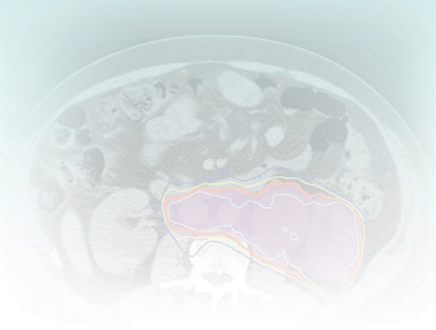
CHAPTER

49 Hepatobiliary Cancer



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INCIDENCE

Globally, hepatobiliary cancer is the fifth-most common cause of cancer and the second cause of cancer death. In 2015, the expected incidence of hepatobiliary cancer in the United States was 46,570 cases, with 28,250 deaths.

BIOLOGIC CHARACTERISTICS

The primary risk factors for hepatocellular carcinoma (HCC) are chronic hepatitis B infection and hepatitis C infection, although liver cirrhosis from any cause increases the risk. The occurrence of cholangiocarcinoma is especially high in patients with primary sclerosing cholangitis. Gallbladder cancer may be related to cholelithiasis.

STAGING EVALUATION

In addition to a history and physical for cancer signs and symptoms, underlying liver disease and liver function need to be considered. The workup includes a complete blood count, liver function tests, liver enzymes, and multiphasic liver computed tomography (CT) or magnetic resonance (MR) imaging, chest and pelvis CT. The evaluation of biliary tumors usually also includes endoscopic retrograde cholangiography or MR cholangiopancreatography.

PRIMARY THERAPY

For hepatobiliary tumors, the best outcomes are seen in patients who are treated with surgery. Patients with resected early stage HCC have a 5-year overall survival (OS) of 30% to 50%; 5-year OS for cholangiocarcinoma ranges from 10% to 40% following surgery, with worse outcomes in hilar cancers. Liver transplantation for selected patients with HCC and hilar cholangiocarcinoma is associated with 5-year OS ranging from 70% to 85% (extrahepatic cholangiocarcinoma [EHCC], transplant alone, 5-year OS 20% to 35%). Preoperative concurrent chemoradiation (chemoRT) plus transplant can result in excellent long-term outcomes (5-year OS of 65% to 74%) in carefully selected patients with EHCC that are unresectable with standard surgery. Five-year OS for gallbladder cancer generally ranges from less than 10% to 30%.

Radiofrequency ablation (RFA) and other ablative techniques can also lead to cure in selected HCC. There is a growing literature on radiation therapy (RT) for early stage HCC, with excellent long-term outcomes in selected patients.

ADJUVANT THERAPY

For HCC, there is no role for adjuvant therapy following surgery or transplant. For biliary carcinoma, it has been suggested that adjuvant chemoRT reduces the risk of relapse, especially in the setting of positive nodes or margins.

LOCALLY ADVANCED DISEASE

For locally advanced HCC, transarterial chemo-embolization (TACE) is associated with a survival benefit compared to best supportive care. Sorafenib is used in patients unsuitable for TACE and also improves survival. RT for locally advanced HCC has been associated with long-term local control, but there is a lack of level-1 evidence.

For locally advanced biliary carcinomas, RT plus concurrent chemotherapy (chemoRT) alone or plus brachytherapy may lead to sustained local control and higher than expected OS. As noted previously, preoperative chemoRT plus liver transplant yields excellent results in carefully selected patients.

PALLIATION

Gemcitabine plus cisplatin had better OS and progression-free survival than gemcitabine alone in a Phase III trial of patients with metastatic or locally advanced biliary cancer (EHCC, gallbladder, or ampullary; 75% had metastases).

Low-dose whole-liver RT may reduce pain or discomfort from HCC unsuitable for standard therapies. RT may also be used for biliary obstruction from cholangiocarcinoma, although biliary stents are the preferred palliative intervention.

Hepatobiliary carcinoma includes HCC, gallbladder cancer, EHCC, and intrahepatic cholangiocarcinoma (IHCC). Globally, hepatobiliary carcinoma is the fifth-most common cause of cancer, and the second-most frequent cause of cancer death.[1] In 2015, the estimated number of new cases in the United States was 46,570, with 28,250 deaths.[2] Relative 5-year survival in the United States has increased from less than 5% in the 1970s to 18% from 2003 to 2009.[1]

Liver cancer is one of the fastest-rising causes of cancer and cancer death in North America, largely as a result of the hepatitis C epidemic.[3] Obesity and nonalcoholic steatohepatitis (NASH) are also an increasing cause of cirrhosis and subsequent HCC. A similar increase in the incidence of IHCC has been reported but for less clear reasons. This may be partially because of the misclassification of hilar cholangiocarcinoma (Klatskin tumors) as IHCC instead of EHCC.[4,5]

The best therapy for hepatobiliary tumors is resection, but only a minority of patients is suitable for surgery because of locally advanced cancer or impaired liver function. Nonsurgical options for HCC include RFA, TACE, sorafenib, and RT. RFA can control HCCs less than 3 cm, which are not adjacent to large vessels. There is a growing literature on the use of RT for the treatment of early stage HCC, with excellent long-term outcomes; however there are no comparative studies. For locally advanced HCC, TACE improves survival compared to best supportive care (2-year OS 63% versus 27% in patients with hepatitis C, and 31% versus 11% in patients with hepatitis B).[6,7] Sorafenib improves survival in HCC unsuitable for TACE. For patients with metastatic or locally advanced biliary carcinoma, gemcitabine plus cisplatin improves median survival from 8.1 to 11.7 months, compared to gemcitabine alone (75% of patients had metastases).[8]

RT did not historically played a role in the treatment of HCC, largely as a result of the low tolerance of the whole liver to RT.[9,10] It was not until conformal RT planning and intensity-modulated radiation therapy (IMRT), that delivery of high doses to focal liver cancers became possible. Protons and more recently stereotactic body radiation therapy (SBRT) have been used to treat selected, hepatobiliary cancers. RT (external beam or brachytherapy) has been associated with improved local control and higher than expected survival rates in locally advanced cholangiocarcinoma, and preoperative chemoRT plus liver transplant can result in excellent 5-year OS in carefully selected patients.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

The most common hepatobiliary cancer is HCC, followed by gallbladder cancer, EHCC, and IHCC. About half of cholangiocarcinomas arise in the perihilar region (Klatskin tumor).[11] Other cancers of the liver, such as carcinoid tumors, hepatoblastoma, angiosarcoma, and leiomyosarcoma, are rare. HCC and IHCC are twice as common in men as in women, gallbladder cancer is about three times more common in women, and EHCC occurs with approximately equal frequency.[5]

Worldwide, liver cancer is the fifth and seventh most common cancer and the second and sixth most common cause of cancer death in men and women, respectively.[12] HCC accounts for 70% to 85% of liver malignancies, and there is considerable variation in the incidence globally, which largely mirrors the variation in the incidence of hepatitis B infection.[12] In Asia, southeast Asia, and middle/western and sub-Saharan Africa, HCC is 15 to 100 times more common than in North America,[13] although the incidence is increasing in the United States and Europe.[14]

Gallbladder cancer also has substantial geographic variation. The incidence in northeastern Europe is more than 20 times higher than in the United States, and it is common in Chile.[15] Although EHCC has a fairly uniform incidence, IHCC is more common in southeast Asia than in other parts of the world, likely because of the higher incidence of liver fluke in this region.

Hepatobiliary carcinoma accounts for about 2% of new cancer cases in the United States[16]; however, there has been a significant increase in HCC incidence and death from HCC and IHCC, in North America, over the past 30 years. From 1992 to 2010, the incidence of HCC and IHCC increased 3.7% and 2.9% per year in males and females, respectively, while deaths increased 2.3% and 1.4% per year in males and females.[1] This change is as a result in part of increasing hepatitis C infection, increase in immigrants from hepatitis B–endemic countries, and increasing NASH.

In the United States, HCC is about four times more common in Asians than whites, and two times more common in African Americans than in whites.[17] Gallbladder cancer is 15 times more common among Native American women than white women in New Mexico.[18] Other hepatobiliary tumors are of approximately equal distribution or show a slight preponderance among whites.

Etiology

Hepatocellular Carcinoma

The primary risk factor for HCC is chronic viral hepatitis B. In developing countries, approximately 60% of HCC is caused by hepatitis B, and 33% is caused by hepatitis C virus. In Korea and Taiwan, approximately 90% of patients with HCC are positive for hepatitis B surface antigen (HBsAg). Prospective studies found that hepatitis B carriers have a 200-fold increase in relative risk for HCC.[19] The risk of HCC is increased in patients with hepatitis C, with a 17-to 20-fold increase compared to people who are negative for hepatitis C. Cirrhosis resulting from nonviral etiologies, including alcohol, NASH, autoimmune chronic active hepatitis, hemochromatosis, and alpha1-antitrypsin deficiency, is responsible for a substantial proportion of HCC in the United States.[14,20] NASH results from metabolic syndrome, obesity, insulin resistance, hypertriglycerimia, and low low-density lipoprotein. Increased free fatty acids in the liver lead to NFKB activation and inflammation and cirrhosis.

Aflatoxin B, a metabolite of *Aspergillus flavus* found in stored grain and peanuts in humid parts of Africa and Asia, has been linked with HCC development.[20] A reactive intermediate metabolite of aflatoxin B binds to guanine, which is excised and replaced with thymidine. This mutation is commonly found in the *TP53* tumor suppressor gene in HCC occurring in areas of high aflatoxin ingestion.

Gallbladder Cancer

Traditional risk factors for gallbladder cancer are female gender and chronic cholelithiasis.[15] Gallbladder cancer is two to six times more common in women than in men, with significant geographic variability correlating with cholelithiasis prevalence.[21] Although more than two thirds of patients with gallbladder cancer have cholelithiasis, only 1% to 3% of patients with cholelithiasis will develop gallbladder cancer.[22] Among patients with cholelithiasis, typhoid carrier state, smoking, high intake of fried food and green leafy vegetables, and diabetes have been associated with gallbladder cancer.[23,24] Additional reported risk factors include smoking, obesity, chemical exposures, family history of gallbladder disease, and reproductive factors including increasing parity, number of pregnancies, and younger age at menarche.[15,18,24,25]

Cholangiocarcinoma

Risk factors for development of cholangiocarcinoma include liver fluke infection, hepatolithiasis, choledochal cysts, and thorium dioxide exposure.[26] Primary sclerosing cholangitis (PSC) is the most common risk factor in the West, with a lifetime risk of 5% to 10%.[27] IHCC development is associated with both hepatitis B and hepatitis C infection, as well as cirrhosis.[28] Other risk factors for cholangiocarcinoma include inflammatory bowel disease independent of PSC, smoking, alcohol consumption, fatty liver disease, diabetes, cholelithiasis, and choledocholithiasis.[26]

PREVENTION AND EARLY DETECTION

Hepatocellular Carcinoma

The prevention of HCC by hepatitis B vaccination has been supported by the reduced childhood HCC rates in Taiwan after introduction of a nationwide vaccination program in 1986.[19] The incidence of HCC among 6- to 14-year olds significantly declined from 0.7 to 0.36 per 100,000, with corresponding reductions in mortality, and larger differences expected in the future as the immunized population ages.

