Neoplasms of the biliary tract tree are uncommon and have a poor overall prognosis. Although numerous risk factors have been identified, little is known about the pathogenesis of these tumors, and no effective screening

Cholangiocarcinoma

**Epidemiology and Pathogenesis**

Cholangiocarcinomas are cancers of the biliary tree. Extrahepatic tumors are more common than tumors within the liver. Hilar cancers, also called Klatskin tumors, are the most common, occurring approximately two to three times more often than distal cholangiocarcinomas. Although more than 10 different histologic subtypes of extrahepatic cholangiocarcinomas have been reported, over 98% are adenocarcinomas. Of the other histologic subtypes, papillary tumors are rarely invasive (and thus have a favorable prognosis), whereas the small-cell subtype metastasizes early and is nearly invariably fatal.

Little is known about the pathogenesis of adenocarcinomas except that these tumors are associated with inflammation of the biliary system. Cholangiocarcinomas express a receptor for interleukin (IL)-6, and exposure to this cytokine stimulates tumor growth in vitro. They also express Fas ligand, which induces apoptosis of lymphocytes, but they escape Fas-mediated apoptosis by expressing an apoptosis inhibitor (I-FLICE). Thus, cholangiocarcinomas can proliferate while avoiding the effector cells activated by the inflammation-triggered immune response.

Risk factors for the development of cholangiocarcinoma are moderately well characterized. Patients with primary sclerosing cholangitis have the highest risk, with a 7% to 10% lifetime risk of developing this cancer. These tumors also occur with increased frequency in patients with hepatitis C-related cirrhosis, ulcerative colitis, and parasitic infestations. Although less common than the association of hepatitis C and hepatocellular carcinoma, as many as 2% of patients with the hepatitis C virus develop cholangiocarcinoma. Environmental factors have also been associated with biliary tumors. An increased incidence of cholangiocarcinomas is seen in patients exposed to the contrast agent thorium dioxide (Thorotrast). Other chemical carcinogens inducing this cancer include cigarette smoke, asbestos, radon, dioxin, and nitrosamines.

**Symptoms**

Cholangiocarcinomas rarely present symptomatically until they are quite large and cause obstruction of the biliary tract. Painless jaundice occurs in up to 90% of patients, with serum bilirubin often exceeding 10 mg/dL. Approximately 50% of patients experience weight loss. Obstruction caused by cholangiocarcinoma can also result in the symptoms of cholangitis, manifesting as fever and right upper quadrant abdominal pain. Unfortunately, none of these symptoms are specific for neoplasm.

**Screening and Early Detection**

Due to the poor outcome of patients with advanced cholangiocarcinomas as well as the fact that surgery can be curative in limited-stage disease, early detection through a dedicated screening program could conceivably decrease mortality. However, the rarity of biliary tumors makes this
Tumor markers have been considered because of their simplicity. The carbohydrate antigen CA 19-9 is often elevated in the serum of patients with cholangiocarcinomas. A study from the Mayo Clinic compared the CA 19-9 levels of 9 patients with primary sclerosing cholangitis and known cholangiocarcinoma to 28 control patients with primary sclerosing cholangitis and no malignancy.[6] In this setting, CA 19-9 levels exceeding 100 U/mL were 89% sensitive and 86% specific for the detection of cancer. Patients with cholangiocarcinoma without primary sclerosing cholangitis have also been studied. A CA 19-9 level exceeding 100 U/mL also correlated with a diagnosis of cholangiocarcinoma in this group.[10] However, the sensitivity decreased to 50%. Unfortunately both of these studies suffered from an imbalance in measured serum bilirubin between cases and controls. Patients with cancer had a mean serum bilirubin of 7.0 to 8.0 mg/dL, compared to controls, with a mean of only 2.0 to 3.6 mg/dL. In nonmalignant processes, high CA 19-9 levels correlate directly with increased bilirubin.[11] Therefore, the sensitivity of CA 19-9 would likely be lower than reported if better matched controls with higher serum bilirubin levels were used. Overall, no tumor marker studied to date has adequate sensitivity and specificity to be recommended for general screening.

