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Cancer of the Liver and Bile Ducts

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Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world and the third most common cause of cancer death worldwide.[1] More than 500,000 deaths per year are attributed to HCC, representing 10% of all deaths from cancer. In select areas of Asia and Africa, HCC is the most common cause of death due to cancer. The incidence in Europe and the United States is relatively low but is increasing. In Europe, HCC is now the leading cause of death among patients with cirrhosis.[2] In the United States, epidemiologic studies have demonstrated a doubling of HCC incidence over the past two decades.[3] This increase, which has been attributed to the increasing prevalence of chronic hepatitis C virus (HCV) infection, is expected to continue over the next two decades, given the lag time between the onset of chronic hepatitis and development of HCC.

Etiology

Unique among many other cancers, HCC has well-defined major risk factors. Cirrhosis is the strongest predisposing factor for development of HCC, present in 80% of patients. Chronic viral infection is the most frequent major risk factor for development of HCC. In Asia and Africa, hepatitis B viral (HBV) infection is common, whereas in the West and Japan, hepatitis C virus (HCV) is the main risk factor. The association of HCC and HBV infection is one of the most well recognized etiologic relationships in cancer biology.[4] In epidemiologic studies, the prevalence of HBV carriers correlates with incidence of HCC. Chronic HBV carriers have a 100-fold relative risk of developing HCC compared with noncarriers.[5] Up to 40% of HBV carriers who develop HCC do not have evidence of cirrhosis, demonstrating the direct carcinogenic potential of HBV infection.[6] Prevention of HBV infection reduces the incidence of HCC, as demonstrated in Taiwan, where vaccination of infants reduced the incidence of HBV carriers and simultaneously decreased the incidence of HCC by 60% compared with nonimmunized children.[7,8] In developed countries, HCC arises in cirrhotic livers as a result of HCV infection or excessive alcohol intake. Approximately 170 million people are infected with HCV.[9] Vaccination for prevention of HCV infection is currently not available. Prevention is focused on preventing transmission by transfusion of blood products and in halting the progression of infected individuals to cirrhosis by antiviral regimens such as pegylated interferon and ribavirin. Cirrhosis independent of the etiology is thought in most instances to increase the risk of HCC. The degree of association between cirrhosis and HCC, however, is dependent on the primary condition. Cirrhosis from HCV, HBV, alcohol abuse, and hemochromatosis portends a greater risk for HCC than other conditions such as autoimmune hepatitis, primary biliary cirrhosis, α_1-antitrypsin deficiency, and Wilson's disease, where HCC is uncommon.[10]

The environmental carcinogen aflatoxin B_1 (produced by *Aspergillus flavus*) is a contaminant found in corn, peanuts, and rice that increases the risk of HCC threefold due to a specific mutation on codon 249 of the p53 tumor suppressor gene, leading to unregulated cell growth.[11] Aflatoxins do not cause chronic hepatitis, but metabolite intermediates bind selectively to guanine residues in hepatocyte DNA, resulting in mutations of the p53 tumor suppressor gene that lead to unregulated cell proliferation.[12] Clinically, aflatoxins likely act as cocarcinogens in the pathogenesis of HCC in patients with underlying cirrhosis or hepatitis.

Clinical Evaluation

Patients with HCC typically present with either constitutional symptoms or abdominal complaints due to advanced disease. Abdominal pain is present in nearly one-half of patients; anorexia, nausea, weight loss, and fatigue also occur commonly. Presentation may also be related to the degree of cirrhosis and hepatic decompensation manifested by ascites, gastrointestinal hemorrhage, or encephalopathy. Physical examination may be significant only for signs of cirrhosis; however, a discrete mass may be palpable in large tumors.

Serum α-fetoprotein levels are increased in more than 80% of patients with HCC, and this marker provides a sensitivity of 85% and specificity of 90% for detecting the presence of HCC. The presence of a liver mass with an α-fetoprotein level of 500 ng/mL or more is virtually diagnostic of HCC. Serum des-γ-carboxyprothrombin, a precursor 1

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of prothrombin, has a sensitivity and specificity similar to α-fetoprotein but is less commonly used.

An accurate assessment of the number, size, and location of HCC is best obtained by using multiple complementary imaging studies. The goals of imaging are to define the number and location of lesions and the relationship of the HCC to major hepatic and portal veins and hepatic ducts and to delineate cirrhosis, splenomegaly, ascites, regional adenopathy, and presence of metastatic disease. Abdominal ultrasonography is a useful initial study in suspected patients based on its noninvasive and cost-effective profile. After the basic characteristics of HCC are defined with ultrasonography, additional imaging with rapid contrast-enhanced computed tomography (CT) is recommended. In addition to confirming ultrasonographic findings, CT further defines evidence for local invasion, vascular invasion, regional and distant metastases, and portal hypertension. It also provides the ability to calculate the resection volume and the expected remnant volume in resection planning, which are essential in determining the functional resectability of HCC, particularly in patients with cirrhosis. Magnetic resonance imaging (MRI) is an accurate method for imaging HCC. It is the single best imaging method to simultaneously evaluate the liver, tumor vascularity, vascular structural relationships, and bile duct anatomy but lacks the clarity of CT for assessment of extrahepatic disease. MRI has largely supplanted the need for angiography in most patients and is the study of choice for patients with impaired renal function. Hepatic angiography in our practice has a decreasing role in diagnostic evaluation, and its primary use is directed in therapy. Hepatic angiography with the contrast agent lipiodol is particularly accurate for the diagnosis of small HCC when CT and MRI are indeterminate. Hepatic angiography with chemoembolization is used to reduce the size of HCC to enhance resectability, as neoadjuvant therapy in patients before transplantation, or as palliative treatment for patients with unresectable disease. Portal vein embolization can be used to increase resectability by inducing hypertrophy of the contralateral lobe when the predicted postresection remnant is small and the risk of hepatic failure is increased.[13–15]

Staging and Prognosis

Prognostic modeling in HCC is complex, because survival is determined not only by the tumor characteristics and metastases but also by the underlying liver function, which in turn affects the applicability of treatment options. HCC is staged according to the tumor, node, and metastases classification of the American Joint Committee on Cancer or the International Union Against Cancer (AJCC-UICC) scheme (Table 44.1). Although improvements in the prognostic value of this staging system have been realized with modifications, accuracy is still limited because of its predominant histopathologic focus and neglect of accounting for underlying liver function. The Okuda classification includes variables related to pathologic staging and liver function and has been used extensively, but it is unable to distinguish between early and advanced stages.[16] Multiple other classifications have been proposed but have not been fully validated or have not received universal acceptance.

TABLE 44.1. American Joint Committee on Cancer (AJCC) staging of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma.

Stage	*Tumor*	*Node*	*Metastasis*
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

T_1, solitary tumor without vascular invasion; T_2, solitary with vascular invasion or multiple tumors less than 5 cm; T_3, multiple tumors greater than 5 cm or tumor involving a major branch of the portal or hepatic vein(s); T_4, tumors(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum; N_1, regional lymph node metastases; M_1, distant metastases.

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, 6th Edition* (2002), published by Springer-Verlag New York, www.springer-ny.com.

Management

The treatment of HCC is broadly divided into curative and palliative. Curative treatments include resection, liver transplantation, and percutaneous ablation and induce complete responses in a high proportion of patients. Palliative treatments are not aimed at cure but may exhibit partial response rates and even improve survival. In the West, only 30% to 40% of patients undergo curative treatments. In Japan, this percentage is increased to 60% to 90%, which is largely attributed to implementation of surveillance. No level I evidence is currently available evaluating the different methods of curative treatment.

Resection

Hepatic resection aimed at complete extirpation of the tumor is the treatment of choice for HCC in noncirrhotic patients. The treatment of patients with underlying cirrhosis may involve either hepatic resection or transplantation, depending on hepatic function and organ availability. Despite the enthusiasm and theoretical advantages of liver transplantation for HCC patients with cirrhosis, hepatic resection plays a predominant role in the treatment of select patients with well-preserved liver function (Child–Pugh class A) as a result of the lack of organ availability for liver transplantation. There are currently no well-designed controlled trials comparing hepatic resection with transplantation for patients with HCC and cirrhosis.

Hepatic resection is reserved for those patients with HCC grossly limited to the liver and is primarily dependent on the intrahepatic extent of the HCC and the hepatic function. Criteria for resectability are exclusion of extrahepatic metastases, anatomic intrahepatic accessibility of the tumor, and adequate hepatic functional reserve. Major resections in experienced centers can be performed with minimal mortality and excellent outcome. Table 44.2 lists the large contemporary series of hepatic resection in patients with HCC. Overall mortality of hepatic resection is 1% to 15% with an overall 5-year survival of 25% to 50%. Perioperative morbidity and mortality is adversely affected by the presence of cirrhosis,

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TABLE 44.2. Hepatic resection for hepatocellular carcinoma.