Serum alpha-fetoprotein (AFP) has limited utility on its own for screening HCC, even in high-risk populations.[29] In contrast, early detection of HCC in endemic areas of hepatitis B was demonstrated with use of liver ultrasonography (US) and AFP for screening high-risk populations. In a Chinese trial, approximately 19,000 people were randomized between screening AFP and US every 6 months compared to observation. Mortality from HCC was significantly lower (83/100,000 versus 132/100,000) and survival was significantly better (5-year OS 46% versus 0%) in screened patients.[30] The National

Comprehensive Cancer Network practice guidelines recommend screening patients at high risk for HCC (hepatitis B carriers and cirrhotics), potentially suitable for treatment, with AFP and US every 6 months.[31]

Cholangiocarcinoma

There is no established screening or early detection method for cholangiocarcinoma. In patients with increased risk as a result of PSC, a screening strategy of serum CA 19-9 along with cross-sectional liver imaging has been employed.[32] Patients with CA 19-9 levels above 20 U/mL or abnormal liver imaging may undergo brushings for cytology, digital imaging analysis (DIA), and florescence in situ hybridization (FISH) analysis for early detection. Preliminary data suggests that the combination aneusomy on FISH and aneuploidy on FISH is associated with 50% to 64% sensitivity, and 100% specificity and positive predictive value.[32]

Potential preventive strategies for cholangiocarcinoma in high-risk regions include preventative and therapeutic programs for liver fluke infection,[33] vaccination against hepatitis B infection,[34] and modification of dietary factors including decreased consumption or alcohol, fermented meats and raw fish, and increased consumption of fruits and vegetables.[35] Even though cholelithiasis is a risk factor for gallbladder cancer[33] and cholangiocarcinoma, there is no evidence to justify cholecystectomy as a preventive measure.[18]

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Hepatocellular Carcinoma

The hepatitis C virus has been implicated in the pathogenesis of HCC but without evidence of host genome integration of the viral DNA.[13] Fragments of hepatitis B viral DNA are frequently found within the genome of the HCC,[13,20] leading to the hypothesis that viral integration activates oncogenes or interferes with tumor suppressor genes. The normal liver of patients with chronic hepatitis B infection shows viral DNA integration early in the course of the disease, suggesting that the HCC originated from clonal expansion of the affected hepatocytes.[36] Against this argument is the finding that the sites of viral DNA integration are not consistent and do not occur near known oncogenes or tumor suppressor genes. The most frequent amplifications of genomic material involve 1q, 8q, 6p, and 17q. Common losses involve 8p, 16q, 4q, and 17p. The viral DNA itself does not contain any known oncogenes. Therefore, if the integration of viral DNA is necessary for carcinogenesis, the mechanism may be caused by genomic instability from deletions and chromosomal rearrangement rather than specific oncogene activation or disruption of tumor suppressor genes.[36]

Hepatocarcinogenesis involves many pathways, such as those involving vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF), and insulin like growth factor (IGF). VEGF binds to VEGFR, promoting HCC angiogenesis. EGF binds to the epidermal growth factor receptor (EGFR), triggering signal transduction via the RAS/MAPK pathway. HGF binds to the c-MET receptor, upstream of the RAS/MAPK pathway. Activation of the RAS/MAPK pathway leads to HCC growth and proliferation. Hepatocarcinogenesis may be related to the ability of the liver to respond to damage by regeneration. The continuous liver damage seen with chronic hepatitis or cirrhosis leads to increased turnover of hepatocytes. During normal hepatocyte regeneration, proto-oncogene activation and inactivation of suppressor genes occur. Chronic liver damage leads to a cellular reproduction, which may allow carcinogenic molecular changes to accumulate without repair.[36] The observation of apparent stepwise progression of small HCCs from regenerating nodules of liver cirrhosis supports this hypothesis.[37]

Cholangiocarcinoma

Inflammation appears to be a contributory factor to cholangiocarcinoma pathogenesis. Inflammatory signaling pathways are associated with DNA damage, blocking of apoptosis, and promotion of cell proliferation.[26] Development of malignant phenotype is associated with overexpression of proinflammatory cytokines in tumor stroma and upregulation of HER-2 signaling in epithelium.[37] Epigenetic factors including promoter region hypermethylation and microRNA dysregulation have been associated with development of cholangiocarcinoma.[8a] Dysregulation of developmental pathways including Notch signaling, Hedgehog signaling, and Wnt signaling may play a role in cholangiocarcinogenesis.[26]

Molecular analysis of IHCC specimens has suggested the presence of two distinct classes of IHCC with different outcomes. The more favorable inflammatory class is characterized by the activation of inflammatory signaling pathways, overexpression of cytokines, and STAT3 activation. The poorer prognosis proliferation class is characterized by activation of oncogenic signaling pathways including RAS, MAPK, and MET.[38] *KRAS* mutations have been associated with poor prognosis and are more commonly found in hilar EHCC than in IHCC or distal EHCC.[26,38a] Genomic profiling of EHCC specimens has suggested a poor prognosis group characterized by HER2 upregulation with frequent coactivation of ERBB3, EGFR, MET, and mTOR.[38]

PATHOLOGY AND PATHWAYS OF SPREAD

Primary liver tumors can be classified as benign or malignant and by their tissue of origin (hepatocyte or biliary). Benign tumors constitute 6% to 12% of all liver tumors and include hepatocellular hyperplasia, adenomas, hepatic cysts, mesenchymal hamartomas or hemangiomas, lipomas and fibromas. Of all malignant primary tumors, 85% to 95% are of epithelial origin (including HCC, fibrolamellar HCC, cholangiocarcinoma, and hepatoblastoma), whereas 1% to 3% are malignant mesenchymal tumors.

Hepatocellular Carcinoma

On gross examination, HCC appears as expanding (well-defined margin), infiltrative (poorly defined margin), or multifocal (with multiple tumors throughout the liver).[39] The microscopic appearance of HCC is similar to normal liver, both in cytologic features and in its platelike growth.[40] HCC commonly invades the portal vein, the inferior vena cava (IVC) and sometimes the hepatic vein. It may also invade the diaphragm. Portal nodes are the most likely nodes to be involved, but spread to celiac, gastric, and peritoneal nodes may also occur.[17] Metastases are uncommon at presentation, most often involving the abdominal cavity, the lungs, or bone.

Fibrolamellar HCC is a unique subtype that makes up about 5% of the cases in North America.[40] It is associated with the longest survival of HCC subtypes and is typically found in young women. Grossly, fibrolamellar carcinoma is an expanding, sclerosing tumor, characterized by septa of retracted collagenous structures radiating from a central region.[39] On cytologic examination, the tumor cells are large and polygonal, with a granular cytoplasm resulting from numerous

mitochondria and abundant fibrous stroma arranged in parallel lamellae around nests, cords, and sheets of tumor cells.[41]

Gallbladder Cancer

More than 98% of gallbladder cancers are adenocarcinomas and two thirds are moderately or poorly differentiated. Rare histologic types include squamous cell carcinoma, adenosquamous carcinoma, carcinoid, gastrointestinal stromal tumor, and small cell carcinoma.[42] Most gallbladder cancers arise in the setting of inflammation and associated gastric type or intestinal type metaplasia that progresses to dysplasia and then cancer.[43] Transformation from adenoma to adenocarcinoma also occurs in the gallbladder but is seen in less than 1% of cases.[42]

The gross appearance of gallbladder adenocarcinoma can vary from localized nodular growths to involvement of the entire organ.[44] Histologically, both grade and vascular invasion are of prognostic value. Papillary adenocarcinoma is a variant histologic type that makes up about 5% of the total number of cases and a significantly better prognosis than the more common type.[45] Mucinous carcinoma is another variant of adenocarcinoma, occurring in about 5% of cases and associated with perforation of the gallbladder.[44] Liver invasion is common and may occur by direct spread through the thin wall and singular muscular layer of the gallbladder or by lymphatic spread along portal tracts.[46] Spread to regional lymph nodes including cystic, pericholedochal, hilar, common hepatic, pancreaticoduodenal, and celiac nodes in found in 45% to 55% of patients treated surgically who undergo pathologic nodal evaluation.[47-49] Up to 80% of T3-4 patients will have involvement of regional nodes.[49] About 40% of patients with gallbladder cancer present with distant metastatic disease, most commonly involving liver or peritoneum.[50] Despite increased use of cholecystectomy for gallstone disease, there has been no decrease in the proportion of patients presenting with advanced disease.[51]

Cholangiocarcinoma

Cholangiocarcinomas are typically classified by location as intrahepatic, perihilar, and distal.[11] Most cholangiocarcinomas are mucin-producing adenocarcinomas arising from cholangiocytes that line the biliary tree.[27,52] IHCC may be classified based on macroscopic growth pattern as mass forming, which is the most common type, periductal infiltrating extending along the bile duct, and intraductal, which may have a papillary or tumor thrombus appearance.[53] EHCC can have an intraductal or exophytic (mass-forming) growth pattern. Exophytic tumors may exhibit a nodular or a periductal infiltrating growth pattern.[54] An abundant fibrous stroma with tumor cells in the center is characteristic.[50] As with gallbladder cancer, the papillary variant histologic type has a better prognosis.[55]

Cholangiocarcinoma typically spreads by direct extension along the biliary tree.[56] Tumor involvement of the cystic, hilar, or celiac lymph nodes is found in 30% to 50% of patients.[11,17,55] The incidence of distant metastases, most commonly involving liver, lung, or distant nodal sites, is about 30%, with a lower incidence of peritoneal disease than for gallbladder cancer.[11,56,57]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

Symptoms and Signs

Site of origin can alter the typical presentation of patients with hepatobiliary cancer. Patients with HCC or IHCC frequently present with right upper abdominal or epigastric pain or discomfort.[13,58-60] The pain is usually dull but may be sharp because of tumors causing capsular stretch. Occasionally, patients with HCC present with sudden, severe pain related to an acute HCC rupture and bleed. Patients may also present with awareness of an abdominal mass or increased girth related to ascites. Occasionally, HCC in patients with known cirrhosis may cause deterioration of liver function, leading to ascites, variceal bleed, jaundice, or encephalopathy. In contrast to primary liver tumors, 90% of patients with EHCC present with painless jaundice.[28] Cholangitis is present in 10% of patients, but more than half have nonspecific symptoms including malaise, abdominal discomfort, nausea, anorexia, and weight loss.[28] Patients with gallbladder cancer commonly present with abdominal pain and jaundice and may also have weight loss, anorexia, and fatigue.[61-63]

The most common physical finding in patients with primary hepatic tumors is hepatomegaly.[59,60] The liver is often smooth but may be nodular from tumor or cirrhosis. Patients with HCC may have a hepatic bruit because of a highly vascular tumor. Splenomegaly is also common in patients with cirrhosis or from portal hypertension secondary to tumor invasion of the portal vein. Ascites is a particularly ominous finding because it represents either peritoneal tumor involvement or hepatic dysfunction resulting from advanced cirrhosis, extensive replacement of the liver with tumor, or vascular tumor invasion. HCC invasion to the hepatic vein may lead to rapid decline in liver function, tense ascites, and tender hepatomegaly.