**Diagnostic Imaging**

Cholangiocarcinoma may appear as an abdominal mass, hypoattenuated relative to the liver, on computed tomography (CT) scans. The sensitivity of CT in detecting this cancer is approximately 70%. Although ultrasound is a less expensive test, it is also much less sensitive, suggesting a diagnosis of cancer in only 25% to 50% of cases. The primary use of ultrasound is to evaluate a patient presenting with obstructive jaundice. Cholangiography is a potentially helpful technique, with reported sensitivity results ranging as high as 80% to 90%. It is useful in both defining the location of the cholangiocarcinoma and determining whether a curative resection can be performed. However, the specificity of cholangiography is only 62% because it cannot always distinguish benign from malignant strictures. Magnetic resonance cholangiopancreatography (MRCP) provides accurate information about tumor extent, including vascular involvement. MRCP in conjunction with transcutaneous duplex ultrasound may soon replace other modalities in the evaluation of resectability. In the immediate preoperative period, percutaneous transhepatic cholangiography may provide additional biliary ductal detail, facilitating the placement of silastic stents that can help guide intraoperative dissection; these stents may be left in place postoperatively to provide access to the ductal system. However, prolonged biliary drainage with stents is not advantageous and increases the incidence of infectious complication.

Due to their avid uptake of fluorodeoxyglucose, cholangiocarcinomas are very conspicuous on positron-emission tomography (PET). Tumors as small as 1 cm can be detected by PET. Although too costly for use as a general screening tool, PET may prove useful in the evaluation of candidates being considered for surgical resection and suspected of having nonlocalized disease.

**Staging**

Several different staging systems have been employed for biliary tract cancers. Table 1 shows the tumor-node-metastasis (TNM) staging classification developed by the 1998 American Joint Committee on Cancer (one of the more widely used systems).[3] Stage T1 and T2 disease can be cured with surgery, with 5-year survival rates of 57% and 39%, respectively.[19] Unfortunately, the cure rate for T3 disease, with which most patients present, is significantly lower. Involvement of the regional lymph nodes also results in poor survival. No patients with N2 tumors and only 10% of patients with N1 tumors survive for 5 years.

A more recently devised staging system has been proposed by Memorial Sloan-Kettering Cancer Center.[21] The T-stage classifications in this system appear to correlate well with resectability and predict the need for hepatectomy. Moreover, these clinical categories seem to be prognostic of 5-year survival. If confirmed by other centers, this schema may become the preferred clinical staging system.

**Treatment**

**Surgery**

Cholangiocarcinomas may advance along the wall of the duct underneath intact mucosa, making determination of the full extent of the tumor impossible before surgical exploration. Findings of tumor extension into secondary biliary radicals, vascular encasement, or metastatic disease...
preclude operative intervention for cure. Despite the array of preoperative studies discussed above, at least 20% to 30% of patients thought to be good surgical candidates will be unresectable at the time of exploration. Because these patients have a mean survival of only 6 months to 1 year,[21,22] exploratory laparoscopy has been advocated to assess resectability prior to proceeding with a standard open procedure.

The overall operative intent is to obtain negative histologic margins (R0 resection), which is thought to be necessary to achieve cure. Advances in intraoperative monitoring and postoperative care, in conjunction with greater experience in hepatic resection, have allowed for more radical resections. Current morbidity and mortality rates are acceptable, with the latter ranging from 4% to 12%. Even with aggressive hepatectomy, there is a 30% to 50% chance of achieving microscopically positive margins (R1 resection).[21,23-26] Median survival in this group of patients is significantly shorter than in those with negative margins (20-25 vs 40-60 months). Extended vascular resections have also been performed, although the effect on outcome is not clear.