Reference	*Year*	*n*	*Level of evidence*	*Median follow-up (months)*	*Mortality (%)*	*5-year disease-free survival (%)*	*5-year actuarial survival (%)*
Wayne[162]	2002	249	III	42	6	N/A	41
Poon[163]	2001	203	III	102	N/A	20[a]	37[a]
Fong[164]	1999	154	III	27	4.5	44[b]	37
Lise[165]	1998	100	III	29	7	26	38
Mazziotti[166]	1998	229	III	40	5	N/A	41
Takenaka[167]	1996	280	III	N/A	2	29	50
Vauthey[168]	1995	106	III	52	6	N/A	41
Kawasaki[169]	1995	112	III	N/A	2	33[c]	79[c]

N/A, not available.

[a]Actual survival data.

[b]For tumors less than 5 cm.

[c]3-year survival data.

which is present in up to 80% of patients. The most frequent serious complications after liver resection in patients with HCC remain perioperative bleeding and liver failure. Several important considerations should be understood when interpreting reports on hepatic resection in patients with HCC. First, each series of patients is highly selected, and overall resectability rate is only 10% of all patients with HCC. Second, the definition of resectability varies widely, with some series excluding patients on the basis of tumor size, vascular invasion, lymph node metastases, and degree of portal hypertension. Third, 75% to 80% of patients who undergo resection have underlying cirrhosis. The degree of hepatic dysfunction, although progressive, may fluctuate and influence perioperative hepatic decompensation and mortality. Moreover, the cause of cirrhosis varies, and the natural history of the underlying liver disease also varies widely. Clearly, there is substantial heterogeneity among patients with resected HCC, and overall comparison of patients frequently neglects these differences.

Tumor recurrence complicates 70% of patients at 5 years, including both true recurrence and de novo tumor.[17] Several predictors of recurrence that have been established include microvascular invasion, poor histologic differentiation, and satellite tumors.[18,19]

Liver Transplantation

Liver transplantation is a well-established treatment option in cirrhotic patients with HCC. Theoretical advantages include simultaneous cure of the tumor and the underlying cirrhosis. Early reports of transplantation for patients with HCC described poor results, with tumor recurrence rates of 32% to 54% and 5-year survival of less than 40%.[20] Careful scrutiny of these reports, however, has enabled identification of optimal candidates for transplantation. With highly selected patients, transplantation has been shown to provide excellent 5-year survival and decreased recurrence rates. Established criteria include patients with one HCC smaller than 5 cm or up to three nodules smaller than 3 cm. With these criteria, 5-year survival of up to 70% and recurrence rates less than 15% have been reported.[17,21–24] Expansion of these criteria has been proposed but remains to be validated.

A crucial consideration in the role of transplantation for treatment of HCC is organ availability, and thus the waiting time, which can exceed 12 months in many centers, results in a dropout rate of 20% to 50%.[18,25] However, because of the disparate number of patients with HCC needing liver transplantation compared to the number of available donors, the United Network of Organ Sharing (UNOS) has adapted the model for end-stage liver disease (MELD) to prioritize the waiting list. This model provides consideration for patients with HCC and underlying liver disease. Living donor liver transplantation is emerging as the most feasible alternative to deceased donor liver transplantation. The theoretical unlimited availability of donors is encouraging but is presently unrealized.

Percutaneous Ablation

For patients with HCC who are not operative candidates, percutaneous approaches are the best option for potential curative treatment. Multiple destructive techniques have been described including both chemical (alcohol, acetic acid) and temperature modification (radiofrequency, microwave, and cryoablation). Percutaneous ethanol injection has been extensively evaluated. Advantages are its procedural simplicity, low cost, and minimal adverse effects. Response rates of 90% to 100% in HCC smaller than 2 cm, 70% in those up to 3 cm, and 50% in those up to 5 cm in diameter have been reported.[26,27] Selected patients with a complete response have been reported to achieve a 5-year survival of 50%.[26,28] Radiofrequency ablation (RFA) represents an alternative percutaneous treatment option for patients with unresectable HCC. Potential advantages over ethanol injection include fewer treatment sessions and better local tumor control. In one randomized controlled trial comparing percutaneous ethanol injection and radiofrequency ablation, RFA-treated patients were associated with better local tumor control; however, there was no difference in overall survival.[29]

Arterial Embolization

Arterial embolization is frequently used for treatment for patients with unresectable HCC. Embolization agents, typically gelatin, may be administered alone or in combination

with selective intraarterial chemotherapy (chemoembolization). Arterial embolization achieves partial responses in 15% to 55% of patients and substantially delays tumor progression and vascular invasion.[30–33] A meta-analysis of randomized controlled trials comparing arterial embolization or chemoembolization with conservative management demonstrated a survival benefit for chemoembolization.[34]

Systemic Treatment

The majority of patients presenting with HCC have advanced disease at the time of presentation. It is estimated that only 15% to 30% of patients have potentially resectable disease. However, on further evaluation only about one-half of these patients truly have tumors that are resectable. For patients with unresectable disease confined to the liver, several options of therapy are available, including chemoembolization and alcohol ablation. For patients with disease that has spread beyond the liver, few effective options are available. Despite multiple prior studies of chemotherapy, either as single agents or in combination, only limited benefit for patients with unresectable or metastatic HCC has been observed (Table 44.3).

A variety of studies have assessed single-agent chemotherapy. Anthracyclines, particularly doxorubicin, have often served as the chemotherapy drug of reference. Only level II and III evidence exists for the efficacy of doxorubicin. Objective responses to doxorubicin have generally been about 10% with an associated short median survival.[35–40] Limited data from trials with epirubicin suggest better response rates but not necessarily longer survival.[41,42] A variety of phase II studies with an anthracycline combined with another agent have not led to a consistent improvement in outcome compared to single-agent studies. However, no phase III trials have been performed.

Fluorouracil (5-FU)- and platinum (CDDP)-based regimens have been evaluated in a large number of clinical trials. All these trials provide level II or III evidence of activity. A combination of 5-FU, CDDP, doxorubicin, and interferon (PIAF) has frequently been cited as an active regimen. Following a complete response to this regimen in a case report,[43] a subsequent phase II clinical trial in 50 patients reported a 26% partial response rate and median overall survival rate of 8.9 months.[44] Although the proportion of patients responding to this regimen was not notably different from that in other platinum-based regimens, 9 of the 13 responding patients were able to undergo surgical resection of previously unresectable tumors. The use of regimens such as PIAF has been limited by the toxicity of the regimens and frequently by the advanced stage of liver dysfunction in most patients with HCC.

Several meta-analyses of published trials have concluded that systemic chemotherapy offers little benefit to patients with HCC.[45–47] Given the apparent limited benefit of chemotherapy, other agents have been evaluated, including hormonal therapy.

Preclinical studies have shown varying levels of sex hormone receptors in HCC, leading to an evaluation of hormonal agents in HCC.[48,49] Several older underpowered phase II trials showed potential benefit with tamoxifen compared to a placebo.[50,51] Subsequently, a number of randomized multicenter trials of tamoxifen, compared to best supportive care, have shown no benefit for tamoxifen.[52–55] Phase II trials of other hormonal-based therapies have not clearly shown a benefit,[56–59] although several small clinical trials have suggested potential activity that has yet to be confirmed.[60,61]

Several clinical trials have evaluated the role of adjuvant therapy for patients undergoing surgical resection of HCC. In one of these trials, 49 patients were randomized to receive chemotherapy with epirubicin and mitomycin or observation.[62] A lower rate of recurrence and better overall survival were observed in patients receiving chemotherapy. The small size of this trial provides only level II evidence of benefit. Most trials have evaluated liver-directed therapy rather than systemic chemotherapy.[63] To date, the various approaches assessed have not shown any clear improvement in overall survival or disease-free survival compared to surgery alone.

Cholangiocarcinoma

Cholangiocarcinoma is the second most common primary liver cancer in the world, after the more common hepatocellular carcinoma. The tumor usually occurs over the age of 50 to 60 years and is slightly more frequent in men than in women. In the United States, the annual incidence of cholangiocarcinoma is approximately 7 per million.[64] Recently, several epidemiologic studies have been published demonstrating an increase in the incidence and mortality of intrahepatic cholangiocarcinoma over the past 30 years in the United States,[64] as well as in numerous other countries.[65,66] According to these analyses, the age-adjusted death rates in the United States increased from 0.15 per 100,000 in the 1970s to 0.66 per 100,000 in the 1990s; similar data were reported for many other Western countries, especially England, Wales, and Australia. The reason for the rising incidence and mortality of cholangiocarcinoma is as yet unclear; it may in part be better recognition of the intrahepatic form of this disease, and some authors have suggested that new and not yet defined environmental factors might contribute to a more frequent development of this disease.

