radical involvement (Table 3) [2, 43, 45]. Moreover, ipsilateral portal vein involvement and/or involvement of secondary biliary radicals do not preclude resection, nor does ipsilateral lobar atrophy.

A significant number of patients have peritoneal implants or locoregional lymph node involvement that is not easily detected on preoperative imaging studies. At centers with expertise, endoscopic ultrasound may be useful to determine the local extent of the tumor and to detect local lymphatic involvement, especially for distal lesions. In addition, diagnostic laparoscopy helps identify many of these patients before committing them to a laparotomy [46]. A study that examined the role of laparoscopy in the staging of hepatobiliary and pancreatic neoplasms detected unknown metastases in 30% of patients [47]. In addition, laparoscopy offers the opportunity for intraoperative hepatic ultrasound, which may be useful for the detection of occult intrahepatic metastases. Ultimately, however, true resectability cannot be determined until a complete abdominal exploration has been performed [48].

There are factors other than tumor location and the status of resection margins that have been found to correlate with postoperative outcome. The patient's nutritional status and risk of postoperative liver failure are important factors to consider before proceeding to exploration for resection. A retrospective review of resected hilar cholangiocarcinoma cases demonstrated that a preoperative serum albumin level <3 g/dl and a total bilirubin level >10 mg/dl were both associated with poorer survival [48].

In general, our approach to suspected hilar cholangiocarcinoma is to perform radiological staging including a triple-phase CT, PET, and MRCP or PTC/ERCP with biliary drainage in patients with serum bilirubin levels >10 mg/dl (Fig. 4). While preoperative biliary drainage has been associated with a greater risk for cholangitis and longer postoperative hospital stay in patients with obstructive jaundice who then undergo resection [49], cholestasis, biliary cirrhosis, and liver dysfunction develop rapidly in the

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                          ┌─────────────┐
                          │   Jaundice  │
                          └─────────────┘
                                 │
                    ┌────────────────────────┐
                    │  Right upper quadrant  │
                    │      ultrasound        │
                    └────────────────────────┘
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┌────────────────────────────┐   ┌────────────────────────────┐   ┌──────────────┐
│ Dilation of intrahepatic, │   │   Intra- and extrahepatic │   │ No dilation │
│ but not extrahepatic ducts:│   │   ductal dilatation: │   └──────────────┘
│ suspect hilar cholangio-   │   │ suspect distal cholangio- │
│ carcinoma   │   │ carcinoma or pancreatic   │
└────────────────────────────┘   │ carcinoma   │
                                 └────────────────────────────┘

                                         → Further evaluation

┌──────────────────────┐
│ Triple-phase CT, PET;│
│   consider MRCP   │
└──────────────────────┘

Radiologically resectable? —Yes→ Bilirubin >10? —No→ Laparoscopy; intraoperative ultrasound
        │No   │Yes
        ↓   ERCP or PTC drainage
ERCP or PTC drainage;   ←——— Yes ——— Intra/extrahepatic mets?
consider metal stent   │No
        ↓   Exploration for resection
Consider biopsy for tissue diagnosis   │
        ↓   Unresectable,   Resectable
Palliative care ←—— consider bilio-enteric bypass   │
                                                    Consider adjunctive therapies
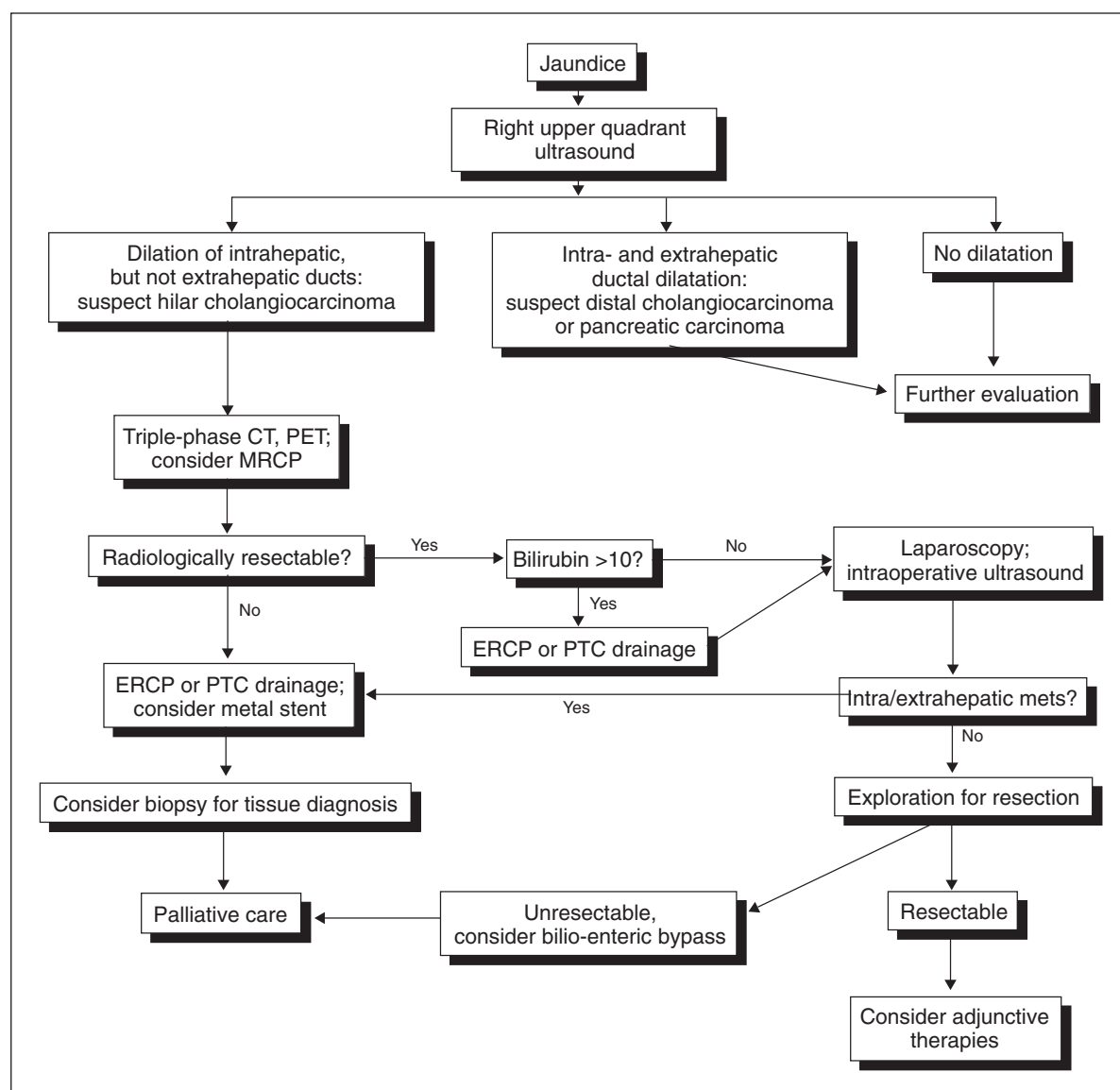
Figure 4. Flowchart depicting the workup and treatment of a patient with suspected hilar cholangiocarcinoma (which accounts for 60%-70% of all cases of cholangiocarcinoma). In most instances, ultrasound can detect dilation of intrahepatic bile ducts without extrahepatic dilatation, suggesting a hilar lesion. Triple-phase CT offers the best detail of the involved vasculature, lymph node basins, and any intrahepatic lesions. PET detects unsuspected distant or intrahepatic metastases in up to 30% of patients with cholangiocarcinoma. MRCP offers good resolution of both the intrahepatic and extrahepatic biliary tree, but should be substituted with PTC or ERCP in patients that will require preoperative or palliative biliary drainage. Patients deemed potentially resectable by radiographic methods should undergo diagnostic laparoscopy, which may detect intra-abdominal metastases in up to 30% of patients. Despite this extensive work-up, not all patients undergoing exploration for resection will be resectable, and when patients are found to be unresectable at exploration, operative biliary-enteric bypass should be considered.