**Transplantation**

The use of liver and/or cluster organ transplantation for cholangiocarcinoma is controversial, and the published experience is limited. Indications for transplantation include hepatic functional reserve not sufficient to permit resection (often due to cirrhosis and/or primary sclerosing cholangitis) or local tumor extension (type IV Bismuth-Corlette).

Investigators at the University of Cincinnati detailed 207 patients who underwent liver transplantation for suspected or incidentally found cholangiocarcinoma.[27] Operative mortality was 10%, and 5-year survival was 23%. Over 80% of recurrences developed within 2 years of transplantation. The majority of recurrences developed in the allograft itself. Among patients with recurrence, 66% died within 6 months, with over 90% ultimately succumbing to the disease within 2 years. These investigators concluded that transplantation will not be a viable treatment option until more effective adjuvant therapies are available.

**Adjuvant Therapy**

No randomized trials of adjuvant chemotherapy have been performed in resected cholangiocarcinoma patients. The role of adjuvant radiation therapy remains controversial, although these tumors are clearly radiosensitive. Several retrospective analyses of radiation therapy in the literature have reported disparate results.

In one retrospective analysis reported by Kamada and colleagues, 9 patients were treated with preoperative radiotherapy and 59 received postoperative treatment.[28] External-beam radiation doses ranging from 10 to 135 Gy and iridium (Ir)-192 seeds were used. Median survival was approximately 1 year for the patients treated preoperatively and 2 years for those receiving postoperative radiation. Complications occurred in 17% of patients and included biliary bleeding, gastroduodenal ulcers, liver dysfunction, and persistent cholangitis. These complications were much more common among patients who received intraluminal therapy.

Todoroki and associates performed a retrospective review of patients with advanced-stage hilar tumors and compared 42 patients who received either intraoperative or postoperative electron-beam radiation therapy to 21 who did not receive radiation treatment.[29] The mean intraoperative and postoperative radiation doses were 21 and 41 Gy, respectively. The authors reported a significant difference in survival, with 39.2% of the patients treated with radiation alive at 5 years, compared to 13.4% of those treated by resection alone. However, 10% of the patients treated with surgery alone died during surgery. Additionally, those treated solely with resection suffered a much higher complication rate. These discrepancies suggest that the comparison groups were not well matched. A prospective study was conducted in 50 patients who underwent resection of perihilar cholangiocarcinomas.[30] Ir-192 seeds were implanted in patients in whom a complete resection could not be performed, and external-beam radiation was also delivered, for a mean total radiation dose of 54 Gy. No significant differences in survival were noted with the addition of radiation therapy (median survival for the treated and untreated groups was 14 and 15 months, respectively). Nevertheless, the investigators found no decrement in the quality-of-life assessments of patients receiving irradiation.

**Locally Advanced Cholangiocarcinoma**

Morganti and associates described the use of combined-modality therapy in a study in 20 patients with either unresectable cholangiocarcinoma or residual disease after surgery.[31] The majority of patients received 50.4 Gy of external-beam radiation combined with continuous-infusion fluorouracil (5-FU) at 1,000 mg/m²/d for 96 hours. Twelve patients also received intraluminal Ir-192. The overall response rate in this subgroup was 33.3%. Median survival for the entire study population was 21.2 months, and two patients with unresectable disease survived for more than 5 years.
Cancers of the Gallbladder and Biliary Ducts
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Metastatic Cholangiocarcinoma
Because many chemotherapy trials in cholangiocarcinomas have also included or even featured patients with gallbladder cancers, discussion of this area of treatment follows.

Gallbladder Cancer

Epidemiology and Pathogenesis
Approximately twice as common as cholangiocarcinoma, gallbladder cancer occurs at high rates in South America, Japan, and Eastern Europe, with Chile having the highest incidence.[2] This type of cancer occurs 1.5 to 2 times more frequently in women than in men,[32] and its incidence increases in frequency after age 50 years.