Etiology and Pathogenesis

In contrast to hepatocellular carcinoma, cholangiocarcinoma does not develop preferentially in the cirrhotic liver; in some studies only 4% to 7% of cholangiocarcinomas originated from cirrhotic livers.[67] A number of risk factors have been established, including primary sclerosing cholangitis, liver fluke infestation, Caroli's disease, congenital choledochal cysts, chronic hepatolithiasis, and Thorotrast deposition. However, many patients who are diagnosed with cholangiocarcinoma have none of these factors in their history.

In the United States and Europe, primary sclerosing cholangitis (PSC) is one of the most important risk factors. The estimated risk of a patient with PSC for cholangiocarcinoma is approximately 0.5% to 1.5% per year after diagnosis, and about 10% to 20% of patients with PSC eventually develop cholangiocarcinoma.[68,69]

Other established risk factors for cholangiocarcinoma include liver flukes (infection with *Clonorchos sinensis* or *Opisthorchis viverrini*), Caroli's disease, congenital choledochal cysts, and chronic hepatolithiasis.[70] In Japan, hepatitis

TABLE 44.3. Review of clinical trials of systemic therapy for hepatocellular carcinoma.

Regimen	*Number of patients*	*Response (95% CI)*	*Overall survival*	*Reference*	*Level of evidence*
Gemcitabine-based					
Gemcitabine 1250 mg/m^2 weekly × 3 over 30 min	28	PR—17.8% (2.7–32.9%)	4.8 months	Yang[170]	II
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	20	PR—5%	7.5 months	Kubicka[134]	II
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	30	No responses	6.9 months	Fuchs[171]	II
Gemcitabine 1. 1250 mg/m^2 weekly × 2 over 30 min 2. 1250 mg/m^2 weekly × 2 at 10 mg/m^2/min	1. 25 2. 23	1. PR—4% (0.1–20.4%) 2. No responses	3.2 months	Guan[172]	II
Gemcitabine 2200 mg/m^2 every 2 weeks over 30 min	17	No responses	8.5 months	Ulrich-Pur[173]	II
Gemcitabine 1250 mg/m^2 over 30 min days 1,8 + doxorubicin 30 mg/m^2 day 1	34	PR—11.8% (0.8–22.8%)	4.6 months	Yang[174]	II
1. Gemcitabine 1000 mg/m^2 at 10 mg/m^2/min day 1 + oxaliplatin 100 mg/m^2 day 2 2. Gemcitabine 1500 mg/m^2 over 30 min + oxaliplatin 85 mg/m^2, day 1	1. 11 2. 10	1. PR—10% 2. PR—10%	5 months	Taieb[175]	III
Fluorouracil-based					
5-FU 370 mg/m^2 + LV 200 mg/m^2 × 5 days	14	No responses	3.2 months	Zaniboni[176]	III
5-FU 425 mg/m^2 + LV 20 mg/m^2 × 5 days	29	PR—10%	5.5 months	van Eeden[177]	II
5-FU 250–450 mg/m^2, days 1–5 + LV 500 mg/m^2/d CI days 1–5	15	PR—7%	3.8 months	Tetef[178]	II
5-FU 370 mg/m^2/d + LV 200 mg/m^2/d, days 1–5	25	1 CR + 6 PR: 28% (10.1–45.9%)	Not stated	Porta[179]	II
5-FU + LV + Hydrea				Gebbia[180]	
5-FU 750 mg/m^2 weekly + IFN 9 MU TIW	10	No responses	10 months	Stuart[181]	III
5-FU 200 mg/m^2/d × 21 days + IFN 4 MU/m^2 TIW	36	PR—14.3% (4–32.7%)	15.5 months	Patt[182]	II
UFT 300 mg/m^2/d + LV 90 mg/d PO TID × 28 days	14	No responses	>10 months	Mani[183]	II
Eniluracil 10 mg/m^2 + 5-FU 1 mg/m^2 PO BID × 28 days	45	No responses	11.5 months	Llovet[184]	II
Eniluracil 10 mg/m^2 + 5-FU 1 mg/m^2 PO BID × 28 days	36	No responses	8 months	Benson[185]	II
Platinum-based					
CDDP 90 mg/m^2	9	PR—11%	2.3 months	Ravry[143]	III
CDDP 75 mg/m^2	35	PR—6% (0–17%)	3.5 months	Falkson[186]	II
CDDP 80 mg/m^2	26	PR—15.4% (4.4–34.9%)	Not stated	Okada[187]	II
5-FU 170 mg/m^2/d CI × 7 days + CDDP 3 mg/m^2/d × 5 days, weekly × 3	37	PR—47%	6.1 months	Tanioka[188]	II
5-FU 250 mg/m^2 × 5 days + CDDP 10 mg/m^2 × 5 days + IFN 2.5 MU TIW	6	PR—33%	Not stated	Komorizno[189]	III
5-FU 400 mg/m^2 days 1–4 + doxoubicin 40 mg/m^2 day 1 + CDDP 20 mg/m^2 days 1–4 + IFN 5 MU/m^2 days 1–4	50	PR—26%	8.9 months	Leung[44]	II
5-FU 200 mg/m^2/d × 21 days + epirubicin 50 mg/m^2 day 1 + CDDP 60 mg/m^2 day 1	7	PR—29%	8 months	Ellis[151]	III
5-FU 200 mg/m^2/d × 21 days + epirubicin 60 mg/m^2 day 2 + CDDP 50 mg/m^2 day 2	21	PR—14.5% (1–28%)	10 months	Boucher[190]	III
Oxaliplatin 85–110 mg/m^2 day 1 + topotecan 0.5–1.5 mg/m^2/d × 5 days	13	PR—8%	8 months	Alexandre[191]	III
CDDP 20 mg/m^2 + topotecan 1.25 mg/m^2 × 5 days	10	PR—10%	Not stated	Lee[192]	III
Anthracycline-based					
Doxorubicin 60 mg/m^2	109	No responses	Not stated	Sciarrino[37]	III
Doxorubicin 75 mg/m^2	46	PR—11%	4.2 months	Chlebowski[35]	III
1. Doxorubicin 60–75 mg/m^2 2. Observation	1. 60 2. 46	PR—3.3%	1. 2.5 months 2. 1.8 months	Lai[36]	II
Liposomal doxorubicin 30 mg/m^2	16	No responses	4.6 months	Halm[38]	II
Liposomal doxorubicin 30–45 mg/m^2	40	PR—13% (2–24%)	3 months	Hong[39]	II
Liposomal doxorubicin 40 mg/m^2	17	CR—7%	12 months	Schmidinger[40]	II
Epirubicin varying doses	18	PR—17% (0–34%)	3 months	Hochster[41]	III
Epirubicin 20 mg/m^2 days 1, 8, 15	44	1 CR + 3 PR: 36%	13.7 months	Pohl[42]	II
Doxorubicin 20 mg/m^2 + IFN 20 MU/m^2	21	PR—10%	Not stated	Feun[193]	II
Doxorubicin 20 mg/m^2, weekly + 5-FUDR 80 mg/kg, weekly + IFN 6 MU/m^2, TIW	30	PR—7%	3 months	Feun[194]	II
Epirubicin 25 mg/m^2, weekly + IFN 3 MU/m^2, days 1–5	30	PR—3%	9.5 months	Bokemeyer[195]	II
Epirubicin 40 mg/m^2 day 1 + VP-16 120 mg/m^2 days 1,3,5	36	1 CR + 13 PR: 39% (23–55%)	10 months	Bobbio[196]	II

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TABLE 44.3. Review of clinical trials of systemic therapy for hepatocellular carcinoma. (continued)