face of unrelieved biliary obstruction. Liver dysfunction is one of the main factors that increases postoperative morbidity and mortality following surgical resection, and thus, biliary drainage in high-risk patients should be performed following preoperative radiological staging. If drainage is elected, definitive operative intervention is usually deferred until the serum bilirubin level is <3 mg/dl. Nevertheless, in those patients who are potentially resectable, laparoscopic staging can be accomplished shortly after the drainage

procedure in the face of elevated bilirubin levels. If extrahepatic disease or a nonresectable tumor is found, curative resection is not possible, and alternative management strategies can be considered at this point.

Results from Resection

Among selected patients who undergo potentially curative resections, 5-year survival rates are generally from 8%-44% [9, 10, 44, 48, 50-58]. While the majority of those

Table 4. Influence of histologic margin-negative resection on survival in patients with cholangiocarcinoma who underwent a resection for curative intent

Study	Total resected	Margin-negative	Perioperative mortality (%)	Median survival (months)	5-year survival (%)
Hadjis et al., 1990 [54]	27	15	7.4	22 versus 14.5	40 versus 10
Pichlmayr et al., 1996 [56]	125	91	10.5	25.7 versus 2.7	31.7 versus 12.2
Su et al., 1996 [48]	24	20	10.2	19 versus 9	34.5 versus 0
Lillemoe et al., 2000 [57]	109	28	4.1	41 versus 18	19 versus 9
Jarnagin et al., 2001 [43]	80	62	10.0	42 versus 21	37 versus 0
Nakeeb et al., 2002 [55]	44	33	4.6	43.6 versus 23.6	47 versus 0

patients have had stage I, II, or III disease, few studies report postoperative survival based on stage due to the difficulties discussed above. More meaningful data can be extracted from studies that report both complete (margin-negative) and incomplete (margin-positive) resections. Those reports demonstrate that the importance of achieving a margin-negative resection cannot be overemphasized. In studies that compared outcomes after a histologically negative margin with those after a positive margin, the 5-year survival rates were greater when a negative margin was obtained, 19%-47% versus 0%-12% (Table 4) [43, 48, 54-57]. Moreover, a recent analysis of prognosis showed only histologic margin status and lymph node involvement as the main correlates of survival [59].

The greatest progress has been made in curative resection for perihilar tumors. More aggressive resections that include hepatic lobectomy have resulted in better outcomes for patients with perihilar tumors. There are now data to suggest that the addition of a partial hepatectomy results in a greater number of patients with margin-negative resections [2, 45, 58, 59]. The rate of margin-negative resections has consistently been reported as >75% when partial hepatectomy including resection of the caudate lobe is added to the biliary resection [55, 60] (Fig. 5). This aggressive approach has increased the 5-year rate survival to >50% in some series [2, 55]. However, the perioperative mortality rates accompanying these more extensive resections are slightly higher than those accompanying local excision only (8%-10% versus 2%-4%) [48, 54-58, 61].

In contrast, two series from a U.S. center failed to demonstrate an association between major hepatectomy and survival. The first report showed 1-, 3-, and 5-year survival rates of 49%, 12%, and 5%, respectively [61]. In a later follow-up series that included 109 patients, the 1-, 3-, and 5-year survival rates were only modestly better at 68%, 30%, and 11%, respectively [57]. The authors of that study reported histologically negative resection margins in only 15% and 26% of resected patients, respectively, despite the use of extended hepatectomy. However, those reports did

demonstrate a significant survival advantage for patients when a negative margin was achieved [57, 61]. Taken together, these data suggest that the addition of a partial hepatectomy is only useful when it allows microscopically negative resection margins to be achieved. To this end, several authors have reported the use of portal vein embolization (PVE) as an important presurgical treatment in patients who will likely need an extensive liver resection [58]. The main purpose of PVE is to induce compensatory hypertrophy of the future remnant liver and thus minimize postoperative liver dysfunction [62]. By allowing a larger volume resection to be carried out safely, PVE may allow negative resection margins to be obtained in patients who would otherwise be unresectable because of concerns of insufficient postoperative residual liver volume [63, 64].