As with cholangiocarcinomas, inflammation appears to play a role in the pathogenesis of gallbladder cancer. Precancerous mucosal lesions have been seen in patients with chronic gallbladder inflammation from a variety of sources.[33] Between 50% and 100% of patients diagnosed with cancer have concurrent stones.[34,35] Overall, gallstone disease increases the likelihood of gallbladder cancer threefold.[36]

Bacterial infection has also been associated with gallbladder cancer. The implicated organisms include *Salmonella typhi,*[37] *Escherichia coli,* and *Helicobacter* sp.[2] In chronic carriers of *S. typhi,* the risk of developing gallbladder cancer is 167 times higher than that of controls. The majority (80%) of gallbladder cancers are adenocarcinomas. Other histologies include cystadenocarcinomas, epidermoid carcinomas, adenosquamous carcinomas, sarcomas, and small-cell carcinomas. The papillary variant of adenocarcinoma may have a more favorable prognosis.

Symptoms
Right upper quadrant pain suggestive of cholelithiasis is the most common presenting symptom of gallbladder cancer. Frank jaundice is a late sign and often suggests advanced disease. Constitutional symptoms such as fever and weight loss occur in approximately one-third of patients.[35]

Diagnostic Imaging
Plain abdominal films may demonstrate the so-called "porcelain gallbladder," resulting from calcium deposition in the wall. However, this manifestation is quite unusual, occurring in fewer than 10% of patients diagnosed with gallbladder cancer. CT and ultrasound have a similar sensitivity (range: 40%-60%) in detecting this tumor. A normal ultrasound examination makes the diagnosis of gallbladder carcinoma unlikely. An abnormal ultrasound without frank neoplasm does not rule out cancer; findings of multiple stones or other luminal irregularities may still mask an occult tumor. Endoscopic retrograde cholangiopancreatography appears to be the best imaging modality for detecting gallbladder cancer, with a reported sensitivity approaching 75%.[38]

Staging
Table 2 shows the TNM classification of gallbladder cancers.[3] Stage I disease is often discovered on pathologic review, after surgical removal of the gallbladder. The survival for this stage is actually quite good, ranging from 60% to 100% at 5 years. However, survival rapidly declines with advancing stage. Five-year survival is only 10% to 20% for stage II disease, 5% for stage III disease, and 0% for stage IV disease. Stage IV cancers still comprise the majority of diagnosed gallbladder cancers, despite a shift toward diagnosis of earlier-stage disease with improved imaging modalities.

Surgery
Prophylactic Cholecystectomy
Most gallbladder carcinomas are discovered at a locally advanced stage and are not curable. For this reason, attempts have been made to identify groups at high risk for this malignancy, who might benefit from preemptive cholecystectomy. The advent of laparoscopic cholecystectomy (and the low morbidity associated with this technique) has made this concept more attractive.

Three retrospective studies have shown that gallstones at least 3 cm in diameter are found in approximately 35% of patients with gallbladder cancer, compared to only about 10% of patients with benign disease.[37,39,40] Overall, the presence of stones this size increases the odds ratio for developing gallbladder cancer 10-fold over the unaffected population. The presence of a porcelain gallbladder, gallbladder polyps greater than 1 cm (especially if solitary, sessile, and echodense on standard or endoscopic ultrasound), or an anomalous junction of the pancreaticobiliary duct also dramatically increase the odds of harboring a gallbladder malignancy.

Prophylactic cholecystectomy is a reasonable approach for patients with any of these risk factors, particularly with the availability of the laparoscopic procedure. No clear recommendations can be made for patients with other risk factors (eg, typhoid carriers, primary sclerosing cholangitis), due to
the paucity of data. Care of these patients should be individualized, and if they undergo abdominal surgery for another indication, incidental cholecystectomy should be considered.