Regimen	*Number of patients*	*Response (95% CI)*	*Overall survival*	*Reference*	*Level of evidence*
Epirubicin 40–60 mg/m^2 day 1 + 5-FU 800 mg/m^2 days 1	22	14	11.7 months	Kajanti[197]	II
Hormonal-based					
Flutamide 750 mg QD	32	No responses	2.5 months	Chao[56]	II
Megestrol 160 mg QD	11	No responses	3 months	Colleoni[57]	III
Megestrol 160 mg QD	46	No responses	4 months	Chao[58]	II
Octreotide 30 mg IM	21	PR—5%	4.2 months	Raderer[59]	II
Tamoxifen 20 mg BID	33	No responses	6 months	Engstrom[198]	II
1. Tamoxifen 60 mg QD 2. Placebo	44	Not stated	1. 17 months 2. 12 months	Elba[50]	II
1. Tamoxifen 10 mg BID 2. Placebo	36	Not stated	1. 8.6 months 2. 5.7 months	Martinez[51]	II
1. Tamoxifen 20 mg QD 2. Placebo	120	No responses	1. 20 months 2. 17 months	Castells[52]	I
1. Tamoxifen 40 mg QD 2. Placebo	77	Not stated	1-year survival 1. 30% 2. 37.8%	Riestra[199]	II
1. Tamoxifen 40 mg QD 2. No treatment	480	Not stated	1. 15 months 2. 16 months	Perrone[53,200]	I
1. Tamoxifen 30 mg QD 2. Placebo	119	Not stated	1. 1.5 months 2. 1.5 months	Liu[54]	I
1. Tamoxifen 120 mg QD 2. Tamoxifen 60 mg QD 3. Placebo	1. 130 2. 74 3. 120	Not assessed	1. 2.2 months 2. 2.1 months 3. 2.7 months	Chow[55]	I
Tamoxifen 40 mg/day + VP-16 50 mg/m^2 days 1–21	33	PR—24.2% (11–42%)	Not stated	Cheng[201]	II
Tamoxifen 40 mg QID, days 1–7 + doxorubicin 60 mg/m^2 day 4	36	PR—33.3% (17–51%)	Not stated	Cheng[202]	II
1. Doxorubicin 60 mg/m^2 2. Tamoxifen 10 mg BID, daily + doxorubicin 60 mg/m^2, day 1	59	1. PR—11% 2. PR—16%	1. 2 months 2. 2.5 months	Melia[203]	II
1. Tamoxifen 30 mg BID 2. Tamoxifen 30 mg BID, daily + doxorubicin 50 mg/m^2, day 1	1. 16 2. 16	Not stated	1. 3.2 months 2. 4.9 months	Schachschal[204]	III
1. Octreotide 250 mcg SQ BID 2. Observation	1. 28 2. 30	Not stated	1. 13 months 2. 4 months	Kouroumalis[60]	II
1. Octreotide 30 mg IM 2. Observation	1. 35 2. 35	No responses	1. 1.9 months 2. 2 months	Yuen[205]	II
1. Tamoxifen + Octreotide 2. 5-FU + MMC	1. 24 2. 15	1. 4 CR + 7 PR 2. No responses	1. 12.8 months 2. 5.5 months	Pan[61]	II
Other agents					
CPT-11 125 mg/m^2	14	PR—7% (0–20%)	8.2 months	O'Reilly[206]	II
Ifosfamide 2.5 gm/m^2/d CI × 5 days	10	No responses	3 months	Lin[207]	III
MMC varying doses	30	PR—48%	7 months	Cheirsilpa[208]	III
Mitoxantrone 12 mg/m^2	18	PR—23% (10–47%)	5 months	Colleoni[209]	II
Mitoxantrone 12 mg/m^2, day 1 + IFN varying doses	38	PR—23% (11–40%)	8 months	Colleoni[210]	II
Paclitaxel 175 mg/m^2	20	No responses	3 months	Chao[211]	II
Thalidomide 200–600 mg QD	63	1 CR + 3 PR: 6.3% (0–12.5%)	4.5 months	Hsu[212]	II
Topotecan		PR—13.9% (4.7–29.5%)	8 months	Wall[213]	II
Vindesine 3 mg/m^2	16	No responses	5 months	Falkson[214]	II

PR, partial response; CR, complete response.

C virus infection is frequently found in patients with cholangiocarcinoma,[71] and Kobayashi et al. found that 3.5% of HCV-infected patients developed cholangiocarcinoma within a 10-year observation period.[72] Moreover, dietary habits have been suggested to contribute to the regional variability in incidence, especially the regular intake of certain salted fish products in Asia, which can contain the bacterial product dimethylnitrosamine.[73,74]

Most of these risk factors have in common that they are causes of chronic inflammation and/or cholestasis. Thus, as is the case in many other gastrointestinal tumors, chronic inflammation of the biliary tree appears to be an important factor in the development of cholangiocarcinoma.

A large number of molecular alterations have been found in human cholangiocarcinoma (Table 44.4). However, it must be noted that the most of these alterations have been described in intrahepatic mass-forming cholangiocarcinomas, and their relevance to the ductal-infiltrating and intraductal growth forms as well as extrahepatic tumors is unclear.

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TABLE 44.4. Molecular alterations in cholangiocarcinoma.

Molecular finding	*Biologic effect*
Chronic inflammation/growth factors	
INOS overexpression	DNA damage and mutation Inhibition of DNA repair COX-2 and IL-6 overexpression Inhibition of apoptosis Angiogenesis
COX-2 overexpression	Inhibition of apoptosis Angiogenesis
IL-6/gp130 overexpression	iNOS induction Proliferation
HGF/c-met overexpression	Proliferation
c-erbB-2 overexpression	Proliferation
Tumor suppressors/oncogenes	
K-*ras* mutation/activation	Proliferation
Retinoblastoma/p16/CDK4 inactivation	Loss of cell-cycle control
p14/MDM/p53 inactivation	Loss of cell-cycle control Apoptosis resistance
p53 mutation/overexpression	Loss of cell-cycle control Apoptosis resistance
Apoptosis resistance and immune escape	
Mcl-1 overexpression	Inhibition of apoptosis
Bcl-2 overexpression	Inhibition of apoptosis
Disruption of TGF-beta signaling	Inhibition of apoptosis Loss of cell-cycle control
FasL expression	T-cell apoptosis
Other	
Telomerase reverse transcriptase	Immortalization

As some of the molecular and genetic changes of cholangiocarcinoma can already be detected in preneoplastic inflammatory bile duct lesions, it is generally presumed that chronic inflammation or cholestasis or both cause a sequence of events leading first to hyperplasia and dysplasia of the biliary epithelia, and eventually to the development of carcinoma. Figure 44.1 gives an overview of this hypothesis.

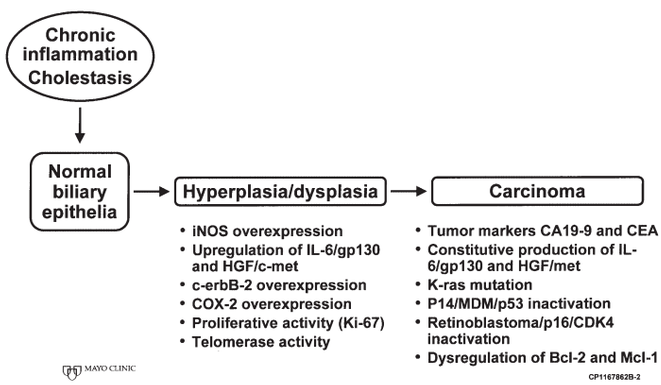

FIGURE 44.1. Molecular alterations in reactive hyper- and dysplasia and in cholangiocarcinoma. Chronic inflammation and cholestasis cause premalignant hyper- and dysplasia of biliary epithelia with distinct molecular alterations such as inducible nitric oxide synthase (iNOS) overexpression, upregulation of growth factors and their receptors, cyclooxygenase (COX)-2 overexpression, increased proliferation, and telomerase activity. With the development of cholangiocarcinoma, malignant cells constitutively express growth factors, mutation of tumor suppressor genes occurs, and oncogenes are observed. There is also dysregulation of antiapoptotic proteins along with expression of classic tumor markers.

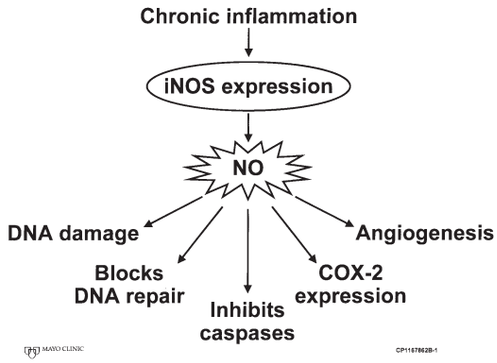

FIGURE 44.2. Nitric oxide in cholangiocarcinogenesis. In chronic inflammation of the bile ducts [e.g., in sclerosing cholangitis (PSC)], cytokines cause biliary epithelia to express iNOS, which in turn generates nitric oxide (NO); NO contributes to carcinogenesis by damaging DNA and inhibiting DNA repair proteins leading to mutation, by inactivating caspases and thus inhibiting apoptosis, by promoting angiogenesis, and by inducing COX-2 expression, which also inhibits apoptosis and triggers angiogenesis.