Distal lesions represent approximately 20%-30% of all cholangiocarcinomas and are usually treated with pancre-
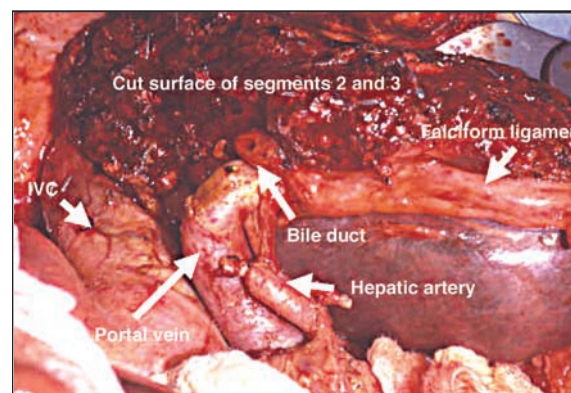

Figure 5. Intraoperative photo following right trisectorectomy and caudate lobectomy. Caudate lobectomy is an important part of the resection, as the ducts to the caudate often insert at the level of the confluence of the left and right hepatic ducts and are frequently involved with the tumor. This photograph indicates the inferior vena cava (IVC) clearly, as the caudate lobe has been removed. The portal vein branch to the left and the left hepatic artery are marked. The open end of the bile duct draining segments 2 and 3 of the liver is indicated. The raw surface of the liver is as marked—only the liver to the left of the falciform ligament was retained.

aticoduodenectomy (Whipple procedure). The same principles of achieving a margin-negative resection apply with these tumors. Multiple case series show 21%-54% 5-year survival rates in selected patients who underwent curative resections [9, 65, 66]. However, the cure rates in those patients may not actually be as high as these reports suggest, since not all series distinguished distal cholangiocarcinoma from carcinoma of the ampulla of Vater, a disease that has a significantly higher cure rate.

Intrahepatic cholangiocarcinoma is usually treated by hepatic resection. A 60% 3-year survival rate was reported in a series of 28 patients who underwent a margin-negative partial hepatectomy [9]. As with perihilar tumors, the preoperative and operative approach to these tumors should be aimed at insuring a margin-negative resection. Some groups are encouraging the use of selective ipsilateral PVE in these patients to allow a more aggressive hepatic resection and increase the number of patients who can undergo a curative resection [62, 67].

Liver Transplantation

Liver transplantation for cholangiocarcinoma is controversial and, because of the high recurrence rate published by most authors, most centers have abandoned this as an indication for liver transplantation [68-70]. However, some reports of success have been published [71], and radical multiabdominal organ "cluster" transplant for selected patients with cholangiocarcinoma has been reported [72]. The most recent review of 207 patients who underwent liver transplantation for cholangiocarcinoma reported 1-, 2-, and 5-year survival rates of 72%, 48%, and 23%, respectively, but >50% of patients had recurrence within 2 years [70]. A second review, with a 30% 3-year survival rate, reported that small tumor size and a single tumor focus are positive prognostic indicators [73].

Given these data, the use of liver transplantation for the treatment of cholangiocarcinoma should be reserved for very select patients as a part of research protocols. As more effective adjuvant and neoadjuvant protocols are developed, transplantation may be a more useful treatment for this disease. This is suggested by early results by *De Vreede* and colleagues in which highly selected patients with stage I and II hilar cholangiocarcinoma underwent neoadjuvant external beam radiation, systemic 5-fluorouracil (FU) therapy, and brachytherapy prior to liver transplantation [74]. That group reported survival times >36 months for 7 of 11 patients transplanted, and 8 of 11 patients in that study, with a median follow-up of 44 months, had no tumor recurrence [74]. A similar study, using neoadjuvant chemoradiation therapy for highly selected patients with stage I-IIIa hilar cholangiocarcinoma, reported a 45% survival rate (5/11) at

a median follow-up of 7.5 years, but two patients died from tumor recurrence [75]. Those studies demonstrate that early-stage cholangiocarcinoma may be an indication for liver transplantation done as part of a research protocol.

Adjuvant Therapy

Radiation

Following complete surgical resection, the most common relapse pattern is local recurrence. Many authors have advocated postoperative radiation therapy alone or in combination with chemotherapy as a strategy for optimizing local control [45]. The most common approaches to radiotherapy include a combination of external beam irradiation and brachytherapy with iridium-192 (^{192}Ir). While this approach offers a theoretical benefit, the available literature on adjuvant radiotherapy following resection of cholangiocarcinoma is absent of prospective, randomized trials. Small retrospective series have demonstrated significantly higher 5-year survival rates in patients with histological margin-positive resections (33.9% versus 13.5%) when postoperative external beam radiation was used [76, 77]. That same group used a combination of intraoperative and postoperative radiotherapy, which resulted in a 5-year survival rate as high as 39.2% [76]. However, other investigators have failed to demonstrate similar results using a combination of adjuvant external beam radiation and brachytherapy [78]. The role of adjuvant radiation following margin-negative resection is less clear. *Pitt* and colleagues published a nonrandomized trial of radiation therapy that failed to show benefit in these patients [39].

Chemotherapy

Chemotherapy has not been shown to markedly improve survival in patients with either resected or unresected cholangiocarcinoma. The majority of reports use 5-FU alone or in combination with methotrexate, leucovorin, cisplatin, mitomycin C, or interferon alpha (IFN-α). The routes of delivery vary in the literature and include systemic infusion, hepatic arterial infusion, and intraductal infusion. The majority of these reports are small, retrospective, single-center reviews and have recently been summarized by *Todoroki* [79]. A recent phase III, multi-institutional trial from Japan included 139 patients with bile duct cancer [80]. Lymph node metastases were present in 84% and 88% of the patients randomly assigned to chemotherapy and surgery or surgery alone, respectively [80]. That study compared postoperative chemotherapy (two courses of mitomycin C plus infusional 5-FU followed by prolonged oral administration of 5-FU until tumor progression) with resection alone. It failed to show any benefit from chemotherapy

[80]. The 5-year survival rates were not significantly different between patients who received chemotherapy and surgery and those who received surgery alone following either margin-negative (41% versus 28%) or margin-positive resections (8% versus 16%).

Chemoradiation Treatment

Given the potential radiosensitization effect of 5-FU, the combination of adjunctive radiation and chemotherapy should theoretically be more effective than either method alone. This combination therapy has been given postoperatively in several series of patients with cholangiocarcinoma, and prolonged survival has been noted in some [81, 82], particularly in patients with histologically positive resection margins [10, 83, 84]. As an example, in a recent series, 84 patients with extrahepatic bile duct cancer (30 with stage I or II disease and 54 with stage III disease) received postoperative radiation (40 Gy by external beam) with concurrent bolus 5-FU [84]. Surgical resection was margin negative in 47 and microscopically or macroscopically margin positive in 25 and 12 patients, respectively. The 5-year survival rates were 36%, 35%, and 0%, respectively. Fifty percent of all patients with node-negative disease were alive at 5 years [84].

There are no prospective randomized trials examining this combined modality; however, at least one retrospective series failed to demonstrate a survival benefit for postoperative chemoradiotherapy compared with radiotherapy alone [49]. The true role of adjuvant chemoradiotherapy following margin-negative resections remains unclear, as it is for radiation alone.