**Laparoscopy and Metastatic Disease Risk**

The widespread adoption of laparoscopic cholecystectomy for cholecystitis, with subsequent case reports of port-site metastases from unsuspected gallbladder cancer, has actually resulted in a stringent reevaluation of the role of laparoscopy. Important but unanswered questions include the following: Does laparoscopic cholecystectomy decrease the long-term survival of gallbladder cancer patients? Are potential port-site metastases sufficient reason to abandon the laparoscopic procedure?

Suzuki et al reviewed 41 patients with gallbladder cancer diagnosed during laparoscopic cholecystectomy.[41] Bile spill occurred in 44% of patients. Tis and T1 tumors were found in 26 patients, T2 in 14, and T3 in 1. Of 11 patients with T2 or T3 disease, 9 underwent an open resection, and all patients with T3 disease were found to have disseminated tumor on reexploration. The 5-year survival was 92% for Tis and T1 patients, and 59% for T2 patients. This survival rate is similar to that in patients with gallbladder cancer detected during open cholecystectomy and suggests that long-term outcome is no worse for tumors detected during or following laparoscopic cholecystectomy.

Valid concern has been raised about the possibility of the pneumoperitoneum enhancing the peritoneal spread of unsuspected cancer during laparoscopic cholecystectomy. There are anecdotal reports of disseminated spread after laparoscopic cholecystectomy for Tis and T1 lesions, but in several of these reports, N1 or N2 dissections were not performed, so the true initial stage of the gallbladder cancer was not clear.

Although port-site recurrence has been cited as a reason not to perform laparoscopic cholecystectomy, it should be noted that wound recurrences from gallbladder cancer develop with open cholecystectomies as well. In the Swedish Tumor Registry, wound recurrence developed in 6.5% of all open cholecystectomies later diagnosed with gallbladder cancer, at a median interval of 5 months.[42] All patients with wound recurrence died (median survival: 10 months). Both port-site and wound recurrences are probable indicators of disseminated disease.

**Extent of Surgery for Established Gallbladder Cancer**

Gallbladder resection can consist of simple removal of the gland or may encompass a radical procedure. The standard radical procedure was defined by Shirai as cholecystectomy, wedge resection of the gallbladder bed, excision of the supraduodenal extrahepatic bile duct, and en bloc dissection of regional lymph nodes.[43] In current practice, radical cholecystectomy includes resection of segments V and IVb of the liver, along with clearance of the hepatoduodenal nodal stations. Overall, as with gastric cancer, the extent of lymphadenectomy necessary is not known. Operative morbidity for extended cholecystectomy generally ranges from 10% to 40%, with a mortality rate of 2% to 6% in current series.

For stage I (T1, N0) gallbladder cancer, several large series have shown that a simple cholecystectomy is adequate and will result in more than a 90% 5-year survival. More radical surgery could not improve on this result for most patients, but it is imperative that margins are clear. Shirai and colleagues noted that the only recurrences in patients with T1 cancers (2/89) occurred in those with positive, cystic duct margins.[43] Additional procedures to clear involved margins found after a simple cholecystectomy may be justified in terms of patient survival.

The potential role of radical surgery in stage II (T2, N0) disease is difficult to assess, because many such cancers are discovered only after the tumor plane has been disturbed during an open cholecystectomy. Also, the literature often includes patients with positive margins found after simple cholecystectomy. Shirai’s benchmark series showed that 3-year survival was close to 50% for those undergoing simple cholecystectomy, compared to 90% for patients with T2 disease who underwent a radical procedure as a second surgery.[43]

Support for extended cholecystectomy can be drawn from additional series. Yamaguchi reported a 60% 5-year survival among patients undergoing extended cholecystectomy.[44] A retrospective study of 20 patients undergoing re-resection for T2 gallbladder cancer compared to 18 who did not.[45] Five-year survival was 70% for the former group vs 20% for patients who did not undergo re-resection. Interestingly (but not surprisingly), close to 40% of stage II gallbladder cancer patients are upstaged on final pathologic analysis, due to the discovery of involved regional nodes. N1 disease is present in 29%, and N2 disease, in 18%.