Chronic Inflammation: DNA Damage

Chronic inflammation is associated with generation of cytokines both by inflammatory cells and by cholangiocytes. A key proinflammatory cytokine is interleukin 6, a strong mitogen for cholangiocytes and cholangiocarcinoma cells. Proinflammatory cytokines including interleukin 6, interleukin 1, interferon-γ, and tumor necrosis factor-α cause cholangiocytes to express the inducible form of nitric oxide synthase (iNOS), a potent generator of nitric oxide (NO). NO itself or NO derivatives (Figure 44.2) can modify or alter DNA bases, resulting in direct DNA damage.[75] NO may also nitrosylate and inactivate DNA repair proteins, leading to an accumulation of damaged DNA bases, thereby further promoting mutagenesis [76]. In addition, NO has been shown to also disable proapoptotic proteins such as caspases.[77]

Consistent with these data, iNOS expression and generation of NO can often be detected in diseases that predispose to cholangiocarcinoma; for example, cholangiocytes in PSC and cholangiocarcinoma cells have been shown to express iNOS,[78] and elevated serum nitrate values as a result of iNOS activity can be observed in patients with fluke infections.[79] Therefore, it has been proposed that iNOS expression and NO generation play an important role in the pathogenesis of cholangiocarcinoma, and that iNOS inhibitors may be chemopreventive in diseases predisposing to the development of cholangiocarcinoma such as PSC, especially because in animal models of intestinal and lung cancer, deletion or inhibition of iNOS can be chemopreventive.[80,81]

Bile Acids: Regulation of Proliferation and Apoptosis

Cholangiocarcinomas often grow within or along the bile duct lumen, suggesting that they may not only have developed mechanisms to survive the toxic constituents in bile but actually use bile to promote growth and survival. Indeed, cholangiocytes and cholangiocarcinoma cells are resistant to apoptosis when exposed to bile acids in vitro, in contrast to hepatocytes and hepatoma cells, for which most bile acids are toxic. Furthermore, bile acids have been shown to transacti-

vate the epidermal growth factor receptor in cholangiocarcinoma cells and induce expression of cyclooxygenase (COX)-2,[82] an enzyme that generates prostanoids and can inhibit apoptosis, facilitate growth, and promote angiogenesis in a variety of malignancies.[83] In addition to inducing COX-2 expression, bile acids also enhance the cellular protein levels of myeloid cell leukemia protein 1 (Mcl-1), a potent anti-apoptotic protein, in vitro.[84] Mcl-1 protein levels are also frequently elevated in human cholangiocarcinoma in vivo.[85]

Thus, chronic inflammation as well as the ability to survive and proliferate in the toxic bile milieu appears to contribute to the development of cholangiocarcinoma. It remains to be elucidated whether cholestasis alone, or alterations in bile composition caused by chronic inflammation, or both are responsible for the antiapoptotic and growth-promoting effects of bile on cholangiocarcinoma.

Histology

Histologically, most cholangiocarcinomas are well to moderately differentiated tubular adenocarcinomas, with formation of glands and an abundance of dense desmoplastic stroma; calcification may be present. Mucus, but not bile secretion, is observed in the majority of tumors. The glandular lumens are lined by well-differentiated columnar or cuboidal cells with uniform nuclei and small nucleoli. In poorly differentiated adenocarcinoma, a definite tubular formation is rarely found, and the cells are pleomorphic with irregular nuclei.

In addition to the most common tubular form of cholangiocellular adenocarcinoma, other variants have been described, such as papillary adenocarcinoma, signet-ring carcinoma, squamous cell or mucoepidermoid carcinoma, a spindle cell variant, and a lymphoepithelioma-like form.

Classification

Cholangiocarcinoma is broadly classified as intrahepatic or extrahepatic. Extrahepatic cholangiocarcinoma is further classified as perihilar, midduct, and distal. Major differences in presentation, evaluation, staging, and operative management warrant separate discussion of intrahepatic and extrahepatic cholangiocarcinoma.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after HCC, with a prevalence of 10% to 30%.[86,87] Cholangiocarcinoma of the intrahepatic ducts is far less common than that of the extrahepatic ducts, typically accounting for less than 10% of all cholangiocarcinoma.

Clinical Evaluation

In a review of 61 patients with ICC surgically treated at the Mayo Clinic over a 31-year period, the most common presenting symptom was abdominal pain, followed by signs of weight loss and anorexia. Jaundice is an unusual finding in ICC that is present in only 15%.[88] The physical examination is frequently nonspecific for ICC; an abdominal mass is the most common finding but is present in only one-third of patients. Other signs such as ascites, cachexia, and splenomegaly are infrequent and nonspecific. Typically, when patients with ICC present with symptoms, the disease is frequently advanced and the likelihood of a curative resection is low.

Other than mild increases in alkaline phosphatase and aminotransferases, laboratory findings are typically normal in patients with ICC. Tumor markers such as the carcinoembryonic antigen (CEA) and α-fetoprotein are infrequently increased, whereas the carbohydrate antigen 19-9 is more frequently elevated in patients with ICC.

The imaging of ICC is similar to that of HCC. Frequently ultrasonography is the initial diagnostic evaluation that is useful to identify the tumor location and characteristics. As for HCC, CT is an excellent imaging modality to assess the tumor location, extent of invasion, and evidence of extrahepatic disease. Because of the intense fibrosis associated with cholangiocarcinoma, a decreased tumoral vascularity of ICC is frequently noted compared to that of HCC.

Pathology and Staging

The gross appearance of intrahepatic cholangiocarcinomas is of a gray-white scirrhous mass, with an abundance of stroma and mucin secretion, but little vascularization. The masses may be solitary or multinodular and can be relatively well demarcated or infiltrating, growing along the intrahepatic bile ducts.

The Liver Cancer Study Group of Japan has further classified intrahepatic cholangiocarcinoma into three principal types: a mass-forming type that is usually localized with a round shape and distinct borders, a periductal-infiltrating type with diffuse infiltration along the bile ducts, and an intraductal growth type showing intraductal papillary or granular growth.[89] Among these, the mass-forming type is the most frequent and the intraductal growth type the rarest; overlap, especially between the mass-forming and the periductal-infiltrating type, is very common. This new classification appears to be useful, because the three forms have been shown to differ not only in gross appearance but also in their genetic alterations and prognosis.[90,91] ICC is staged using the same AJCC tumor, node, and metastases classification as for HCC (see Table 44.1).

Operative Management

Resection remains the only curative treatment in the management of ICC. In our experience, patients with resected ICC are the only long-term survivors, with a 3-year survival of 60% with resection compared to 7% without resection.[88] Operative mortality and morbidity for resection in patients with ICC are typically less than 2% and 15%, respectively.

Hepatic resection is the standard for intrahepatic cholangiocarcinoma. The extent of resection is determined by the anatomic location of the tumor and by the objective of achieving a complete macroscopic and microscopic (R0) resection. Recent series of outcomes after resection of ICC are shown in Table 44.5. Factors associated with decreased survival are stage, vascular invasion, intrahepatic metastases, and positive lymph nodes. Intrahepatic cholangiocarcinoma spreads along

TABLE 44.5. Hepatic resection for perihilar cholangiocarcinoma.

Reference	*Year*	*N*	*Level of evidence*	*Mortality (%)*	*Hepatectomy (%)*	*Negative margin (%)*	*5-year survival (%)*
Rea[122]	2004	46	III	9	100	80	26
Jarnagin[101]	2001	80	III	10	78	78	27
Kitagawa[215]	2001	110	III	10	95	N/A	31[a]
Nimura[102]	2000	142	III	9[b]	90	76	26
Gazzaniga[111]	2000	75	III	10	67	61	18
Lee[119]	2000	128	III	6	87	70	22[c]
Launois[216]	1999	40	III	13	63	80	13
Neuhaus[120]	1999	80	III	8	83	44	22
Burke[97]	1998	30	III	7	73	83	45
Iwatsuki[217]	1998	34	III	15	100	59	9
Miyazaki[218]	1998	76	III	15	86	71	26

N/A, not available.

[a]For node-negative patients

[b]For patients with curative resection.

[c]For patients with hepatic resection.

Glisson's sheath by way of lymphatics to metastasize to regional lymph nodes. The incidence of lymph node metastases for ICC ranges from 6% to 46%.[92,93] In an autopsy series of ICC, lymph node metastases were present in up to 72%.[94] Patients with lymph node metastases have an extremely poor prognosis. Inohue and colleagues evaluated 52 patients with intrahepatic cholangiocarcinoma and reported an overall 5-year survival rate of 36%, but no long-term survivors among 21 patients with lymph node metastases.[95] Routine lymph node dissection in patients with ICC remains controversial. Currently, there is no strong evidence to suggest that lymph node dissection offers a survival benefit, and no randomized trials have been performed. Additionally, hilar lymphadenectomy does not ensure removal of lymph node metastases because the lymphatic drainage of the liver is not exclusively via the hepatoduodenal ligament but also through the coronary, falciform, and triangular ligaments. The presence of lymph node metastases, however, is an ominous finding and should preclude hepatic resection.[95,96] Routine lymphadenectomy with frozen section analysis before proceeding to hepatic resection has been advocated.[96]

Extrahepatic Cholangiocarcinoma

Perihilar cholangiocarcinoma (PCC) accounts for approximately 60% of extrahepatic cholangiocarcinomas. Midduct (15%) and distal (20%) cholangiocarcinomas comprise the remainder.