Neoadjuvant Therapy

Neoadjuvant therapy is rarely an option for patients with cholangiocarcinoma, the majority of whom are jaundiced and have poor functional statuses at presentation. However, selected patients may benefit. *McMasters et al*. reported a small series of patients who received preoperative chemoradiotherapy [85]. Of the nine patients who received neoadjuvant therapy, three had pathologic complete responses, and the margin-negative resection rate in those patients was 100% [85]. These data are promising, but require confirmation. There are insufficient data at this time to support the routine use of neoadjuvant chemoradiotherapy in these patients outside of a clinical trial.

Palliation

It cannot be overemphasized that all patients should be properly evaluated with a goal of resection by an experienced hepatobiliary specialist. Nevertheless, 50%-90% of patients with cholangiocarcinoma are not candidates for curative resection [86, 87]. In this setting, given the short life expectancy, the goal of care should be focused first on quality of life and relief of symptoms (pain, pruritus, jaundice) and second on extending survival. When a patient is deemed unresectable, the diagnosis should be confirmed by biopsy, if this is easily accomplished, in order to assist in palliative chemotherapy and/or radiation therapy planning. A patient with clinical evidence of unresectable cholangiocarcinoma should not have palliative treatments withheld due to absence of pathologic tissue.

Palliative Biliary Drainage

Traditionally, biliary-enteric bypass via hepaticojejunostomy, choledochojejunostomy, intrahepatic segment III/IV bypass, or rarely cholecystojejunostomy has been the primary method of palliation for patients with unresectable cholangiocarcinomas and biliary obstruction. Although associated with the morbidity of a major operation, surgical palliation generally lasts the remaining lifetime of the patient [87]. Because most studies comparing nonsurgical biliary stenting procedures with surgical biliary-enteric bypass demonstrate similar palliative and survival results, the indications for operative drainage have narrowed [88]. However, patients found to be unresectable at the time of exploration remain ideal candidates for biliary-enteric bypass. If an operative bypass is performed for palliation, there may be a role for cholecystectomy in order to prevent potential complications of cholecystitis.

Endoscopic biliary drainage with a self-expandable metal endoprosthesis (metal stent) has become the favored palliative drainage procedure, and it can be successfully performed on most patients with a hilar obstruction. However, the patency rates for hilar tumors are less than those achieved for distal tumors [89, 90]. Hilar lesions often involve all the major hilar ducts and require two or more stents to be placed for adequate drainage [87, 91]; stents in this setting require repeat intervention in about 25% of patients [89, 91, 92]. As one example, stenting achieved successful palliation without the need for reintervention in 69% of 36 patients with unresectable hilar cholangiocarcinoma [93]. In select patients, a combined percutaneous transhepatic and endoscopic approach may provide the highest success rate for bypassing these lesions. In addition, patients in whom internal stenting cannot be performed or provides inadequate drainage because of advanced tumor are candidates for percutaneous external biliary drainage.

There has been debate over the use of plastic versus metal stents, and several controlled clinical trials have addressed this question [94-96]. Almost all of these studies show that metal stents are associated with a longer patency and, therefore, reduce the number of stent reinterventions needed and the associated cost.

The role for prophylactic gastrojejunostomy in patients with cholangiocarcinoma is unclear. There are no data to support its routine use in patients with hilar cholangiocarcinoma, although one paper did find a higher incidence of obstruction in this population of patients following radiation therapy [97]. Patients with distal cholangiocarcinoma may progress similarly to those with carcinoma of the pancreatic head. Prophylactic gastrojejunostomy is debated in this population of patients [98, 99]. Selective, rather than routine, gastrojejunostomy is recommended by most investigators for patients with periampullary tumors, such as distal cholangiocarcinoma.

Palliative Radiation Therapy and Chemotherapy

Patients who are unresectable due to locally advanced disease but have no evidence of distant metastases may be candidates for palliative radiation therapy. The majority of studies that show benefit of this therapy use a combination of external beam radiation and intraluminal ^{192}Ir [87]. While no controlled trials have examined this method, several groups have demonstrated its feasibility [61, 100-102]. The results of those studies are mixed, with the longest reported median survival at 14.5 months [100]; other reports show no survival benefit [101]. Higher doses of radiation may be required in order to obtain a survival advantage. This was illustrated by *Alden* and colleagues in a study of 24 patients with extrahepatic cholangiocarcinoma who received postoperative external beam radiation therapy, brachytherapy, and 5-FU (with or without adriamycin or mitomycin C) [103]. Patients who received doses of radiation higher than 55 Gy experienced a significantly greater 2-year survival rate (28% versus 0%) [103].

While the survival benefit of palliative radiation therapy is debated, there appears to be a role for radiation therapy in the control of local disease. The use of radiation therapy with or without concomitant chemotherapy may contribute to biliary decompression and relieve pain [82, 104]. *Todoroki* and colleagues reported significantly better local control in patients with locally advanced recurrent cholangiocarcinoma using radiotherapy (79% versus 31%) [76], and other investigators have made similar observations [100, 102, 103, 105]. In addition, a combination of regional chemotherapy and conformational radiotherapy has been reported to have promising results for controlling local disease. In a small series of 22 patients, 11 of whom had cholangiocarcinoma, conformational radiation (1.5-1.65 Gy/fraction twice a day) directed at liver lesions was combined with intrahepatic fluorodeoxyuridine (0.2 mg/kg/day) [81]. Fifty percent of patients receiving this regimen were free of hepatic progression after 2 years.

Radiation therapy alone or in combination with regional chemotherapy is not appropriate for patients with widespread disease, and debate over the routine use of palliative radiotherapy in this patient population remains. For patients with widespread disease, systemic chemotherapy is an option; however, the reported response rates are poor [106, 107]. In general, palliative systemic chemotherapy for cholangiocarcinoma offers no benefit over biliary drainage alone [108, 109]. However, some reports using 5-FU in combination with other agents have suggested better response rates than those using single-agent 5-FU [109-115]. One study comparing best supportive care with 5-FU and leucovorin (with etoposide for patients with a Karnofsky performance status ≥70%) demonstrated a trend toward superior survival in 37 patients with biliary tract cancer (6.5 months versus 2.5 months, $p = 0.10$) [116]. Despite partial responses documented by objective tumor shrinkage, no survival benefit has been attributed to these regimens.