Patients with EHCC or gallbladder cancer are usually jaundiced and may have hepatomegaly or right upper quadrant tenderness on examination. Although a mass may be palpable, patients with gallbladder cancer are often thought to have benign disease until laparotomy and cholecystectomy.

Laboratory Studies

The goals of the workup of patients with malignant hepatobiliary tumors are to define the extent of the tumor and to assess liver function. The workup includes a complete blood count, liver function tests (albumin, bilirubin and coagulation studies), liver enzymes, and routine biochemistry (Table 49-1).

TABLE 49-1 Diagnostic Algorithm for Hepatobiliary Cancers

GENERAL
• History
• Physical examination
LABORATORY STUDIES
• Complete blood count
• Biochemistry panel, including liver function studies (albumin, bilirubin) and liver enzymes
• Coagulation studies (INR)
• Serum CA19-9 (if suspicious for cholangiocarcinoma)
• Alpha-fetoprotein (if suspicious for hepatocellular carcinoma)
• Hepatitis studies (HBsAg, HBsAb, HBcAb, anti-HCV)
RADIOGRAPHIC STUDIES
• Multiphasic liver CT or MR
• Transhepatic or endoscopic cholangiography (if bile duct blockage is present)

Anti-HCV, *Antibody to hepatitis C virus;* CT, *computed tomography;* HBcAb, *hepatitis B core antibody;* HBsAb, *hepatitis B surface antibody;* HBsAg, *hepatitis B surface antigen;* MR, *magnetic resonance;* INR, *international normalized ratio.*

Serum AFP is a widely used tumor marker for HCC, with normal values of 20 µg/L or less, and levels greater than 400 µg/L (4000 µg/L in patients with hepatitis) strongly suggestive of HCC.[64] Elevations in AFP between 20 µg/L and 400 µg/L may represent either an exacerbation of hepatitis or HCC.[29] Approximately 10% to 15% of HCCs do not secret AFP.[65] Serum CA19-9 has value as a tumor marker for cholangiocarcinoma but is less specific for EHCC than for IHCC as levels are affected by cholestasis and cholangitis.[26]

HCC outcomes in patients with hepatitis B or hepatitis C differ, as does toxicity and tolerability of treatment. High viral load before therapy has been associated with worse survival,[66] and reactivation of hepatitis B has been reported following treatment for HCC. Screening for viral hepatitis should be considered in all at-risk individuals.[67]

Approximately 5% of patients with HCC have a paraneoplastic syndrome,[68] such as hypoglycemia, erythrocytosis, hypercalcemia, or hypercholesterolemia.[59]

Radiographic Studies

Patients with suspected hepatic malignancy are often evaluated initially with US, which is operator dependent and less helpful in obese patients. The use of Doppler contrast US and harmonic imaging have improved its usefulness.[68,69] In planning for treatment, CT and MR imaging are the primary imaging modalities because of their ability to display hepatic segmental anatomy, the extent of tumor invasion to vasculature, and extrahepatic spread. Multislice spiral CT is required for liver imaging to be done in a single breath-hold to improve spatial resolution. Multiphasic imaging (arterial hepatic, portal venous, and delayed phase) is vital for assessing lesion vascularity, extent of tumor, and for diagnosis.[69] HCC is hypervascular and typically displays enhancement during the hepatic arterial phase with washout in venous and delayed phases (Figure 49-1), whereas cholangiocarcinoma demonstrates delayed enhancement. Modern MR protocols usually include parenchymal imaging with one or more types of contrast agents, MR angiography, or MR cholangiopancreatography (MRCP). Some have suggested that MR should be the imaging examination of choice for the liver in patients with cirrhosis because of the superior contrast resolution and inherent capability of multiplanar evaluation.[69,70] CT of the thorax, abdomen, and pelvis is recommended to rule out extrahepatic spread. Positron emission tomography (PET)-CT has been used to evaluate extrahepatic metastases; it is not as sensitive as multiphasic liver CT or MR for evaluating the hepatic extent of tumor, but it may be complementary to CT, MR, and MRCP, especially for Klatskin tumors.

In patients with hilar cholangiocarcinoma, MRCP has limited the role of endoscopic cholangiopancreatography to instances when drainage and decompression of the biliary system are required.[68] In addition to being noninvasive, MRCP has an accuracy of 95% in defining the location and extent of bile duct involvement.[71,72] The accuracy of prediction of vascular involvement and hepatic parenchyma invasion is around 70% to 80%[73,74] PET-CT has not been shown to be better than contrast enhanced CT scan for the detection of cholangiocarcinoma. Both modalities are poor for detection of regional lymph node metastases.[75] Endoscopy US with fine-needle aspiration of regional nodes has the highest sensitivity for the detection of nodal metastases.[54]

The usual appearance of EHCC on cholangiography is a stricture at the site of involvement with dilatation of the biliary

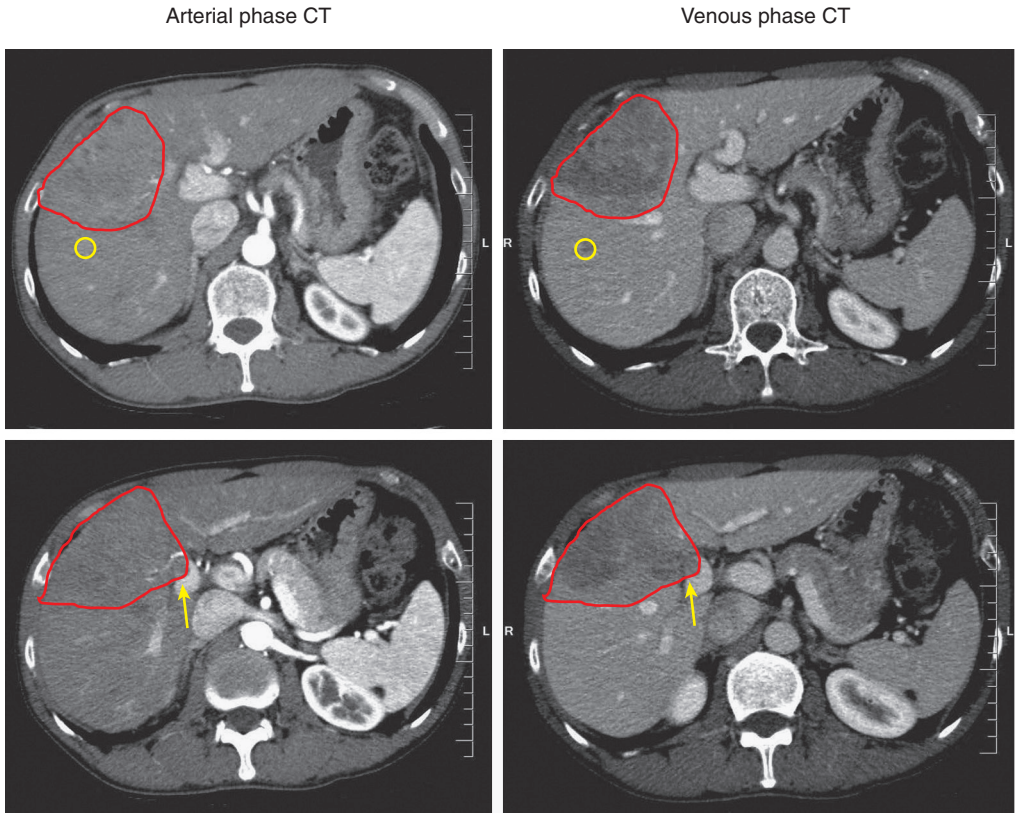


Figure 49-1 Arterial and delayed venous phase exhale breath-hold CT simulation images. The primary HCC *(red)* and satellite HCC *(yellow)* demonstrate arterial enhancement and washout on venous phase images. The *yellow arrow* highlights HCC invasion to the portal vein.

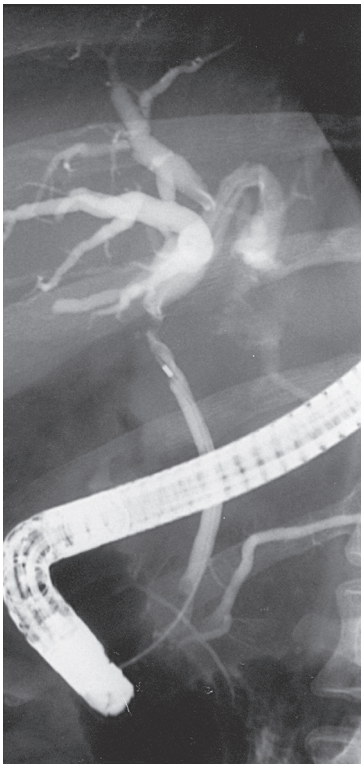


Figure 49-2 Endoscopic retrograde cholangiogram of a patient with a cholangiocarcinoma of the common hepatic duct. A stricture of the common hepatic duct can be seen proximal to the catheter, with dilatation of the intrahepatic biliary tree.

tract proximal to the stricture (Figure 49-2). The tumor itself may extend for some distance along the biliary tract. US, CT, and MR imaging of the abdomen frequently show only intrahepatic biliary dilatation (with or without hepatic atrophy) but no identifiable mass.[76] One area of particular difficulty is distinguishing bile duct cancer from PSC, with the latter typically showing diffuse rather than focal biliary narrowing.[77]

Although US is frequently obtained in patients suspected of having gallbladder disease, it is rarely helpful in diagnosing gallbladder cancer.[63] CT scan is the imaging modality of choice for postoperative evaluation of residual and metastatic disease.

Diagnosis

Hepatocellular Carcinoma

Multiphasic CT or MR imaging is most often used to obtain a HCC diagnosis with high predictive value, so that a biopsy can be avoided in most patients. Guidelines recommend no need for a biopsy of lesions greater than 1 cm in diameter in at-risk patients if there is classic arterial enhancement and delayed washout.[78] If there are nonclassic changes, a second imaging modality should be used. If that imaging study does not demonstrate classic HCC characteristics, then a biopsy is required. Repeat imaging is recommended for lesions less than 1 cm. There is a small risk of bleeding or tumor spillage following percutaneous biopsy.