Clinical Evaluation

The majority of patients with extrahepatic cholangiocarcinoma present with progressive, painless jaundice. Biochemical confirmation typically prompts diagnostic ultrasonography. Albeit operator dependent, ultrasonography can demonstrate several salient features of PCC such as tumor morphology, portal vein or hepatic artery obstruction, intrahepatic metastases, and regional lymph node metastases. Because distant disease precludes curative resection and evidence of unresectability will prompt palliative stenting, CT should precede cholangiographic evaluation. CT provides an excellent overall assessment and can characterize local tumor extension, hepatic lobar atrophy, portal vein compression in invasion, and lymph node and other metastases. The presence of lobar atrophy is frequently associated with ipsilateral portal vein involvement, is a major harbinger of unresectable disease, and should prompt a thorough vascular evaluation.

Cholangiography provides the best evaluation of ductal involvement and extension. Critical in the ductal evaluation is the proximal extent of the disease. Clear delineation of the confluence and proximal biliary system is imperative to correctly classify the tumor and plan surgical resection and reconstruction. Endoscopic retrograde cholangiography (ERC) may not provide sufficient evaluation of the proximal extent of the disease, and percutaneous transhepatic cholangiography may be necessary. The Bismuth–Corlette classification, although not intended to stage PCC, provides a useful conceptualization based on preoperative imaging when considering the extent of resection necessary for a curative intent and communication in reporting (Figure 44.3).

Magnetic resonance imaging (MRI) provides several advantages in the evaluation of cholangiocarcinoma. It provides a noninvasive assessment of the liver, bile ducts, and vessels. Unlike direct cholangiography, however, MRI does not provide equivalent cholangiographic image resolution,

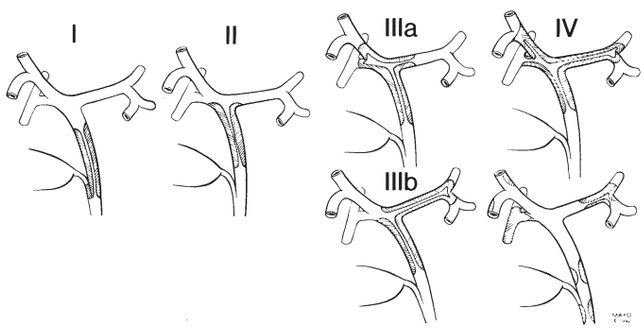

FIGURE 44.3. Bismuth–Corlette classification of perihilar cholangiocarcinoma. (Reprinted by permission of Mayo Foundation for Medical Education and Research.)

access for brush cytology, or the ability of biliary ductal drainage for relief of obstruction and palliation.

A thorough clinical evaluation of the patient's functional status and coexisting medical comorbidities is important before extensive radiographic evaluation. Patients deemed unfit for operative intervention do not need such extensive evaluations, and alternate palliative goals should be considered.

In determining the resectability of PCC, four key issues must be addressed: extent of biliary involvement, vascular (hepatic artery or portal vein) invasion, hepatic atrophy, and metastatic disease. Specific criteria of unresectability have been suggested[97]: these include (1) bilateral ductal extension to the secondary or segmental biliary radicals; (2) encasement or occlusion of the main portal vein proximal to its bifurcation; (3) lobar atrophy with encasement of the contralateral portal vein branch or hepatic artery; (4) lobar atrophy with contralateral involvement of secondary biliary radicals; (5) unilateral segmental ductal extension with contralateral vascular encasement; and (6) distant metastases.

Pathology and Staging

Extrahepatic cholangiocarcinomas have also been subclassified based on their gross appearance as either papillary, nodular, or sclerosing.[98,99] Sclerosing tumors comprise approximately 70% of hilar cholangiocarcinomas and cause an annular thickening of the bile duct wall with longitudinal and radial tumor infiltration as well as infiltration and fibrosis of the periductal tissue. Nodular tumors are characterized by a firm nodule projecting into the bile duct lumen. Tumors featuring characteristics of both nodular and sclerosing forms are relatively frequent. The papillary variant only accounts for approximately 10% and is most commonly seen in the distal bile duct; its prognosis is generally more favorable than that of the two other forms.[98,100] Extrahepatic cholangiocarcinoma is staged according to the AJCC-UICC tumor, node, and metastases classification (Table 44.6). Unlike intrahepatic cholangiocarcinoma where staging is combined with other primary liver tumors, the extrahepatic cholangiocarcinoma staging system is unique to cholangiocarcinoma and has undergone significant revisions. Previous editions of the AJCC staging were criticized for neglect of vascular invasion or hepatic atrophy, which are thought to affect resectability and outcome. Jarnagin and colleagues, in a review of 225 patients with hilar cholangiocarcinoma, proposed a modification of the T staging to include these two factors.[101] On univariate analysis, both vascular invasion and hepatic lobar atrophy were prognostic indicators; however, on multivariate analysis they failed to demonstrate prognostic validity. Although both these factors are clinically useful for evaluating resectability and planning resection, the staging system proposed by Jarnagin and colleagues does not appear to have been adapted by others, albeit the *AJCC Cancer Staging Manual, 6th Edition* now includes vascular invasion as part of the tumoral staging.

TABLE 44.6. American Joint Committee on Cancer (AJCC) staging for extrahepatic cholangiocarcinoma.

Stage	*Tumor*	*Node*	*Metastasis*
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

T_{is}, carcinoma in situ; T_1, tumor confined to the bile duct histologically; T_2, tumor invades beyond the wall of the bile duct; T_3, tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left); T_4, tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as colon, stomach, duodenum, or abdominal wall; N_1, regional lymph node metastases; M_1, distant metastases.

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual, 6th Edition* (2002), published by Springer-Verlag New York, www.springer-ny.com.

Operative Management

Complete tumor resection currently offers the only opportunity for cure. As such, all patients with cholangiocarcinoma should be offered an attempt at resection unless specific contraindications exist. Both patient-related factors and tumor-related factors must be considered when assessing patients for potential operative intervention. Clearly, the patient's functional status must be sufficient to tolerate a major operation, and the preoperative tumor assessment must suggest that a curative resection is possible with opportunity for prolonged survival.

The role of preoperative percutaneous or endoscopic biliary drainage in patients with PCC remains an area of controversy. Proponents argue that the improved hepatic function, reduction of cholangitis, and assistance with hilar dissection afforded by biliary drainage warrant its use.[102,103] Opponents claim that the increased rate of wound infection, bacterobilia, and potential for tumor seeding contraindicate preoperative biliary drainage.[104] Outcome comparisons regarding regeneration after portal vein embolization, hepatic function, and liver failure with or without drainage for hepatic resection in patients with PCC are lacking, and practice guidelines are based on institutional preference.

Patients in whom resection of up to 70% to 75% of the functional liver volume is expected are candidates for portal vein embolization (PVE). The rationale for PVE is to induce hypertrophy and hyperplasia in the anticipated hepatic remnant before resection, theoretically increasing functional capacity and decreasing the risk of postoperative liver failure. In a prospective nonrandomized trial of patients undergoing right hepatectomy for either primary or metastatic liver disease, Farges and colleagues demonstrated a decreased incidence of postoperative complications including liver dysfunction or failure among patients with chronic liver disease who had preoperative PVE.[13] Similar findings of reduced postoperative liver dysfunction or failure were reported by Hemming and colleagues in patients undergoing extended hepatectomy with PVE compared to those without PVE.[14] No randomized controlled trials have been performed assessing the role and utility of PVE in patients undergoing major hepatic resection. The authors have not employed PVE to treat PCC. Although the potential use of PVE has merit, extended hepatic resections are generally well tolerated if the planned liver remnant is well drained preoperatively and if evidence for adequate hepatic function exists.

Intraoperative assessment of patients undergoing exploration for potential curative resection includes exclusion of metastases and assessment of the extent of local invasion. Overall resectability among patients undergoing exploration is nearly 65%. The pendulum of operative management of extrahepatic cholangiocarcinoma has swung from a bile-duct-only resection to that of a combined bile duct and hepatic resection. This change is attributed to the recognition of the propensity for intrahepatic ductal extension and hepatic parenchymal invasion as well as the ability to perform hepatic resection with lower morbidity and mortality. With bile duct resection alone, resectability rates of 15% to 20% were reported.[105–107] Multiple reports have confirmed that increases in hepatic resection for PCC correlate with increases in negative margin resections (R0 resection).[108,109] With hepatic resection rates of 20% to 29%, negative margin rates were achieved in only 15%, compared to a negative margin rate of 60% to 88% with hepatic resection rates of 60% to 89%. Multiple other series have demonstrated that resectability rates parallel hepatic resection rates.[110–112] Level I data are currently unavailable comparing outcomes of bile-duct-only resection versus that combined with hepatic resection. Outcomes of aggressive hepatic resection for management of PCC are shown in Table 44.5.