Leucovorin in combination with 5-FU has modest activity in studies of patients with biliary tract cancers. In a recent study of 28 patients with advanced tumors, 5-FU (375 mg/m^2/day) was followed by leucovorin (35 mg/m^2/day) on days 1-5 every 3 weeks [111]. There were two complete responses in that group and the overall response rate was 32%. However, a more recent series of 30 patients receiving this regimen showed only a 7% response rate [115]. The response rate when cisplatin (100 mg/m^2 on day 2) was given with 5-FU (1 g/m^2 every day for 5 days) was reported as 24% [117]. A second trial evaluating cisplatin (60 mg/m^2 on day 1 every 21 days) and epirubicin (50 mg/m^2 given with cisplatin) with 5-FU (200 mg/m^2/day throughout treatment) reported a response rate of 40%, with a median duration of response of 10 months [118]. The newest form of platinum to be studied in biliary tract cancer is oxaliplatin. Sixteen patients were treated with oxaliplatin (85 mg/m^2 on day 1) in combination with 5-FU (1.5-2 g/m^2 over 22 hours on days 1-2) and leucovorin (500 mg/m^2 on day 1) [119]. Of the 16 patients, three (19%) responded and six others achieved disease stabilization. The overall reported survival was >9 months.

IFN-α given with 5-FU has been reported in several series. In a regimen giving 5-FU (750 mg/m^2/day on days 1-5) and IFN-α2b (5 MU/m^2 s.c. on days 1, 3, and 5) with cycles repeated every 14 days, a partial response rate of 34% was reported [109]. The addition of other drugs (cisplatin, doxorubicin) to that regimen has been reported to result in greater toxicities, but not a greater response rate [108].

There are preliminary data suggesting that gemcitabine and docetaxel are active agents against cholangiocarcinoma. In a phase II multicenter trial, gemcitabine (1,000 mg/m^2/week

for 3 out of 5 weeks) was given alone or gemcitabine (1,000 mg/m^2 on days 1 and 8, every 21 days) was given with 5-FU (400 mg/m^2 bolus followed by 22-hour infusion of 600 mg/m^2 every 21 days) and leucovorin (100 mg/m^2 on day 1 every 21 days) [120]. Partial responses occurred in 22% and 36% of patients, respectively. A second study that evaluated docetaxel (100 mg/m^2 every 21 days) in 25 patients with unresectable biliary tract carcinoma resulted in two complete and three partial responses (20% overall response rate) [121]. Unfortunately, it appears that the combination of gemcitabine with docetaxel has minimal usefulness [122]. However, the combination of gemcitabine with oxaliplatin showed promise in 33 patients with good performance statuses and adequate hepatic function [123]. Responses were seen in 35.5% of 31 patients with measurable disease. In 23 patients with poor performance statuses, the response rate was still 22%. Finally, a novel tumor antibiotic, rebeccamycin analogue, produced responses in 3 of 27 patients treated and stable disease in 9 of the 27 patients (disease control in 45%) [124].

Photodynamic Therapy

Photodynamic therapy involves the injection of a photosensitizer followed by the endoscopic direct illumination of the tumor bed with a specific wavelength of light. This causes activation of the photosensitizing compound and the generation of oxygen free radicals that kill cancer cells. In recent studies of small numbers of patients with unresectable cholangiocarcinoma with failed endoscopic stents, photodynamic therapy induced a decrease in bilirubin levels, improved quality of life, and led to a slightly better survival [125-127]. Another study failed to show such clinical benefits, but the therapy did induce local tumor necrosis [128]. However, those studies were not randomized, and comparison in a randomized controlled fashion with other palliative procedures is needed to define the real value of this modality.

Recently, a report on the use of neoadjuvant photodynamic therapy in seven patients with advanced cholangiocarcinoma demonstrated local tumor response allowing a margin-negative resection [129]. However, 17% of those patients had recurred by 1 year. Further investigation is needed in order to determine if photodynamic therapy is a useful neoadjuvant tool.

SUMMARY

Cholangiocarcinoma is a rare tumor that continues to present formidable challenges in diagnosis and treatment. Newer radiological techniques including dynamic CT, MRCP, and PET have been developed and are allowing more reliable preoperative staging. In patients who are potentially resectable, careful preoperative planning, potentially including biliary drainage and PVE, should be carried out in order to increase the possibility of achieving a histological margin-negative resection, as this is the patient's only hope for long-term survival. In general, there are only sporadic reports of successful adjuvant or neoadjuvant chemotherapy or radiation therapy. There are currently no data supporting the routine use of neoadjuvant or adjuvant therapies outside a clinical trial. These are avenues of study that need to be undertaken. Similarly, palliative therapies have failed to show any significant survival benefit, and thus, the palliation of patients with unresectable cholangiocarcinoma should be centered on quality-of-life concerns.

REFERENCES

1 Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995;75(suppl 1):171-190.

2 Burke EC, Jarnagin WR, Hochwald SN et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 1998;228:385-394.

3 Broome U, Olsson R, Loof L et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 1996;38:610-615.

4 Pitt HA, Dooley WC, Yeo CJ et al. Malignancies of the biliary tree. Curr Probl Surg 1995;32:1-90.

5 Hewitt PM, Krige JE, Bornman PC et al. Choledochal cysts in adults. Br J Surg 1995;82:382-385.

6 Lipsett PA, Pitt HA, Colombani PM et al. Choledochal cyst disease. A changing pattern of presentation. Ann Surg 1994;220:644-652.

7 Kubo S, Kinoshita H, Hirohashi K et al. Hepatolithiasis associated with cholangiocarcinoma. World J Surg 1995;19:637-641.

8 Ahrendt SA, Pitt HA. Biliary tract. In: Townsend C, editor. Sabiston Textbook of Surgery. Philadelphia: W.B. Saunders Company, 2001:1076-1111.

9 Nagorney DM, Donohue JH, Farnell MB et al. Outcomes after curative resections of cholangiocarcinoma. Arch Surg 1993;128:871-877; discussion 877-879.

10 Nakeeb A, Pitt HA, Sohn TA et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996;224:463-473; discussion 473-475.

11 Que FG, Phan VA, Phan VH et al. Cholangiocarcinomas express Fas ligand and disable the Fas receptor. Hepatology 1999;30:1398-1404.

12 Harnois DM, Que FG, Celli A et al. *Bcl*-2 is overexpressed and alters the threshold for apoptosis in a cholangiocarcinoma cell line. Hepatology 1997;26:884-890.

13 Terada T, Nakanuma Y, Sirica AE. Immunohistochemical demonstration of MET overexpression in human intrahepatic cholangiocarcinoma and in hepatolithiasis. Hum Pathol 1998;29:175-180.