Cholangiocarcinoma

Establishing a diagnosis of hilar cholangiocarcinoma can be difficult given the desmoplastic nature of the malignancy and the scant number of cells obtained by endoscopic brushing.[52] Conventional exfoliative or brush cytology has a sensitivity of around 50% for detection of cholangiocarcinoma.[79] The finding of polysomy using FISH is specific for malignancy with a positive predictive value approaching 100%.[225,226] The finding of polysomy on FISH combined with a dominant malignant stricture may be considered sufficient for diagnosis of cholangiocarcinoma.[52] Endoscopic US may be useful for evaluation of patients with suspected hilar cholangiocarcinoma, but transperitoneal fine-needle aspiration of the primary tumor is not recommended because of the potential for tumor seeding.[80]

Staging

The American Joint Committee on Cancer staging manual, seventh edition, has defined separate TNM staging systems for HCC, IHCCs, gallbladder tumors, and EHCCs and is divided into perihilar and distal bile duct lesions[81] (Table 49-2). The staging for both gallbladder cancers and EHCC tumors is primarily surgical.

For HCC, the Barcelona Clinic Liver Cancer (BCLC) staging system is widely used for treatment decision making (Figure 49-3). It is dependent on tumor factors, liver function (Child-Pugh score), and performance status. Very early (O) and early (A) BCLC stage HCC are potentially curable, whereas regional and systemic therapies are generally used for intermediate stage (B) and advanced stage (C) BCLC stage HCC.

Follow-up

After transplant or locoregional therapy with surgery, RT or RFA, imaging is recommended every 3 to 6 months for 2 years, and then every 6 to 12 months for 3 more years.

PRIMARY THERAPY

Hepatocellular Carcinoma

Very early and early (BCLC stage O and A) HCC are potentially curable with a variety of treatment. The most established treatments are hepatectomy, liver transplant, and RFA. Resection and transplantation result in the best outcomes, with 5-year OS of 50% to 85%. RFA has excellent outcomes in selected small HCC, with 5-year OS of 50% to 70%.[83-86] There is an emerging literature on the use of definitive RT for early stage HCC.

Surgical Resection

HCC resection is challenging because most patients have underlying liver dysfunction. The potential for tumor control needs to be balanced against the risk of complications. Tumor location, baseline liver function, and tumor biology should all be considered when making the decision for resection. In patients with cirrhosis considered for resection, portal hypertension is one of the strongest predictors of poor outcome, and surgery should not be offered in patients with manifestations of portal hypertension including hepatic encephalopathy, gastrointestinal bleeding, ascites, esophageal varices, splenomegaly, platelet count less than 100,000/mm^3, or a hepatic venous pressure gradient greater than or equal 10 mm Hg. Portal vein embolization (PVE) is sometimes used before hepatectomy to assess the ability of the future liver remnant to hypertrophy following surgery. The ability to hypertrophy after PVE is correlated with lower risk of liver failure postoperatively, and lack of hypertrophy has been suggested to be a contraindication to hepatectomy.

Anatomic resections are recommended for HCC, provided that adequate remnant liver volume can be preserved; however, nonanatomic resections are an option, and there is a growing literature on laparoscopic resections. Complications and

TABLE 49-2 TNM Classification for Hepatobiliary Cancers

PRIMARY TUMOR: LIVER	
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion, or multiple tumors, none more than 5 cm
T3a	Multiple tumors, any more than 5 cm
T3b	Tumors involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastases
M1	Distant metastases
PRIMARY TUMOR: INTRAHEPATIC BILE DUCT	
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present
PRIMARY TUMOR: GALLBLADDER	
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscle layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) or directly invades the liver or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, or portal vein
N2	Metastases to periaortic, pericaval, superior mesentery artery, or celiac artery lymph nodes
PRIMARY TUMOR: PROXIMAL EXTRAHEPATIC CHOLANGIOCARCINOMA/PERIHILAR (RIGHT, LEFT, AND COMMON HEPATIC DUCT)	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, common hepatic artery, or the second-order biliary radicals bilaterally, or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
N2	Metastasis to periaortic, pericaval, superior mesenteric artery, or celiac artery lymph nodes
PRIMARY TUMOR: DISTAL EXTRAHEPATIC CHOLANGIOCARCINOMA (FROM CYSTIC DUCT INSERTION INTO COMMON HEPATIC DUCT)	
Tis	Carcinoma in situ
T1	Tumor confined to the bile duct wall
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
DISTANT METASTASIS	
M0	No distant metastasis
M1	Distant metastasis

From Edge SB, Byrd DR, Compton C, et al, editors: AJCC cancer staging manual, ed 7, New York, 2009, Springer.

postoperative liver insufficiency are closely associated with increased mortality following hepatectomy. State-of-the-art surgery is associated with operative mortality rates of 1% to 3% and 5-year OS of 40% to 50%.[87] Approximately 40% to 80% of patients relapse. Positive resection margins, microvascular invasion, poorly differentiated HCC, and satellite lesions predict for relapse.[87]

Adjuvant Therapy

Adjuvant or neoadjuvant systemic, regional chemotherapy, or TACE has not been shown to be beneficial following surgery in high-risk HCC.[88] There is limited evidence that adjuvant Lipiodol therapy or immunotherapy may improve disease free survival after HCC resection.[89]

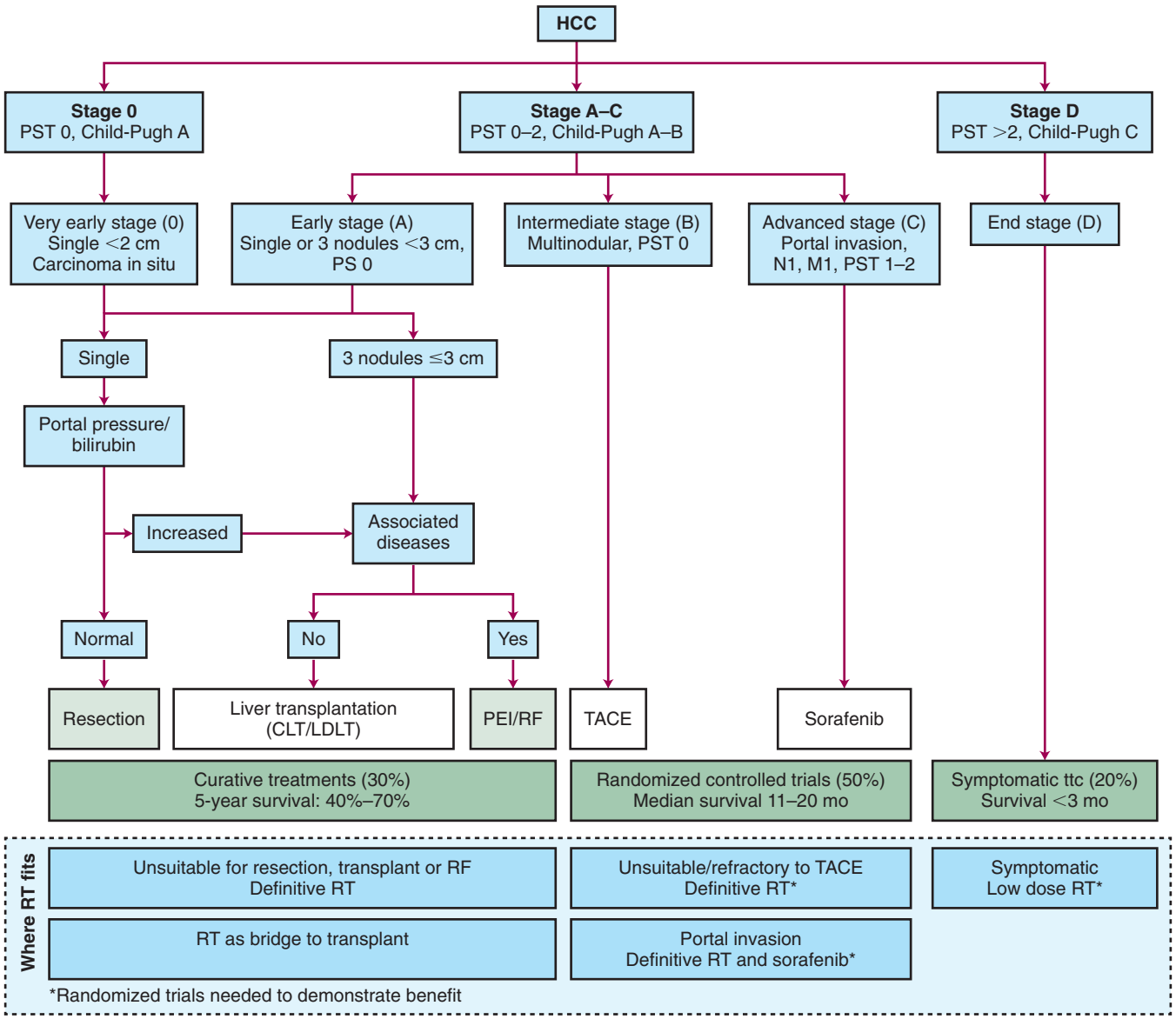


Figure 49-3 BCLC classification for HCC with potential role for RT highlighted in bottom two rows. CLT, cadaver liver transplant; LDLT, living donor live transplant; M, metastases; N, nodal stage; *PEI,* Percutaneous ethanol injection; *ttc,* treatment.
From Dawson LA: Overview: where does radiation therapy fit in the spectrum of liver cancer local-regional therapies? Seminars in radiation oncology, vol 21, no 4, Philadelphia, 2011, WB Saunders.

Liver Transplantation

An advantage of liver transplantation for patients with HCC and underlying cirrhosis is that the entire liver is removed, eradicating all microscopic and gross hepatic HCC and treating the underlying cirrhosis. Limitations of liver transplantation are the shortage of donor organs and the high cost. Only selected early HCC are eligible for transplantation (e.g., one lesion less than 5 cm),[90] and many patients drop off the wait list for a transplant because of HCC progression. Five-year OS of at least 70% and relapse rates lower than 15% are expected after transplant for HCC.[90,91] TACE, RFA, or RT are often used as bridging therapies for patients with HCC at risk of growing while on the wait list.