Significant consideration has been given to the caudate lobe in the operative management of PCC. Caudate biliary ductal tributaries frequently drain into the posterior aspect of the right or left hepatic ducts near the confluence.[113,114] Careful histopathologic examination of resected specimens has demonstrated caudate lobe involvement in 42% to 100% of patients.[114–117] The impact of caudate lobe resection for treatment of PCC is evident by a 20% local recurrence in the caudate lobe when it is not resected.[110] In contrast, when the caudate lobe was incorporated into the hepatic resection, local recurrence decreased and 5-year survival increased from 8% to 25%.[111]

Resection of PCC mandates removal of the gallbladder, the extrahepatic duct from the hepatic hilus to the pancreas, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy. Hepatic resection is generally not required for Bismuth–Corlette type I PCC. Type II and III require resection of caudate and additional segments, dependent on local invasion or ductal extension.

Perioperative mortality and 5-year survival for patients with hepatic resection are shown in Table 44.5. The most frequent serious complications after hepatic resection for PCC are hepatic failure, infection, hemorrhage, and renal or cardiorespiratory failure.

Although no level I data are available comparing outcomes of patients with resected versus nonresected PCC, survival of patients with unresected or advanced-stage PCC has ranged from 6 to 12 months.[118] Before acceptance of hepatic resection, 5-year survival was infrequent and only marginally better than patients without resection.[105] In contrast, the 5-year survival in series utilizing hepatic resection ranges from 9% to 45% (see Table 44.5).

Clearly, the major predictor of long-term survival is complete resection with negative margins (R0 resection).[102,119,120] Existing data suggest that patients with positive margins at resection demonstrate no consistent survival advantage compared to patients without resection.[101,121] In a recent review of our experience with 46 patients undergoing major hepatic resection for PCC, an R0 resection was achieved in 80% with an operative mortality rate of 9%. Actual 1-, 3-, and 5-year survival rates were 80%, 39%, and 26%, respectively.[122] On multivariate analysis, the only predictor of recurrence was tumor grade 3 or 4, whereas negative predictors of survival were history of hepatitis, direct bilirubin at presentation greater than 6.4 mg/dL, blood transfusion requirement greater than 4 units, and male sex. Factors demonstrated to be adversely associated with survival include distant lymph node metastases, vascular invasion, and lobar atrophy.[102,119,120]

Systemic Treatment

The role of palliative chemotherapy in patients with unresectable hepatobiliary cancer has been assessed in a number of clinical trials. The potential benefit of chemotherapy for this group of cancers is derived primarily from trials providing level II and III evidence (Table 44.7), consisting primarily of phase II and insufficiently powered phase III clinical trials. As such, the standards of therapy for unresectable disease remain uncertain. Even less evidence exists on the potential benefit of either adjuvant or neoadjuvant therapy.

For patients with metastatic disease, chemotherapy remains the primary form of therapy, principally for palliation of symptoms. A randomized trial of chemotherapy [5-fluorouracil (5-FU) and leucovorin (LV) or 5-FU, LV, and etoposide] and best supportive care compared to best supportive care alone in patients with metastatic pancreatic or biliary tract cancers demonstrated improved quality of life and overall survival in those receiving chemotherapy.[123]

A variety of chemotherapy agents have been evaluated, but in general the response to these agents has been limited (see Table 44.7). Several older studies evaluated 5-FU alone or in combination with other forms of chemotherapy and showed mixed results. Many of these studies were statistically underpowered and combined biliary cancers with pancreatic cancer or hepatocellular carcinoma, making their interpretation difficult. In general, 5-FU as a single agent produces few responses and an overall survival of less than 6 months.[124,125] However, several recent small trials have suggested high-dose 5-FU or 5-FU in combination with other agents may produce partial responses in up to one-third of patients.[126–130] Despite improved response rates, the duration of response is generally short and little increase in overall survival with 5-FU is seen. Only one phase III study has been performed to assess the added benefit of 5-FU combined with other agents to 5-FU alone.[124] That trial indicated that 5-FU, used alone, was equivalent to or superior to combination therapy. However, this trial provided only level II evidence based on the inadequate sample size.

More recently, trials have focused on gemcitabine as well as other newer agents. Several recent case reports have suggested that gemcitabine may have activity in biliary tract and gallbladder carcinoma.[131,132] A variety of phase II trials have now been published providing level II evidence for the use of gemcitabine.[127,133–139] The appropriate dose and schedule of gemcitabine continue to be evaluated. In a phase II trial of gemcitabine in patients with biliary tract or gallbladder carcinoma, two different schedules were evaluated.[139] Gemcitabine at 1,200 mg/m^2 given weekly for 3 weeks, followed by a 2-week rest period, resulted in 4 of 24 patients (17%) achieving a partial response. The median survival was

TABLE 44.7. Review of clinical trials of systemic therapy for biliary tract and gallbladder cancer.

Regimen	*Number of patients*	*Response (95% CI)*	*Overall survival*	*Reference*	*Level of evidence*
Gemcitabine-based					
Gemcitabine 800 mg/m^2 weekly over 30 min	Gallbladder—14 Biliary tract—14	PR—30%	14 months	Tsavaris[133]	II
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Biliary tract—23	PR—30%	9.3 months	Kubicka[134]	II
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Gallbladder—26	PR—36% (17.1–57.9%)	7.5 months	Gallardo[135]	II
Gemcitabine 1200 mg/m^2 weekly × 3 over 30 min	Gallbladder—5 Biliary tract—14	PR—16%	6.5 months	Raderer[127]	II
Gemcitabine 2200 mg/m^2 every 2 weeks over 30 min	Gallbladder—10 Biliary tract—22	PR—21.9% (9.3–40%)	11.5 months	Penz[136]	II
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Gallbladder—5	PR—60%	9.8 months	Teufel[137]	III
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Biliary tract—13	PR—8%	16 months	Metzger[138]	III
Gemcitabine 1. 1200 mg/m^2 weekly × 3 over 30 min 2. 2200 mg/m^2 every 2 weeks over 30 min	1. Gallbladder—8 Biliary tract—16 2. Gallbladder—5 Biliary tract—9	1. PR—16.7% (5–37%) 2. PR—28.6% (8–58%)	1. 6.8 months 2. 10.5 months	Valencak[139]	III
Gemcitabine 24-h infusion weekly × 3 1. 150 mg/m^2 (no prior therapy) 2. 100 mg/m^2 (prior therapy)	Biliary tract—9 Pancreas—15 Unknown—1	1. PR—8% 2. 0%	Not stated	Eckel[219]	III
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Gallbladder—case report	PR	Not stated	Castro[131]	IV
Gemcitabine 1000 mg/m^2 weekly × 3 over 30 min	Gallbladder—case report	PR	Not stated	Gallardo[132]	IV
Gemcitabine 1000 mg/m^2 over 30 min + 5-FU 500 mg/m^2 over 3 h, weekly × 3	Biliary tract—9	PR—33%	Not stated	Murad[140]	III
Gemcitabine 1000 mg/m^2 over 30 min + 5-FU variable doses, weekly × 3	Gallbladder—1 Biliary tract—3	PR—25%	14.8 months	Boxberger[141]	IV
Gemcitabine 1000 mg/m^2 over 30 min, days 1,8 + CDDP 70 mg/m^2 day 1	Gallbladder—11	CR—9% PR—55%	10.5 months	Malik[220]	III
Gemcitabine 1000 mg/m^2 over 30 min + CPT-11,100 mg/m^2, day 1, 8	Gallbladder—10 Biliary tract—6	PR—14% (interim report)	Not stated	Bhargava[221]	II
Gemcitabine 1000 mg/m^2 over 30 min + docetaxel 35 mg/m^2 over 3 h, weekly × 3	Gallbladder—26 Biliary tract—15	PR—9.3%	11 months	Kuhn[222]	II
Fluorouracil-based					
5-FU 375 mg/m^2/d + LV 25 mg/m^2/d, days 1–5	Gallbladder—9 Biliary tract—19	CR—2% PR—25%	6 months	Choi[223]	II
5-FU 2600 mg/m^2 + LV 150 mg/m^2 over 24 h, weekly × 6	Gallbladder—6 Biliary tract—13	PR—33% (14–57%)	7.0 months	Chen[126]	II
UFT 300 mg/m^2/d + LV 90 mg/d daily for 28 days	Gallbladder + Biliary tract—13	No responses	7 months	Mani[224]	II
1. 5-FU 600 mg/m^2/d × 5 2. 5-FU 600 mg/m^2/d + STZ 500 mg/m^2/d, days 1–5 3. 5-FU 500 mg/m^2/d, days 1–5 + MeCCNU 150 mg/m^2, day 1	1. 30 patients 2. 26 patients 3. 31 patients	GB / Biliary 1. 11% / 8% 2. 13% / 0 3. 5% / 17%	GB / Biliary 1. 5.25 / 5.25 2. 3.5 / 3.0 3. 2.5 / 2.0	Falkson[124]	II
5-FU 750 mg/m^2/d days 1–5 + IFN_2b 5 MU/m^2, days 1, 3, 5	Gallbladder—25 Biliary tract—10	PR—34% (18.6–53.2%)	12 months	Patt[182]	II
5-FU 2000 mg/m^2 + LV 500 mg/m^2 over 24 h, weekly × 6 + CTX 300 mg/m^2 monthly + tamoxifen 20 mg BID	Gallbladder—7 Biliary tract—23	No responses	7.3 months	Eckel[225]	II
5-FU 400 mg/m^2 + LV 200 mg/m^2, days 1–4 + mito C 8 mg/m^2, day 1	Gallbladder—7 Biliary tract—13	PR—25%	9.5 months	Raderer[127]	II
5-FU 2600 mg/m^2 + LV 150 mg/m^2 over 24 hours, weekly × 6 + MMC 10 mg/m^2 day 1, every 8 weeks	Gallbladder—3 Biliary tract—22	PR—26% (14–57%)	6 months	Chen[128]	II
5-FU 350 mg/m^2 + LV 350 mg/m^2, days 1–4 + MMC 10 mg/m^2, day 1	Gallbladder—4 Biliary tract—9	PR—23% (5–54%)	4.5 months	Polyzos[129]	II
5-FU 600 mg/m^2, days 1, 8, 29, 36 + ADR 30 mg/m^2, days 1, 29 + MMC 10 mg/m^2, day 1	Biliary tract—17	PR—31%	Not stated for entire group	Harvey[130]	II
1. 5-FU 310 mg/m^2, days 1–5, 22–26 2. 5-FU 310 mg/m^2, days 1–5, 22–26 + ADR 12 mg/m^2, day 8 + MMC 6 mg/m^2, day 1	1. Gallbladder—10 Biliary tract—8 2. Gallbladder—10 Biliary tract—8	No responses in either arm	Not stated	Takada[125]	II
5-FU 600 mg/m^2 + epirubicin 20 mg/m^2 + MTX 150 mg/m^2, weekly × 3	Gallbladder—6 Biliary tract—16	No responses	9 months	Kajanti[226]	II