14 Aishima SI, Taguchi KI, Sugimachi K et al. c-erbB-2 and c-Met expression relates to cholangiocarcinogenesis and progression of intrahepatic cholangiocarcinoma. Histopathology 2002;40:269-278.

15 Isa T, Tomita S, Nakachi A et al. Analysis of microsatellite instability, K-*ras* gene mutation and p53 protein overexpression in intrahepatic cholangiocarcinoma. Hepatogastroenterology 2002;49:604-608.

16 Ahrendt SA, Rashid A, Chow JT et al. p53 overexpression and K-*ras* gene mutations in primary sclerosing cholangitis-associated biliary tract cancer. J Hepatobiliary Pancreat Surg 2000;7:426-431.

17 Tannapfel A, Weinans L, Geissler F et al. Mutations of p53 tumor suppressor gene, apoptosis, and proliferation in intrahepatic cholangiocellular carcinoma of the liver. Dig Dis Sci 2000;45:317-324.

18 Taniai M, Higuchi H, Burgart LJ et al. p16^{INK4a} promoter mutations are frequent in primary sclerosing cholangitis (PSC) and PSC-associated cholangiocarcinoma. Gastroenterology 2002;123:1090-1098.

19 Tannapfel A, Benicke M, Katalinic A et al. Frequency of p16(INK4A) alterations and K-*ras* mutations in intrahepatic cholangiocarcinoma of the liver. Gut 2000;47:721-727.

20 Chari RS. Tumor markers in primary and secondary liver tumors. In: Clavien PA, Fong Y, Morse MA et al., eds. Malignant Liver Tumors. Boston, MA: Blackwell Science, 2003.

21 Nakeeb A, Lipsett PA, Lillemoe KD et al. Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. Am J Surg 1996;171:147-152; discussion 152-153.

22 Nichols JC, Gores GJ, LaRusso NF et al. Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. Mayo Clin Proc 1993;68:874-879.

23 Patel AH, Harnois DM, Klee GG et al. The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. Am J Gastroenterol 2000;95:204-207.

24 Siqueira E, Schoen RE, Silverman W et al. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointest Endosc 2002;56:40-47.

25 Ramage JK, Donaghy A, Farrant JM et al. Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 1995;108:865-869.

26 Bjornsson E, Kilander A, Olsson R. CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. Liver 1999;19:501-508.

27 Carpelan-Holmstrom M, Louhimo J, Stenman UH et al. CEA, CA 19-9 and CA 72-4 improve the diagnostic accuracy in gastrointestinal cancers. Anticancer Res 2002;22:2311-2316.

28 Saini S. Imaging of the hepatobiliary tract. N Engl J Med 1997;336:1889-1894.

29 Sharma MP, Ahuja V. Aetiological spectrum of obstructive jaundice and diagnostic ability of ultrasonography: a clinician's perspective. Trop Gastroenterol 1999;20:167-169.

30 Hann LE, Greatrex KV, Bach AM et al. Cholangiocarcinoma at the hepatic hilus: sonographic findings. AJR Am J Roentgenol 1997;168:985-989.

31 Chen CY, Shiesh SC, Tsao HC et al. The assessment of biliary CA 125, CA 19-9 and CEA in diagnosing cholangiocarcinoma—the influence of sampling time and hepatolithiasis. Hepatogastroenterology 2002;49:616-620.

32 Valls C, Guma A, Puig I et al. Intrahepatic peripheral cholangiocarcinoma: CT evaluation. Abdom Imaging 2000;25:490-496.

33 Tillich M, Mischinger HJ, Preisegger KH et al. Multiphasic helical CT in diagnosis and staging of hilar cholangiocarcinoma. Am J Roentgenol 1998;171:651-658.

34 Zhang Y, Uchida M, Abe T et al. Intrahepatic peripheral cholangiocarcinoma: comparison of dynamic CT and dynamic MRI. J Comput Assist Tomogr 1999;23:670-677.

35 Guthrie JA, Ward J, Robinson PJ. Hilar cholangiocarcinomas: T2-weighted spin-echo and gadolinium-enhanced FLASH MR imaging. Radiology 1996;201:347-351.

36 Schwartz LH, Coakley FV, Sun Y et al. Neoplastic pancreaticobiliary duct obstruction: evaluation with breath-hold MR cholangiopancreatography. Am J Roentgenol 1998;170:1491-1495.

37 Guibaud L, Bret PM, Reinhold C et al. Bile duct obstruction and choledocholithiasis: diagnosis with MR cholangiography. Radiology 1995;197:109-115.

38 Yeh TS, Jan YY, Tseng JH et al. Malignant perihilar biliary obstruction: magnetic resonance cholangiopancreatographic findings. Am J Gastroenterol 2000;95:432-440.

39 Pitt HA, Nakeeb A, Abrams RA et al. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. Ann Surg 1995;221:788-797; discussion 797-798.

40 Kluge R, Schmidt F, Caca K et al. Positron emission tomography with [(18)F]fluoro-2-deoxy-D-glucose for diagnosis and staging of bile duct cancer. Hepatology 2001;33:1029-1035.

41 Delbeke D, Martin WH, Sandler MP et al. Evaluation of benign vs malignant hepatic lesions with positron emission tomography. Arch Surg 1998;133:510-515; discussion 515-516.

42 Anderson CA, Rice M, Pinson CW et al. FDG PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. J Gastrointest Surg 2003 (in press).

43 Jarnagin WR, Fong Y, DeMatteo RP et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-517; discussion 517-519.

44 Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31-38.

45 Chari RS, Anderson CA, Saverese DMF. Treatment of cholangiocarcinoma. I. In: Rose BD, editor. UpToDate. Wellesley, MA: UpToDate, 2003.

46 Corvera CU, Weber SM, Jarnagin WR. Role of laparoscopy in the evaluation of biliary tract cancer. Surg Oncol Clin N Am 2002;11:877-891.

47 Callery MP, Strasberg SM, Doherty GM et al. Staging laparoscopy with laparoscopic ultrasonography: optimizing resectability in hepatobiliary and pancreatic malignancy. J Am Coll Surg 1997;185:33-39.

48 Su CH, Tsay SH, Wu CC et al. Factors influencing postoperative morbidity, mortality, and survival after resection for hilar cholangiocarcinoma. Ann Surg 1996;223:384-394.

49 Figueras J, Llado L, Valls C et al. Changing strategies in diagnosis and management of hilar cholangiocarcinoma. Liver Transpl 2000;6:786-794.