Although the presence of involved regional nodes predicts for a lower 5-year survival (17% for N1 and 40% for N2 disease), it has not been proven that resection of these nodes will increase the percentage of patients who are cured. Overall, retrospective series suggest that, compared to simple
cholecystectomy, extended cholecystectomy for stage II disease increases survival, particularly in those with positive margins.

The optimal extent of resection for patients with stage III gallbladder cancer (N1 disease, or T3 tumor) is unclear. Based on retrospective series demonstrating a 5-year survival as high as 50% in those undergoing extensive procedures, resection of liver segments IVb and V may be indicated, as well as resection of the extrahepatic bile duct to help clear margins and/or N1 disease.[16,17,24,46] The addition of extended hepatic resection (more extensive than bisegmental excision) has been reported in some patients who are long-term survivors. However, there are no data to support this operative conduct on a routine basis.

Although usually not amenable to surgical approaches, some patients with stage IV disease have been treated with aggressive combined resection. These patients are highly selected, and long-term survival may be due as much to favorable tumor biology as to the resection. Todoroki’s series included 57 stage IV patients undergoing combination resection, including hepato-pancreaticoduodenectomy (a subset were treated with adjuvant radiation therapy for microscopic positive margins).[23] Five-year survival in this group was 11%. However, 17 major complications were reported, and the mortality rate was 4%.

**Adjuvant Therapy**

As with cholangiocarcinomas, adjuvant chemotherapy does not have a proven role after resection of gallbladder cancer. Similarly, there are no randomized controlled trials of adjuvant radiation therapy reported in the literature. That said, small case series have been reported. Bosset and colleagues published a trial employing 55 Gy of postoperative external-beam radiation therapy in seven gallbladder cancer patients in whom all visible gross tumor had been removed.[47] Of the seven patients, two had a recurrence within 12 months, and the median survival was not reached after an average follow-up of 22 months.

The neoadjuvant approach has also been tested. In a phase II trial of preoperative combined-modality therapy, 18 patients were treated with 45 Gy of radiation plus continuous-infusion 5-FU at 350 mg/m2, administered on days 1 to 5 and 28 to 32.[48] Primary toxicities included thrombocytopenia and leukopenia. Treatment delays occurred in six patients, and two were unable to undergo surgery. Median survival in this study was 16 months, which is similar to that of historical controls who do not receive treatment.

**Systemic Chemotherapy for Biliary Tract Cancers**

Because cholangiocarcinomas and gallbladder cancer occur infrequently but share a common pathology and metastatic behavior, many chemotherapy studies have enrolled patients with both pathologic types. Standard drugs with activity against gastrointestinal malignancies have been assessed in this setting.

For example, 5-FU has a reported single-agent response rate of approximately 10%,[49] and mitomycin (Mutamycin) has a similar level of activity.[50] Oral capecitabine (Xeloda), a prodrug of 5-FU, was recently discovered to have activity in biliary malignancies; Patt and colleagues reported overall response rates of 50% in advanced gallbladder cancer and 6% in cholangiocarcinoma in a phase II trial.[51]

**Combination Therapy**

5-FU has been combined with doxorubicin (Adriamycin) and mitomycin (FAM) for the treatment of biliary tract tumors.[52] This combination resulted in a 31% response in 14 patients with advanced disease, with minimal toxicity. 5-FU has also been combined with carboplatin (Paraplatin) and leucovorin. In a study in 14 patients with unresectable biliary tract carcinomas, Sanz-Altamira and associates reported one complete response and two partial responses.[53] The primary dose-limiting toxicity was myelosuppression, with more than 50% of patients developing a neutropenic fever. Thrombocytopenia and anemia were also observed with this regimen. The median survival was 5 months.