Percutaneous Ablation

RFA is an alternative treatment for small HCC with long-term survival in selected patients.[85,92] RFA involves placing a needle electrode in the tumor and applying a high-frequency alternating current to heat the surrounding tissue to produce necrosis. The best results are seen in tumors less than 3 cm that are not adjacent to large vessels.[92] In one review of 3670 patients treated by RFA, the mortality rate was 0.5% and the complication rate was 9%.[93] Subcapsular location and poorly differentiated HCC have been implicated in needle-track seeding. Comparative studies of RFA with surgery have been inconclusive. Ablation may also be accomplished with microwave, laser coagulation, or cryoablation or with the alcohol injection. A randomized trial demonstrated reduced rates of local progression (2% versus 11%) and improved survival (74% versus 57%) with RFA compared with percutaneous ethanol injection.[94] Cryoablation is associated with higher complications and inferior outcomes. Microwave and laser coagulation clinical data are emerging.[95]

Radiation Therapy As Definitive Therapy

Proton therapy has been used to treat early stage HCC with excellent outcomes, as recently reviewed by Dionisi et al.[96] Most studies, predominantly retrospective from Asia, have used standard or hypofractionation (e.g., 77 GyE in 35 fractions for tumors less than 2 cm from luminal tissues, 72.6 GyE in 22 fractions for tumors less than 2 cm from the porta hepatis, and 66 GyE in 10 fractions for peripheral tumors). Excellent 5-year OS ranging from 34% to 45% and 5-year local control (LC) of 83% to 90% have been observed, as summarized in Table 49-3.[97-101] Smaller prospective studies reported similar outcomes for 51 patients with peripheral HCC[101] and complete responses in selected patients who went on to liver transplantation following 63 GyE in 15 fractions.[102] Carbon ions (49.5 GyE to 79.5 GyE in 15 fractions) have also been used to treat early stage HCCs, with 5-year LC and OS of 80% and 25%, respectively.[100,103] Hypofractionated carbons (e.g., 40 GyE in 4 fractions) has also been used with excellent local control.[104]

A French multiinstutional prospective Phase II study of conformal RT (66 Gy in 2 Gy per fraction) in 25 Child-Pugh A and B patients with cirrhosis with early stage HCC (less than or equal to 5 cm for single nodules and less than or equal to 3 cm for two nodules) reported 78% local control at a median follow up of 29 months. Grade-4 toxicities occurred only in patients with Child-Pugh B (22%).[105]

SBRT (33 Gy to 60 Gy in three to eight fractions) results have also been reported in small prospective and larger retrospective studies for definitive treatment,[106-119] or as a bridge to transplant,[120] in patients with early stage HCC (Table 49-3). A Korean registry study of 93 patients with HCC (26% with Child-Pugh B, 1 cm to 6 cm) treated with 30 Gy to 40 Gy in three to four fractions reported 3-year LC and OS of 92% and 54%, respectively.[109] LC was 100%, 93%, and 76% for tumors less than 2 cm, 2 cm to 3 cm, and 3 cm to 6 cm, respectively. A Japanese retrospective study of 185 patients (84% T1, 27 Child-Pugh B) reported 3-year LC and OS of 91% and 70%, respectively, following 35 Gy to 40 Gy in four fractions.[107] A decline in Child-Pugh score was seen in 10% at 3 months. Other studies have had similar outcomes, as shown in Table 49-3.

Intrahepatic Cholangiocarcinoma

Surgery is the treatment of choice for resectable patients, but less than 20% are candidates for resection, usually as a result of the extent of hepatic involvement.[121] Of those who are resected, more than 60% relapse, most commonly in the remnant liver.[121,122] R0 resection is predictive of survival, but positive margins are common.[11] Five-year OS following resection ranges from 17% to 40% for all patients and 44% to 63% for R0 patients[11] and median survival is about 3 years.[121,122] In addition to margin status, other factors predictive of survival include regional node metastases, multiple tumors in the liver, tumor diameter greater than 5 cm, and cirrhosis.[11,121-123] Liver transplantation for IHCC is not standard because of high relapse rates and 5-year OS of only 20% to 30%.[124] The strategy of neoadjuvant therapy with chemotherapy and locoregional therapy with TACE or SBRT before transplant is being investigated.[124]

Gallbladder Carcinoma

Complete surgical resection is the only curative therapy for gallbladder cancer, but most nonincidentally discovered gallbladder cancers are not resectable for cure.[125,126] Even when surgery is performed with curative intent, complete resection (R0) is only achieved in about half of cases.[127] Most T1 cancers are discovered incidentally after cholecystectomy for cholelithiasis.[128] T1a cancers are adequately treated with simple cholecystectomy with 5-year OS of about 60%.[129] Extended cholecystectomy including resection of 2 cm of liver margin and dissection of N1 lymph nodes may be beneficial for patients with T1b cancers.[128,129] Five-year OS may be increased from 40% with simple cholecystectomy to 60% with extended cholecystectomy.[129] Diagnosis of incidental gallbladder cancer laparoscopically may require excision of the port sites given the 10% to 20% rate of port site recurrence.[128]

For patients with T2 cancers, extended cholecystectomy is associated with improved survival.[51,127,128] The most important prognostic factor for relapse is lymph node metastases. Positive nodes are found in about half of T2, most commonly in the pericholedochal and pericystic nodal regions followed by portal vein, hepatic artery, and peripancreatic nodes.[129a,130,131] Five-year OS may exceed 50% in pT2N0 patients, but falls to around 20% in patients who are node-positive.[48]

A minority of patients with T3-4 or node-positive disease may be cured with radical surgery alone.[132-138] Five-year OS is 20% to 25% for T3N0 or T1-2N1 disease but falls to less than 10% for T3N1 or T4 disease.[48] Lymph node metastases are found in 70% to 80% of T3 patients.[48,49] The role of more extensive surgery, including pancreaticoduodenectomy, right colectomy, and nephrectomy, has not been established. Paraaortic lymph node metastasis is present in 19% to 25% of patients with locally advanced disease,[139] but paraaortic lymphadenectomy is not warranted.[140]

Adjuvant Therapy

The majority of patients with gallbladder cancer experience disease relapse following curative intent surgery.[57] Following simple cholecystectomy, one literature review reported an 86% rate of local relapse in patients dying within 5 years of surgery.[141] Although isolated locoregional relapse is less common following extended cholecystectomy, locoregional relapse may approach 30%.[57] Despite the high risk of disease relapse, there are no prospective trials demonstrating a survival benefit to adjuvant therapy.

Retrospective studies suggest the possibility of benefit of adjuvant chemoRT. A Mayo Clinic series evaluated adjuvant chemoRT in 73 patients who underwent curative-intent surgery, 25 of whom received postoperative chemoRT (median dose of 50.4 Gy in 28 fractions with 5-fluorouracil [5-FU]–based concurrent chemotherapy).[142] Patients receiving adjuvant therapy had disease of a significantly higher stage, with 80% of the patients in the adjuvant group having stage II disease compared with only 21% in the surgery alone group ($p < 0.0001$). In the multivariate Cox model, increasing T and N classification as well as histologic type other than adenocarcinoma were significant predictors for worse OS rates. Additionally, adjuvant chemoRT was statistically significant for improved OS after adjusting for these multivariate prognostic factors (hazard ratio [HR] for death, 0.3; 95% CI, 0.13 to 0.69; $p = 0.004$). A Korean retrospective series of 100 patients and a Surveillance, Epidemiology and End Results (SEER) analysis both suggest a survival benefit to adjuvant chemoRT following resection in patients who are node positive.[143,144] In patients with pathologically evaluated lymph nodes, another SEER analysis found adjuvant RT to be associated with a 35% risk of death reduction.[48] A propensity score–matched analysis using SEER data also suggested a survival benefit to adjuvant RT (chemoradiation not evaluated) at 1 year, but not at 5 years.[145]

Extrahepatic Cholangiocarcinoma

Curative options for hilar EHCC include surgical resection and neoadjuvant chemoradiation followed by liver

TABLE 49-3 Selected Series of Radiation Therapy for Predominantly Early-Stage Hepatocellular Carcinoma

Study	No. Pts	CP Class	Tumor Size cm med (range)	PVT	Dose (Gy) GyE	No. Fx	Local Control				Survival				Grade ≥3 Toxicity
							1 year	2 year	3 year	5 year	1 year	2 year	3 year	5 year	
PROTONS															
Fukmitsu	51	A 80%, B	NA	0%	66	10	100%	92%	92%	88%	94%	70%	48%	39%	
Bush	76	A, B, C	5.7 (1.5-10) cm	5%	63	15	90%	75%	—	—	75%	55%	—	—	—
Nakayama	318	A 73%, B 24%, C 3%	NA	17%	72.6-77	22-35	—	—	—	83%	—	—	—	45%	1 gr 3 GI
Komatsu	242	A, B, C	<15	26%	56-84	10-38	—	—	—	90%	—	—	—	38%	8 pt
Chiba	162	A 51% B 38% C 11%	3.8 (1.5-14.5)	6%	50-84	10-26	—	—	—	87%	—	—	—	24%	3 biliary
SBRT					**Gy**										
Sanuki	185	A 96%, B	2.7 (0.8-5)	NR	30-40	5	99%	—	91%	—	95%	—	70%	—	13%, 10% decline in CP class
Jang	108	A, B	1 cm-7 cm	NR	51 (33-60)	3	—	87%	—	—	—	63%	—	—	10%
Yoon	93	A 76%, B	1 cm-6 cm	0%	45 (30-60)	3-4	95%	—	92%	—	86%	—	54%	—	10% decline in CP class
Bibault	75	A, B	3 cm-4.4 cm	NR	45 (24-45)	3	90%	—	—	—	79%	—	—	—	16%
Honda	30	A, B	1 cm-3 cm	0%	48-60	4-8	100%	—	—	—	100%	—	100%	—	14%
Huang	36	A, B, C	1.1-12.3 cm	NR	37 (25-48)	4-5	98%	—	—	—	—	64%	—	—	3%
Andolino	60	A 60%, B	3.1 (1-6.5)	NR	44 (24-48)	3-5	—	90%	—	—	—	67%	—	—	37%, 20% decline in CP class
Kwon	42	A 90%, B	3.0 mL-82 mL	0%	30-39	3	72%	—	68%	—	93%	—	59%	—	2%

CP Class, *Child-Pugh class;* Fx, *fractions;* NR, *not reported;* Pts, *Patients;* PVT, *portal vein thrombosis.*

transplantation.[26] Standard surgical resection consists of lobar hepatic and bile duct resection, regional lymph node dissection, and Roux-en-Y hepaticojejunostomy.[26] Contraindications to standard resection include contralateral or bilateral vascular encasement or extension to secondary biliary branches.[26] Major prognostic factors include margin and nodal status. A minimum of seven lymph nodes should be evaluated.[146] R0 resection is possible in 20% to 40% of patients explored with curative intent.[11,147,148] R0 resection is more likely to be achieved with hepatic resection than with bile duct resection alone.[148] Five-year OS is in the range of 30% to 40% after R0 resection and 10% to 25% after R1 resection.[11] In a series of 44 patients with hilar EHCC from the University of Louisville treated since 2002, R1 resection followed by EBRT with or without chemotherapy was associated with better survival than nonoperative management (median survival 21 months versus 8 months).[149]

Distal cholangiocarcinoma is best treated by pancreaticoduodenectomy.[26] R0 resection is more frequently achieved with rates approaching 80%.[11] Lymph node metastases are more commonly reported compared with hilar EHCC with rates as high as 60%.[11] Five-year OS is usually in the range of 20% to 30%[11,153a-156a] but may exceed 50% in patients who are node-negative who undergo R0 resection.[154] A minimum of 11 lymph nodes should be evaluated in resected patients.[155] For patients who undergo R0 resection, survival rates are similar for hilar and distal EHCC.[156]

Adjuvant Therapy

Potential indications for postoperative chemoradiation include positive margins (R1 resection) and regional lymph node metastases. Locoregional relapse is the predominant failure pattern for hilar EHCC and locoregional relapse has been reported in 50% or more of patients who were resected.[150,151] Locoregional relapses have been reported to comprise 65% of all relapses of hilar EHCC and nearly 60% of patients with relapse have isolated locoregional disease.[57] Despite this, there is a paucity of prospective data evaluating adjuvant therapy following resection.