50 Washburn WK, Lewis WD, Jenkins RL. Aggressive surgical resection for cholangiocarcinoma. Arch Surg 1995;130:270-276.

51 Nagino M, Nimura Y, Kamiya J et al. Segmental liver resections for hilar cholangiocarcinoma. Hepatogastroenterology 1998;45:7-13.

52 Nakagohri T, Asano T, Kinoshita H et al. Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma. World J Surg 2003;27:289-293.

53 Saldinger PF, Blumgart LH. Resection of hilar cholangiocarcinoma—a European and United States experience. J Hepatobiliary Pancreat Surg 2000;7:111-114.

54 Hadjis NS, Blenkharn JI, Alexander N et al. Outcome of radical surgery in hilar cholangiocarcinoma. Surgery 1990;107:597-604.

55 Nakeeb A, Tran KQ, Black MJ et al. Improved survival in resected biliary malignancies. Surgery 2002;132:555-563; discussion 563-564.

56 Pichlmayr R, Weimann A, Klempnauer J et al. Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg 1996;224:628-638.

57 Lillemoe KD, Cameron JL. Surgery for hilar cholangiocarcinoma: the Johns Hopkins approach. J Hepatobiliary Pancreat Surg 2000;7:115-121.

58 Nimura Y, Kamiya J, Kondo S et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000;7:155-162.

59 Klempnauer J, Ridder GJ, von Wasielewski R et al. Resectional surgery of hilar cholangiocarcinoma: a multivariate analysis of prognostic factors. J Clin Oncol 1997;15:947-954.

60 Tsao JI, Nimura Y, Kamiya J et al. Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience. Ann Surg 2000;232:166-174.

61 Cameron JL, Pitt HA, Zinner MJ et al. Management of proximal cholangiocarcinomas by surgical resection and radiotherapy. Am J Surg 1990;159:91-97; discussion 97-98.

62 Nagino M, Nimura Y, Kamiya J et al. Right or left trisegment portal vein embolization before hepatic trisegmentectomy for hilar bile duct carcinoma. Surgery 1995;117:677-681.

63 Hemming AW, Reed AI, Howard RJ et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg 2003;237:686-691; discussion 691-693.

64 Abdalla EK, Barnett CC, Doherty D et al. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-680; discussion 680-681.

65 Fong Y, Blumgart LH, Lin E et al. Outcome of treatment for distal bile duct cancer. Br J Surg 1996;83:1712-1715.

66 Wade TP, Prasad CN, Virgo KS et al. Experience with distal bile duct cancers in U.S. Veterans Affairs hospitals: 1987-1991. J Surg Oncol 1997;64:242-245.

67 Nagino M, Nimura Y, Kamiya J et al. Selective percutaneous transhepatic embolization of the portal vein in preparation for extensive liver resection: the ipsilateral approach. Radiology 1996;200:559-563.

68 Goldstein RM, Stone M, Tillery GW et al. Is liver transplantation indicated for cholangiocarcinoma? Am J Surg 1993;166:768-771; discussion 771-772.

69 Jeyarajah DR, Klintmalm GB. Is liver transplantation indicated for cholangiocarcinoma? J Hepatobiliary Pancreat Surg 1998;5:48-51.

70 Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69:1633-1637.

71 Iwatsuki S, Todo S, Marsh JW et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998;187:358-364.

72 Alessiani M, Tzakis A, Todo S et al. Assessment of five-year experience with abdominal organ cluster transplantation. J Am Coll Surg 1995;180:1-9.

73 Shimoda M, Farmer DG, Colquhoun SD et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. Liver Transpl 2001;7:1023-1033.

74 De Vreede I, Steers JL, Burch PA et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl 2000;6:309-316.

75 Sudan D, DeRoover A, Chinnakotla S et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002;2:774-779.

76 Todoroki T, Ohara K, Kawamoto T et al. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. Int J Radiat Oncol Biol Phys 2000;46:581-587.

77 Todoroki T, Kawamoto T, Otsuka M et al. Benefits of combining radiotherapy with aggressive resection for stage IV gallbladder cancer. Hepatogastroenterology 1999;46:1585-1591.

78 Gonzalez GD, Gouma DJ, Rauws EA et al. Role of radiotherapy, in particular intraluminal brachytherapy, in the treatment of proximal bile duct carcinoma. Ann Oncol 1999;10(suppl 4):215-220.

79 Todoroki T. Chemotherapy for bile duct carcinoma in the light of adjuvant chemotherapy to surgery. Hepatogastroenterology 2000;47:644-649.

80 Takada T, Amano H, Yasuda H et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002;95:1685-1695.

81 Robertson JM, Lawrence TS, Andrews JC et al. Long-term results of hepatic artery fluorodeoxyuridine and conformal radiation therapy for primary hepatobiliary cancers. Int J Radiat Oncol Biol Phys 1997;37:325-330.

82 Whittington R, Neuberg D, Tester WJ et al. Protracted intravenous fluorouracil infusion with radiation therapy in the management of localized pancreaticobiliary carcinoma: a phase I Eastern Cooperative Oncology Group Trial. J Clin Oncol 1995;13:227-232.

83 Serafini FM, Sachs D, Bloomston M et al. Location, not staging, of cholangiocarcinoma determines the role for adjuvant chemoradiation therapy. Am Surg 2001;67:839-843; discussion 843-844.

84 Kim S, Kim SW, Bang YJ et al. Role of postoperative radiotherapy in the management of extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys 2002;54:414-419.

85 McMasters KM, Tuttle TM, Leach SD et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. Am J Surg 1997;174:605-608; discussion 608-609.

86 Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. Semin Liver Dis 1994;14:109-114.

87 Chari RS, Anderson CA, Saverese DMF. Treatment of cholangiocarcinoma II. In: Rose BD, ed. UpToDate. Wellesley, MA: UpToDate, 2003.

88 Prat F, Chapat 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.

89 Becker CD, Glattli A, Maibach R et al. Percutaneous palliation of malignant obstructive jaundice with the Wallstent endoprosthesis: follow-up and reintervention in patients with hilar and non-hilar obstruction. J Vasc Interv Radiol 1993;4:597-604.

90 Cheung KL, Lai EC. Endoscopic stenting for malignant biliary obstruction. Arch Surg 1995;130:204-207.

91 Schima W, Prokesch 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;52:213-219.

92 Stoker J, Lameris JS. Complications of percutaneously inserted biliary Wallstents. J Vasc Interv Radiol 1993;4:767-772.

93 Cheng JL, Bruno MJ, Bergman JJ. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents. Gastrointest Endosc 2002;56:33-39.