TABLE 44.7. (continued)

Regimen	*Number of patients*	*Response (95% CI)*	*Overall survival*	*Reference*	*Level of evidence*
Platinum-based					
CDDP 90 mg/m^2 every 3 weeks	Biliary tract—9	No responses	Not stated	Ravry[143]	III
CDDP 80 mg/m^2 every 4 weeks	Gallbladder—1 Biliary tract—12	PR—7.7% (0.2–36%)	5.5 months	Okada[144]	II
5-FU 1000 mg/m^2/d × 5 days + CDDP 100 mg/m^2 day 2	Gallbladder—11 Biliary tract—14	PR—25% (6–42%)	10 months	Ducreux[145]	II
LV 200 mg/m^2 days 1, 2 + 5-FU 400 mg/m^2 bolus followed by 2200 mg/m^2 over 22 h, days 1, 2 + CDDP 50 mg/m^2 day 2	Gallbladder—6 Biliary tract—23	CR 1 + PR 9: 34% (23–45%)	9.5 months	Taieb[146]	II
LV 500 mg/m^2 + 5-FU 2–2.6 g/m^2 weekly × 6 + CDDP 50 mg/m^2 every other week	Biliary tract—4	No responses	3.9 months	Caroli-Bosc[147]	III
5-FU 500 mg/m^2/d × 5 days + epirubicin 50 mg/m^2 day 1 + CDDP 80 mg/m^2 day 1	Gallbladder—32 Biliary tract—5	PR—19% (6–32%)	6 months	Morizane[150]	II
5-FU 200 mg/m^2/d × 21 days + epirubicin 50 mg/m^2 day 1 + CDDP 60 mg/m^2 day 1	Gallbladder—9 Biliary tract—12	PR—40% (19–64%)	11 months	Ellis[151]	II
5-FU 500 mg/m^2/d × 3 days + doxoubicin 40 mg/m^2 day 1 + CDDP 80 mg/m^2 day 1 + IFN	Gallbladder—19 Biliary tract—22	1 CR + 7 PR 21% (10–37%)	14 months	Patt[152]	II
5-FU 400 mg/m^2 + LV 25 mg/m^2, days 1–4 + CBDCA 300 mg/m^2 day 1	Gallbladder—4 Biliary tract—10	1 CR + 2 PR 21.4%	5 months	Sanz-Altamira[148]	II
LV 500 mg/m^2 days 1, 2 + 5-FU 1.5–2 g/m^2 over 22 h, days 1, 2 + oxaliplatin 85 mg/m^2 day 1	Gallbladder—7 Biliary tract—9	PR—19% (0–41%)	9.5 months	Nehls[149]	II
Other agents					
CPT-11 100–125 mg/m^2 weekly × 4	Gallbladder—24 Biliary tract—15	1 CR + 2 PR: 8% (2–23%)	6.1 months	Alberts[153]	II
CPT-11 125 mg/m^2 weekly × 4	Gallbladder—10 Biliary tract—15	PR—8% (0–18%)	10 months	Sanz-Altamira[154]	II
Docetaxel 100 mg/m^2 every 3 weeks	Gallbladder—16 Biliary tract—9	2 CR + 3 PR—20% (4–36%)	8 months	Papakostas[155]	II
MMC 15 mg/m^2 every 6 weeks	Gallbladder—13 Biliary tract—17	PR—10% (2–27%)	4.5 months	Taal[227]	II
Paclitaxel 170–240 mg/m^2 every 21 days	Gallbladder—4 Biliary tract—11	No responses	Not stated	Jones[156]	II

6.8 months and the time to progression was 3.5 months. In the second arm of this study, gemcitabine 2,200 mg/m^2 was given every 2 weeks, and 4 of 14 patients (29%) achieved a partial response. The median survival with this schedule was 10.5 months and the median time to progression was 4.8 months. In 2002, on review of the available data, the FDA approved a diagnosis of cholangiocarcinoma as an indicator for the use of gemcitabine. Phase III studies to establish the efficacy of gemcitabine have yet to be performed.

Gemcitabine combined with other agents have produced responses ranging from 25% to 64% with median survivals of 10 to 15 months.[140–142] However, this finding is based on level III and IV evidence and as such is of uncertain value. No phase III trials or appropriately powered phase II trials have been published. It therefore remains unclear if multiagent therapy, using gemcitabine, has any benefit over gemcitabine alone. The potential added toxicity of a second agent has also not been assessed in comparison to gemcitabine.

In addition to 5-FU and gemcitabine, platinum compounds represent the other most commonly evaluated chemotherapy drugs. Most studies have evaluated cisplatin (CDDP) alone or in combination with 5-FU and LV and provide level II or III evidence of activity.[143–147] There appears to be no justification for the use of single-agent CDDP, with less than 10% of patients having a response and overall survival under 6 months.[143,144] An improved response rate is seen with the addition of 5-FU and LV. Prolonged infusion of 5-FU appears to increase the response rate to approximately one-third of patients.[146] However, overall survival does not appear to differ between infusional and bolus regimens of 5-FU.[145,146] The use of other platinum drugs, such as carboplatin (CBDCA) or oxaliplatin, also does not appear to change response rates or overall survival.[148,149] Finally, the addition of an anthracycline (doxorubicin or epirubicin) to CDDP and 5-FU does not improve its activity.[150–152] No level I evidence is currently available to establish the activity of platinum-based regimens in comparison to other regimens or single agents such as gemcitabine.

The activity of several newer chemotherapy drugs has been assessed in phase II trials. These trials have shown no obvious improvement in outcome, based on level II evidence, when the drugs CPT-11, docetaxel, or paclitaxel were used.[153–156] Clinical trials with novel or targeted agents have not yet been published.

Until recently, no randomized trials had assessed the potential benefit of chemotherapy following resection of gallbladder or biliary tract carcinoma. In a study of resected pancreatic (n = 173), bile duct (n = 135), gallbladder (n = 140), or ampulla of Vater (n = 56), patients were randomized to either surgery alone or to adjuvant chemotherapy following surgery.[157] For those randomized to adjuvant chemotherapy, patients were given mitomycin C (MMC) and 5-FU for two cycles followed by oral 5-FU until the time of recurrence. Patients with resected gallbladder cancer who received adjuvant chemotherapy had a significantly better 5-year survival rate if they received chemotherapy (26% versus 14%; P =

0.0367). No benefit of adjuvant chemotherapy was seen in patients with resected bile duct cancers. Although this study provides level I evidence for use of adjuvant chemotherapy, at least for resected gallbladder cancer, further studies are needed to confirm the findings of this study and to evaluate the potentially more active chemotherapy drugs including gemcitabine.

The role of adjuvant radiotherapy with or without chemotherapy in combination with hepatic resection for extrahepatic cholangiocarcinoma remains controversial. Although some institutions have demonstrated improved local control and improved overall survival,[158,159] others have reported no benefit.[160,161]

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