Retrospective series have suggested the possibility of a survival benefit associated with adjuvant RT. In an EORTC multiinstitutional survey of 55 resected hilar EHCC patients (51 of 55 R1), adjuvant radiation in 38 patients was associated with a 19-month median and 31% 3-year survival compared to 8-month median and 10% 3-year survival in 17 patients treated with surgery alone ($p = 0.0005$).[152] A University of Amsterdam report of 91 patients with resected hilar EHCC found an 8-month median survival in 20 patients with surgery alone compared to 24 months in 71 patients treated with adjuvant EBRT with or without brachytherapy ($p < 0.01$).[153] A systematic review of 20 adjuvant studies evaluated chemotherapy alone, RT alone, and chemoradiation (chemoRT) in EHCC and gallbladder cancer. A trend toward improved survival was observed with any adjuvant therapy (OR, 0.74, $p = 0.06$) with better results in patients treated with chemotherapy or chemoRT. Significant benefit for adjuvant therapy was noted in node positive patients and following R1 resection.[157]

A prospective single arm SWOG (S0809) study evaluating postoperative chemoRT in 80 patients with EHCC or gallbladder cancer has been completed. Eligibility included T2-T4 primary or positive nodes or positive margins and treatment consisted of four cycles of gemcitabine and capecitabine followed by RT with capecitabine (three-dimensional: 54 Gy in 30 for RO, 59.4 Gy in 33 for R1 resection, and 52.5 Gy to 55 Gy in 25 for R0 and R1 resections). Two-year overall survival was 65% in 79 eligible patients (54 R0 67%, 25 R1 60%).

Neoadjuvant Chemoradiation Plus Transplant

Given the predominant local relapse pattern of hilar EHCC, liver transplant has been investigated as a curative option for patients who are unresectable. Early results with transplant alone were disappointing with relapse rates of 53% to 84% and 5-year OS in the 25% to 30% range. Interestingly, about half of the relapses were in the liver allograft.[158,159] A small group of patients at Mayo Clinic were treated with EBRT with 5-FU and brachytherapy with a 22% 5-year OS (Table 49-4).[160] Based on this observation, a protocol of neoadjuvant chemoRT including brachytherapy followed by liver transplantation was developed.[161] Patients with unresectable hilar cholangiocarcinoma above the cystic duct, less than 3 cm maximum diameter without intrahepatic or extrahepatic metastases, are potential candidates for liver transplantation. In addition, any patient with PSC with hilar cholangiocarcinoma is a potential candidate. The diagnosis may be established by transcatheter biopsy or brush cytology or by the combination of a malignant appearing stricture on imaging and a CA 19-9 >100 U/mL or polysomy on FISH. Concurrent chemoradiation, EBRT of 45 Gy in 1.5 Gy fractions twice daily over 3 weeks with concomitant PVI 5-FU or capecitabine, is followed by transcatheter iridium (20 Gy to 30 Gy to a 1-cm radius with low dose rate [LDR] or 16 Gy in four twice daily fractions over 2 days with high dose rate [HDR] brachytherapy). Exploratory laparotomy or laparoscopy with sampling of regional nodes is performed before liver transplant to confirm lymph nodes are not involved.[26,159-164]

From 1992 to 2011, 215 patients initiated neoadjuvant therapy at Mayo Clinic and 136 have undergone liver transplant. Overall survival at 5 years is 56% in patients who initiated neoadjuvant therapy and 74% in transplanted patients (Table 49-4). Five-year OS is higher in transplanted patients with PSC (79% versus 64%). Only 18% of transplanted patients have experienced disease relapse. Vascular complications including portal vein stenosis with or without thrombosis have been observed in 20% of patients.[158,164] Five-year OS in a contemporary group of patients who are resectable treated with standard resection at Mayo Clinic was 21% (Table 49-4).[163]

A multiinstitutional report from 12 transplant centers found neoadjuvant chemoradiation followed by transplant to be associated with 53% 5-year survival in all patients and 65% in patients who underwent transplant.[158] Patients with tumors greater than 3 cm maximum diameter and those who underwent transperitoneal biopsy had shorter survival times[158] In addition, CA 19-9 ≥ 500 U/mL and tumors greater than 3 cm at presentation predicted for dropout before transplant and elevated CA 19-9, portal vein encasement, and residual tumor in explant predicted for disease relapse after transplant.[151]

LOCALLY ADVANCED DISEASE AND PALLIATION

Hepatocellular Carcinoma

Intermediate Stage

BCLC intermediate (B) and advanced (C) stage HCC are most often unresectable and thought to be incurable. If resection may be conducted safely, it is associated with the best outcomes. In patients who are unresectable Child-Pugh A, regional and systemic therapies improve survival. Experience with RT is increasing, although there are no published comparative studies. Prognostic factors for patients with unresectable HCC include Child-Pugh score, AFP levels, portal vein tumor thrombosis, the presence of serologic markers for hepatitis B or C virus, and overall HCC burden.[164,165] More patients

TABLE 49-4 Results of High-Dose Radiotherapy or Chemoradiation in Extrahepatic Bile Duct Cancers

Series/Treatment Method	No. Patients	Survival Time				*p* Value
		Median (mo)	12 Mo (%)	24 Mo (%)	60 Mo (%)	
IWASAKI ET AL (JAPAN)[210]						
Noncurative Resection						
Alone	13	—	44	8	—	
Plus IORT	13	—	46	15	—	
Unresected						
Biliary drainage only	21	—	<5	—	—	
Plus IORT	6	—	33	17	—	
MAYO CLINIC						
Unresected						
EBRT ± 5-FU[151]	11	12	55	—	—	
EBRT ± 5-FU + ^{192}Ir[160]	24	12.8	67	19	14	
EBRT + 5-FU + ^{192}Ir	9	13	67	22	22	
EBRT + ^{192}Ir	15	12	67	16	8	
EBRT ± 5-FU + IOERT[211,212]	14	18.5	71	29	7	
EBRT/5-FU/^{192}Ir ± transplant[159,161-164]	215	60+	81	62†	56	
EBRT/5-FU/^{192}Ir + transplant	136	60+	92	81†	74	
Standard resection ± EBRT/5-FU[163,164]	26	35	82	70	21	
THOMAS JEFFERSON UNIVERSITY HOSPITAL[207]						
No irradiation	24	5.5	—	17	—	
Irradiation ± 5-FU ± ^{192}Ir			—		—	
<55 Gy	14	7	36		—	
>55 Gy	18	17	67		—	
EORTC[152]						
Noncurative resection alone	17	8.3	36	18	—	
Noncurative resection plus EBRT	38	19	85	42	—	<0.05
UNIVERSITY OF HEIDELBERG[150]	30	10	34	18	8	
EBRT + HDRB	21	7.9	38	5	0	
EBRT + HDRB + noncurative resection	9	12.1	64	32	32	<0.05
UNIVERSITY OF PITTSBURGH						
EBRT ± 5-FU ± resection[227]	55	9	32	10	—	
EBRT ± 5-FU + transplant	9/55	12	50	22	—	
EBRT + chemotherapy; Bx or partial resection[228]	38*	14	60	20	0	
EBRT + chemotherapy; transplant or total resection	23*	60+	82	68	53.5	<0.05

5-FU, *5-Fluorouracil;* Bx, *biopsy;* chemotherapy, *5-FU/leucovorin/interferon alpha or paclitaxel;* EBRT, *external beam irradiation;* HDRB, *high-dose-rate brachytherapy;* IOERT, *intraoperative electron irradiation.*

**Biopsy, 34; subtotal resection, 4; orthotopic liver transplantation, 17; other total resection, 6.*

†*3-year survival.*

ultimately develop liver failure because of HCC progression, underlying liver dysfunction, or treatment inducted liver toxicity.

Regional Treatment

Because HCC derives 80% of its blood supply from the hepatic artery compared to the liver parenchyma that derives most its blood supply from the portal vein, hepatic arterial–directed therapies are attractive options for HCC. Hepatic arterial chemotherapy, transarterial embolization (TAE), TACE, and transarterial radiation embolization (TARE) have been used on their own or combined with other therapies. Although hepatic arterial chemotherapy has had good response rates,[166] there was no significant improvement in survival in one randomized trial.[167]

TACE refers to delivery of embolization material (typically gelatin sponge, polyvinyl alcohol, or starch microspheres) with or without chemotherapy via injection into the right or left hepatic artery or a first-, second-, or third-order branch, depending on the disease extent. Meta-analyses and Phase III studies have shown a survival advantage to TACE versus supportive care in locally advanced HCC (2-year OS, 33 versus 11% in predominantly patients with hepatitis B[7] and 63% versus 27% in predominantly patients with hepatitis C.[6] The best results have been confined to patients with Child-Pugh A without main branch portal vein thrombosis. TACE is often delivered multiple times until the HCC no longer enhances, if toxicity is acceptable. Common transient complications from TACE include abdominal pain, nausea, fever, fatigue, and elevation of liver enzyme levels. Rare complications include exacerbation of liver failure, liver abscess, gastrointestinal bleeding, and bile duct injury. TAE has not been as extensively studied, but it is sometimes used to treat a ruptured HCC.

There is an emerging experience with TARE, or selective internal RT, which involves delivery of radioactive particles

(e.g., iodine-131 [^{131}I]–labeled Lipiodol or yttrium-90 [^{90}Y]–tagged microspheres) via the hepatic artery, with minimal embolization. Studies of ^{131}I Lipiodol have suggested efficacy, but it is not available in the Unites States.[168] There are many single institutions series of ^{90}Y-tagged microspheres (delivered via glass [TheraSphere MDS Nordion, Ottawa, Canada]) or resin spheres (SIR-Spheres SIRTeX Medical, Lake Forest, IL) showing response rates of 40% to 60% and median time to progression of 7.9 months in one prospective series of 291 patients, with worse outcomes in patients with Child-Pugh B and patients with tumor thrombosis.[169] Side effects include fatigue, pain, nausea/vomiting, and liver toxicity.