94 Davids PH, Groen AK, Rauws EA et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992;340:1488-1492.

95 Kaassis M, Boyer J, Dumas R et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc 2003;57:178-182.

96 Prat F, Chapat O, Ducot B et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc 1998;47:1-7.

97 Mogavero GT, Jones B, Cameron JL et al. Gastric and duodenal obstruction in patients with cholangiocarcinoma in the porta hepatis: increased prevalence after radiation therapy. Am J Roentgenol 1992;159:1001-1003.

98 Sohn TA, Lillemoe KD, Cameron JL et al. Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. J Am Coll Surg 1999;188:658-666; discussion 666-669.

99 Deziel DJ, Wilhelmi B, Staren ED et al. Surgical palliation for ductal adenocarcinoma of the pancreas. Am Surg 1996;62:582-588.

100 Kuvshinoff BW, Armstrong JG, Fong Y et al. Palliation of irresectable hilar cholangiocarcinoma with biliary drainage and radiotherapy. Br J Surg 1995;82:1522-1525.

101 Bowling TE, Galbraith SM, Hatfield AR et al. A retrospective comparison of endoscopic stenting alone with stenting and radiotherapy in non-resectable cholangiocarcinoma. Gut 1996;39:852-855.

102 Vallis KA, Benjamin IS, Munro AJ et al. External beam and intraluminal radiotherapy for locally advanced bile duct cancer: role and tolerability. Radiother Oncol 1996;41:61-66.

103 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;28:945-951.

104 Ohnishi H, Asada M, Shichijo Y et al. External radiotherapy for biliary decompression of hilar cholangiocarcinoma. Hepatogastroenterology 1995;42:265-268.

105 Robertson JM, Lawrence TS, Dworzanin LM et al. Treatment of primary hepatobiliary cancers with conformal radiation therapy and regional chemotherapy. J Clin Oncol 1993;11:1286-1293.

106 Kajanti M, Pyrhonen S. Epirubicin-sequential methotrexate-5-fluorouracil-leucovorin treatment in advanced cancer of the extrahepatic biliary system. A phase II study. Am J Clin Oncol 1994;17:223-226.

107 Takada T, Kato H, Matsushiro T et al. Comparison of 5-fluorouracil, doxorubicin and mitomycin C with 5-fluorouracil alone in the treatment of pancreatic-biliary carcinomas. Oncology 1994;51:396-400.

108 Patt YZ, Hassan MM, Lozano RD et al. Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. Clin Cancer Res 2001;7:3375-3380.

109 Patt YZ, Jones DV Jr, Hoque A et al. Phase II trial of intravenous fluorouracil and subcutaneous interferon alfa-2b for biliary tract cancer. J Clin Oncol 1996;14:2311-2315.

110 Sanz-Altamira PM, Ferrante K, Jenkins RL et al. A phase II trial of 5-fluorouracil, leucovorin, and carboplatin in patients with

unresectable biliary tree carcinoma. Cancer 1998;82:2321-2325.

111 Choi CW, Choi IK, Seo JH et al. Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. Am J Clin Oncol 2000;23:425-428.

112 Penz M, Kornek GV, Raderer M et al. Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 2001;12:183-186.

113 Chen JS, Jan YY, Lin YC et al. Weekly 24 h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract carcinomas. Anticancer Drugs 1998;9:393-397.

114 Berger B, Vierbuchen M. [Opisthorchiasis simulating a malignancy]. Z Gastroenterol 2001;39:173-175. German.

115 Malik IA, Aziz Z. Prospective evaluation of efficacy and toxicity of 5-fu and folinic acid (Mayo Clinic regimen) in patients with advanced cancer of the gallbladder. Am J Clin Oncol 2003;26:124-126.

116 Glimelius B, Hoffman K, Sjoden PO et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996;7:593-600.

117 Ducreux M, Rougier P, Fandi A et al. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Ann Oncol 1998;9:653-656.

118 Ellis PA, Norman A, Hill A et al. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 1995;31A:1594-1598.

119 Nehls O, Klump B, Arkenau HT et al. Oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas: a prospective phase II trial. Br J Cancer 2003;87:702-704.

120 Gebbia V, Giuliani F, Maiello E et al. Treatment of inoperable and/or metastatic biliary tree carcinomas with single-agent gemcitabine or in combination with levofolinic acid and infusional fluorouracil: results of a multicenter phase II study. J Clin Oncol 2001;19:4089-4091.

121 Papakostas P, Kouroussis C, Androulakis N et al. First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicentre phase II study. Eur J Cancer 2001;37:1833-1838.

122 Kuhn R, Hribaschek A, Eichelmann K et al. Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangio-carcinomas. Invest New Drugs 2002;20:351-356.

123 Maindrault-Goebel F, Selle F, Rosmorduc O et al. A phase II study of gemcitabine and oxaliplatin (GEMOX) in advanced biliary adenocarcinoma (ABA). Final Results. Proc Am Soc Clin Oncol 2003;22:293a.

124 Dowlati A, Posey J, Ramanathan RK et al. Multicenter phase II and pharmacokinetic study of rebeccamycin analogue (RA) in advanced biliary cancers. Proc Am Soc Clin Oncol 2003;22:267a.

125 Ortner MA, Liebetruth J, Schreiber S et al. Photodynamic therapy of nonresectable cholangiocarcinoma. Gastroenterology 1998;114:536-542.

126 Ortner M. Photodynamic therapy for cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2001;8:137-139.

127 Dumoulin FL, Gerhardt T, Fuchs S et al. Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma. Gastrointest Endosc 2003;57:860-867.

128 Zoepf T, Jakobs R, Rosenbaum A et al. Photodynamic therapy with 5-aminolevulinic acid is not effective in bile duct cancer. Gastrointest Endosc 2001;54:763-766.

129 Wiedmann M, Caca K, Berr F et al. Neoadjuvant photodynamic therapy as a new approach to treating hilar cholangiocarcinoma: a phase II pilot study. Cancer 2003;97:2783-2790.

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Erratum

DIAGNOSIS AND TREATMENT OF CHOLANGIOCARCINOMA
The Oncologist 2004;9:43-57

On page 53, the last paragraph in the Photodynamic Therapy section should read, "However, 17% of those patients had recurred by 1 year," rather than, "However, 83% of those patients had recurred by 1 year." In fact, 83% of patients had tumor-free survival at one-year follow up in this study. The authors would like to thank *Dr. Marcus Wiedmann* for bringing this to their attention. The online version has been corrected in departure from print.