Given the relatively poor response of biliary tract tumors to traditional agents, biological agents have been added in hopes of improving efficacy. Patt and colleagues added interferon alfa-2b (Intron A) to a 5-day infusion of 5-FU, resulting in a partial response rate of 34%.[54] Median survival was 12 months. Hematologic toxicity, diarrhea, and mucositis were the most commonly reported adverse effects of this treatment regimen.

**Newer Agents**

**Taxanes**

Paclitaxel has demonstrated no activity in biliary tract tumors. Jones and associates tested paclitaxel
doses of 170 to 200 mg/m² repeated every 21 days in 15 patients with bile duct (11) or gallbladder (4) carcinoma, and reported no responses.[55]

The activity of docetaxel (Taxotere) in biliary cancers remains unclear. Pazdur treated 17 cholangiocarcinoma patients with docetaxel (at a starting dose of 100 mg/m², given every 21 days).[56] Neutropenic fever developed in 11 (65%) of these patients, and no objective responses were observed. In another study employing the same dose of docetaxel in 21 patients, Papakostas observed two complete responses and three partial responses.[57] In that trial, 16% of patients developed neutropenic fever.

**Irinotecan**

Although clearly shown to improve survival in patients with metastatic colon cancer, irinotecan (CPT-11, Camptosar) has only minimal activity in biliary tract malignancies. Fishkin and colleagues treated 21 patients with irinotecan at 100 to 125 mg/m² on days 1, 8, 15, and 22, repeated every 42 days.[58] Two responses were reported among the 19 evaluable patients (9%), with 25% suffering grade 3/4 hematologic and gastrointestinal toxicities.

**Gemcitabine**

Gemcitabine (Gemzar) is well tolerated and FDA-approved for the treatment of patients with advanced pancreatic cancer. It has also been studied in patients with cholangiocarcinoma and gallbladder cancer. Raderer treated 19 patients (15 with cholangiocarcinoma and 4 with gallbladder cancer) with gemcitabine at 1,200 mg/m² on days 1, 8, and 15, followed by a 2-week rest period.[59] Three partial responses (16%) were reported, with few side effects other than a rare case of thrombocytopenia. In a South American study of gemcitabine, 42 patients with advanced biliary tract cancer showed a 36% response rate (including one complete response).[60]

**Novel Combinations**

Modeled after regimens effective in lung and bladder cancer, two studies incorporating gemcitabine and cisplatin were recently reported. A study conducted in India enrolled 30 patients with gallbladder carcinoma.[61] Among the 17 evaluable patients, one complete response and eight partial responses were seen. Nearly 20% suffered grade 3/4 neutropenia. The second trial, from Argentina, reported three complete responses and two partial responses in 11 patients with either gallbladder cancer or cholangiocarcinoma.[62] Grade 4 neutropenia occurred in only one patient.

Kuhn and associates treated 43 biliary tree cancer patients with the combination of gemcitabine (1,000 mg/m²) and docetaxel (35 mg/m²) administered weekly for 3 weeks with a 1-week break.[63] In this group, no complete remissions and four partial remissions (9%) were observed. Nearly 20% of patients developed significant nausea. This combination appears more toxic than either single agent, with no demonstrable benefit over either agent alone.

**Conclusions**

Cancers of the biliary tree occur infrequently and have a poor overall prognosis. To date, surgery remains the only curative treatment. The role of adjuvant therapy remains controversial, as there are no randomized trial data to demonstrate a clear benefit. Chemoradiation is still offered by many physicians, particularly for patients with positive margins or more advanced disease. Although gemcitabine (as a single agent and in combinations) demonstrates activity in these cancers, it is unclear whether use of this agent will translate into an improved quality of life and survival for patients with unresectable, metastatic, or recurrent biliary cancers. Future trials will likely utilize this agent in conjunction with irradiation in earlier-stage disease.

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