Systemic Treatment

Sorafinib, an oral multikinase inhibitor that has activity against Raf-1, B-Raf, VEGFR2, DGFR, c-Kit, and other tyrosine kinases, improves survival in patients with advanced HCC unsuitable for TACE. In the SHARP trial of 602 patients, patients randomized to sorafenib had improved median survival (10.7 months versus 7.9 months, $p < 0.001$), and time to progression (5.5 months versus 2.8 months).[170] Side effects including diarrhea, hand-foot skin reaction, and weight loss were tolerable. A second randomized trial in Asia reported an improvement in median survival from 4.2 months to 6.5 months with sorafenib, ($p < 0.05$).[171] Chemotherapy is generally toxic for patients with HCC and has not been associated with high response rates.[172,173] Doxorubicin has activity against HCC and is being investigated in a Phase III study comparing sorafenib to sorafenib plus doxorubicin (NCT01840592).

Radiation Therapy

Although RT has not been accepted as a standard therapy for locally advanced HCC, HCC is a radiosensitive tumor and should be considered in selected patients, especially if other local therapies are not feasible. The challenge is to delivery enough RT for tumor control, without causing liver toxicity. HCC tends to remain liver confined and frequently invades the portal vein, providing rationale for a local therapy such as RT.

The University of Michigan group first showed that tumoricidal doses could be delivered to focal unresectable HCC, with dose based on volume of spared liver or estimate of normal tissue complication probability (NTCP).[174-177] The prescribed dose ranged from 40 Gy to 90 Gy (median 60.75 Gy) in 1.5 Gy twice daily with hepatic arterial FudR. One-year LC and survival were 81% and 57%, respectively, in 35 patients with unresectable HCC without portal vein invasion.[177]

Conformal RT has been used to treat unresectable HCC, sometimes in combination with TACE, mostly in Asia (Table 49-5).[178-186] A recent review[178] suggested that patients treated with TACE plus RT had improved survival rates compared with patients treated with TACE alone (OR, 2.23); however, there is a need for confirmatory studies. Definitive RT has been used to treat HCC with tumor vascular invasion, with high local control and median survival generally better than that expected following other therapies.[186a,186b,187-192] One notable Phase II study from Korea, reported a median survival of 13.1 months in 40 patients with HCC with portal vein tumor thrombosis after 45 Gy in 25 fractions delivered with concurrent 5-FU.[190]

SBRT has also been used, with or without TACE, for locally advanced HCC, including patient with portal vein tumor thrombosis, with doses ranging from 30 Gy to 50 Gy in doses per fraction of 6 Gy to 15 Gy[186b,193-195] (Table 49-5). In sequential Phase I (Trial 1) and Phase II (Trial 2) trials at Princess Margaret Cancer Centre, SBRT was used to treat 102 patients with unresectable HCC unsuitable for TACE or RFA (55% with vascular invasion). LC at 1 year was 87% following a median dose of 36 Gy in six fractions (24 Gy to 54 Gy in six fractions). Median survival was 17 months and on multivariate analysis, absence of tumor vascular thrombosis and being treated on Trial 2 were associated with improved survival.[195] Five-fraction SBRT is being investigated in a Phase III study comparing sorafenib with SBRT followed by sorafenib (NCT01910909). Protons have also been used to treat locally advanced HCC with excellent outcomes.[196]

Advanced Stage

BCLC terminal stage (D) HCC has a poor prognosis and best supportive care is generally recommended. Many patients develop hepatic pain or discomfort, and low-dose palliative RT may be used with the sole goal of reducing patient pain. In one study, 8 Gy in one fraction to the whole liver resulted in a patient reported improvement of pain in 50% of patients.[197] Other palliative fractionations include 10 Gy in five fractions and 21 Gy in seven fractions.

TABLE 49-5 Selected Series of Radiation Therapy for Predominantly Advanced Stage Hepatocellular Carcinoma

Author	Year	No. Pts	Tumor Size (range)	PVT %	Dose (Gy)	No. Fx	Median Survival (months)	Grade ≥3 Toxicity
SBRT								
Bujold et al	2013	102	9.9 (1.8-43.1) cm	55%	36 (24-54)	6	17 (PVT-11.0; No PVT-20.5)	36%
Xi et al	2013	41	NA	100%	36 (30-48)	6	13	2%
Choi et al	2008	31	3.9 mL-47.7 mL	30%	36 (30-39)	3	8	16%
CONFORMAL RT								
Han et al	2008	40	NA	100%	45	25	13.1	
Huang et al	2009	326	≥10 cm in 39%	100%	60	20-30	3.8	0%
Kim	2005	59	11 cm	100%	30-54	10-24	10.7	
Rim et al	2012	45	1.5 cm-17.3 cm	100%	61.2 (38-65)	20-30	13.9	2%
Toya	2007	38	4 (0.9-9.3) cm*	100%	17.5-50.4	15-25	9.6	
Yoon et al	2012	412	2 cm-21 cm	100%	40 (21-60)	8-30	10.6	10%

CP Class, *Child-Pugh class;* Fx, *fractions;* NA, *not available;* Pts, *Patients;* PVT, *portal vein tumor thrombosis.*
**Diameter of PVT.*

Intrahepatic Cholangiocarcinoma

For the majority of patients with unresectable disease, a number of locoregional therapies have been investigated. TACE is associated with a 12-month to 15-month median survival in several series.[198] TARE with ^{90}Y has been shown to be tolerable with partial response or stable disease in 85% of patients and median survival of 22 months.[199] Preliminary reports on the use of SBRT for IHCC using doses of 24 Gy to 60 Gy in three to six fractions suggest the treatment is well tolerated with local control rates in excess of 50% and median survival of 11 months to 15 months.[188,200] RFA for IHCC <5 cm in diameter was associated with a 39-month median survival and 15% 5-year survival in a small series of 13 patients.[201]

Gallbladder Cancer and Extrahepatic Cholangiocarcinoma

The combination of gemcitabine and cisplatin was compared to gemcitabine alone in the 410 patient ABC-02 Trial, which included patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer. Seventy-five percent of patients on the trial had metastatic disease. A significant survival benefit was demonstrated for the two-drug combination with median survival of 12 months versus 8 months ($p < 0.001$). Progression-free survival was 8 months versus 5 months ($p < 0.001$). Most patients died within 3 years.[8]

Patients with unresectable hilar cholangiocarcinoma experience progressive bile duct obstruction resulting in hepatic dysfunction and potentially fatal sepsis.[202] Palliative of obstruction may be accomplished with operative bilioenteric bypass or preferably with endoscopic or percutaneous stent placement.[203,204] For patients who are not surgical candidates, metal stents are preferred over plastic because of longer patency and fewer re-interventions.[203] The median survival for patients treated with palliative stent placement alone is generally 3 months to 6 months.[202] Small prospective studies evaluating photodynamic therapy (PDT) in addition to stenting have suggested improvement in median survival to 14 months to 16 months compared to 3 months to 6 months with stent alone.[202,205] Three-year survival is less than 10%.[204]

External Beam Irradiation with or without Chemotherapy or Brachytherapy

A summary of published series of high dose RT (alone or plus brachytherapy or concurrent chemotherapy) for EHCC is shown in Table 49-4.[150-152,159-164,207,210-214] The combination of EBRT and brachytherapy has been used in selected patients with unresectable hilar EHCC and is associated with a median survival of approximately 12 months.[206] Some investigators have reported better survival in patients receiving >55 Gy,[207] and brachytherapy allows for significant dose escalation. A SEER analysis found a median survival of 11 months in patients whose treatment included a brachytherapy component compared to 4 months without brachytherapy.[206] In contrast to the predominantly locoregional pattern of relapse observed after surgical resection, some investigators have reported distant relapse, primarily in liver and peritoneal cavity, to be the predominant relapse pattern following chemoRT with or without brachytherapy.[208]

The combination of concomitant 5-FU–based chemotherapy with EBRT and brachytherapy appears promising. In a Mayo Clinic analysis of 24 patients with proximal EHCC treated with EBRT and brachytherapy, 9 patients received concurrent 5-FU and 5-year OS was observed in 22%.[160] In the Mayo Clinic transplant experience with this regimen of concurrent chemoRT plus brachytherapy given before transplant, there was pathologic complete response in 53% of patients.[159,161-164]

Early experience with charged particle therapy also supports the concept of dose response in cholangiocarcinoma. In a series of 28 patients with primary and recurrent cholangiocarcinoma including IHCC, EHCC, and gallbladder cancer treated with protons, biologic effective doses (BEDs) >70 Gy[10] was associated with 83% local control at 1 year compared to 22% for lower effective doses.[209]

Intraoperative RT is another technique that has been used to achieve dose escalation.[210-212]

IRRADIATION TECHNIQUES AND TOLERANCE

Dose-Limiting Organs

The potential for serious treatment related intolerance (RT or concurrent chemoRT) necessitates individualization of prescription dose for patients with hepatobiliary carcinoma, based on the volume of liver that may be spared from RT, baseline liver function (Child-Pugh A, B7 versus higher), and proximity of tumor to luminal gastrointestinal tissues. The major dose-limiting organ for RT to the hepatobiliary system is the liver. RT or chemoRT-induced liver disease (RILD) is separated into "classic" and "nonclassic" RILD. Classic RILD presents with anicteric hepatomegaly and ascites, typically occurring between 2 weeks to 3 months after RT or chemoRT, with an elevated alkaline phosphatase.[214] Nonclassic RILD is more challenging to prevent and includes any liver toxicity occurring within 3 months of radiation (e.g., decline in Child-Pugh score or elevated liver enzymes). It is more likely in patients with baseline cirrhosis or Child-Pugh B or C liver disease. Reactivation of hepatitis B has been reported after RT, and antiviral therapy before RT can reduce this risk.[213,214] For any patients with RILD, restaging, possible paracentesis of the ascitic fluid to rule out disease relapse, and referral to hepatology is recommended. RILD has been treated with diuretics, steroids, and occasionally anticoagulation.[214]

The risk for RILD is dependent on the volume of liver irradiated (or volume of liver spared from RT).[214] For patients with Child-Pugh A, whole-liver RT to a total dose less than 28 Gy in 2 Gy fractions has a low risk of toxicity, whereas 36 Gy in 2 Gy fractions is associated with a 50% risk of toxicity. With conformal RT planning, far higher doses can be delivered to partial liver volumes safely. Using standard fractionation, it is recommended that the mean liver dose be kept less than 28 Gy for patients with Child-Pugh A HCC. For SBRT, it has been recommended to maximize the volume of liver spared from RT (e.g., >800 cc to receive <10 Gy to 18 Gy in three to five fractions). Effective liver volume irradiated (Veff) or mean dose to the liver (minus the GTV) has also been used to allocate dose for SBRT. Patients with Child-Pugh B or C are at far higher risk for liver toxicity than those with Child-Pugh A liver cancer. For patients with Child-Pugh B treated with four to six fractions, the mean liver dose should be kept as low as possible (<6 Gy). Patients with Child-Pugh B7 fare better than those with Child-Pugh scores of B8 or higher,[215] who are not recommended to be treated outside the bridge to transplant setting.[214]

The luminal gastrointestinal (GI) tissues often limit the safe dose that may be delivered to HCCs in close proximity to GI luminal tissues. Of 128 University of Michigan patients with primary hepatobiliary malignant tumors treated with 40 Gy to 90 Gy (in 1.5 Gy per fraction, twice daily), 7% developed upper GI bleeding. The maximum dose to the stomach or duodenum was <68 Gy. A dose of 60 Gy to one third of the stomach has been associated with a 5% risk of ulceration or

perforation.[216] The Mayo Clinic data for biliary tract cancer suggest that a dose of approximately 55 Gy to the stomach or duodenum is associated with a 5% to 10% risk of severe GI complications[217]; and the risk increases to 30% to 40% with doses of more than 55 Gy. For SBRT, the maximal doses to luminal GI tissues should be kept to a minimum (<30 Gy to 36 Gy in five to six fractions), and there is a suggestion that delivering SBRT every other day may reduce the risk of toxicity.[218] The proximity of HCC to luminal GI tissues was an independent risk factor for local failure in one proton series.[100]

Biliary toxicity may lead to biloma and cholangitis 1 to 3 years post RT,[102] and the risk is higher hypofractionation or brachytherapy. It has been suggested that doses less than 40 Gy in five fractions to the common bile duct are associated with a low risk of toxicity, but the number of long-term survivors investigated is low.

Kidney toxicity is a theoretical consideration, although few patients develop clinical toxicity. Mean dose to both kidneys should be less than 18 Gy, and traditional three-dimensional treatment planning goals are to spare at least two thirds of a functioning kidney from 18 Gy or more. Other toxicities such as skin toxicity, rib pain, or fracture are uncommon toxicities seen after SBRT.

Irradiation Technique

Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma

Radical RT of hepatobiliary tumors is only possible with three-dimensional CT–based, conformal techniques. Ideally arterial, venous, and delayed phase CT or MR images should be obtained in breath-hold at the time of simulation and fused for optimal contouring (Figure 49-4). If that is not possible, image registration of diagnostic quality images with the planning CT is needed. MR is often complementary to CT. The gross target volume (GTV) should include all enhancing parenchymal tumor and vascular HCC. The clinical target volume should include the GTV as well as any adjacent regions at risk such as a RFA cavity or prior TACE zone. Care is needed to ensure delineation of the entire extent of tumor thrombus, often best seen on delayed phase imaging.

Breathing motion management is important to allow the planning target volumes (PTV) to be reduced, sparing more nontumor liver and reducing the risk of toxicity. Voluntary breath-hold, active breathing control (ABC), gating the beam to a specified phase of the respiration cycle and abdominal compression are common strategies used to reduce the impact of breathing motion. Measuring reproducibility of breath-hold or patient-specific tumor motion is important for individualization of PTV margins. Four-dimensional CT, kV fluoroscopy, and cine MR can be used to measure liver (or tumor) motion. Typical PTV margins for breath-hold or gated patients treated with image guided radiation therapy (IGRT) are 5 mm. PTV margins need to be larger in the cranial-caudal direction and sometimes the anterior-posterior directions for patients who are nonbreath-hold.

Three-dimensional conformal RT, arc therapy, IMRT, volumetric arc therapy (VMAT), and ions have all been used to treat HCC. HDR RT has the advantage of allowing the treatment beam-on time to be reduced, with less chance for patient movement during a single fraction. Planning goals are to cover the PTV with the prescription isodose (e.g., to 95% PTV), maintain dose limits to the luminal GI tissues and other critical organs, and to conform dose to the PTV, with most rapid dose fall off in adjacent critical normal tissues. Sometimes, less conformality is acceptable, to reduce the dose to a fragile cirrhotic liver. Although IMRT and VMAT allow high doses to be more conformal around complex PTVs (Figure 49-5; see Figure 49-4), there is the potential for interplay of residual

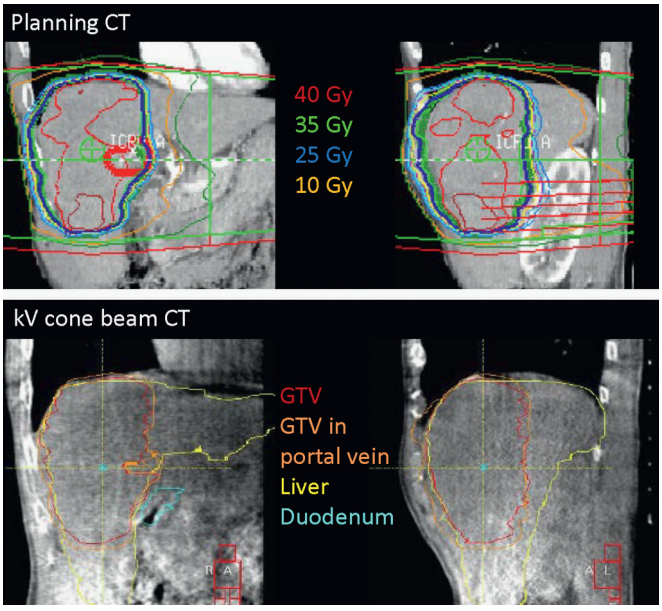


Figure 49-4 Breath-hold SBRT VMAT plan and breath-hold kV cone beam CT (CBCT) for a patient with HCC with invasion to the right portal vein, treated with 35 Gy in five fractions. The PTV around primary HCC I shown in thick blue and the HCC portal vein thrombus is shown in thick red. Contours from planning (GTV, red and orange; liver, yellow; duodenum, light blue) are overlaid on the CBCT to aid in IGRT (based on liver-matching). *CBCT,* Cone beam CT; *HCC,* hepatocellular carcinoma; *IGRT,* image guided radiation therapy; *kV,* kilovoltage; *PTV,* planning target volume; *SBRT,* stereotactic body radiation therapy; *VMAT,* volumetric modulated arc therapy.

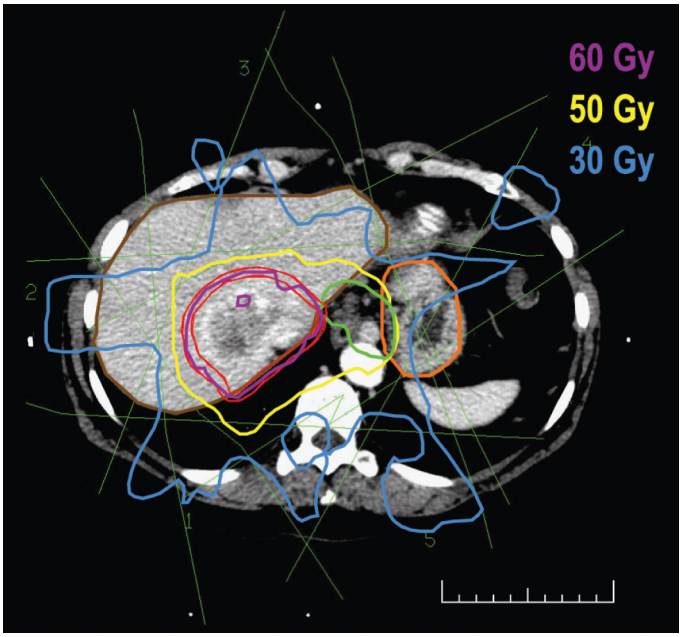


Figure 49-5 IMRT treatment plan for a patient with T3N1 intrahepatic cholangiocarcinoma, treated with definitive chemoradiation. Doses were 61.6 Gy to the primary site *(red)* and 50.4 Gy to regional nodes *(green)*, in 2.2-Gy and 1.8-Gy daily fractions, respectively.

tumor motion with moving multileaf collimators. Thus, a prudent goal should be to reduce the RT plan complexity when possible.[219] The doses required to control small HCCs are lower than those needed to control secondary liver tumors (e.g., high local control following 50 Gy in 20 fractions or 35 to 40 Gy in 5 fractions). The prescription dose may need to be modified based on volume or spared liver or proximity to organs at risk.[220]

IGRT is crucial to account for shifts in the liver position that may occur day-to-day, despite the use of breathing motion management. Such shifts occur even when breathing motion is of a small magnitude, providing rationale for the use of daily, soft-tissue guided IGRT. Inserted radioopaque fiducial markers or Lipiodol from prior TACE treatment may be used with two-dimensional planar kV imaging, fluoroscopy, or cone beam CT for targeting. The liver itself can be used for guidance using kV cone beam CT; accuracy is improved with breath-hold and four-dimensional respiratory sorted CBCT[220-222] (see Figure 49-4).

Gallbladder and Extrahepatic Cholangiocarcinoma

For gallbladder cancer, the treatment fields should be designed to include the gallbladder fossa and the hilar and celiac lymph node-bearing areas (eFigure 49-1). Doses in the range of 45 Gy to 54 Gy (1.8-Gy to 2-Gy fractions) for subclinical disease and 60 Gy to 65 Gy for microscopically positive margins are appropriate. Fields may be reduced to exclude the regional nodes and boost the tumor bed after 45 Gy. IMRT may be used to spare liver or kidney and may be especially useful when high doses are required for treatment of microscopic residual disease. A 25-fraction dose painting regimen with 45 Gy to the regional nodes, 52.5 Gy to the tumor bed following R0 resection and 55 Gy to the tumor bed following R1 resection is appropriate.

The target volume for EHCC can require inclusion of large portions of normal liver if the tumor is located in the hilum. In this case, the target volume may be extended to between 3 cm and 5 cm within the liver to include subclinical spread along the biliary tree. Although more distal EHCC requires considerably less irradiation of the hepatic parenchyma, higher duodenal or distal gastric doses may be necessary. On the basis of Mayo Clinic tolerance data, if doses greater than 55 Gy are indicated for tumor control (i.e., unresectable or residual disease), IMRT should be used to decrease normal tissue high-dose volumes. IMRT may also be indicated for lower doses to spare liver and both kidneys. Caution with regard to liver dose in the adjuvant setting should be exercised because RT may impact liver regeneration following major resection and liver tolerance may be significantly lower.

Brachytherapy[150,160,223] has frequently been used for EHCC and is an excellent technique for dose escalation for unresectable disease. Brachytherapy is typically given as a supplement to 45 Gy to 50 Gy EBRT (1.8-Gy to 2-Gy fractions) of EBRT. For patients who are not having transplants, brachytherapy may be delivered using transhepatic catheters or via endoscopically placed 10-FR nasobiliary catheters.[223] Potential transplant candidates should not have placement of transhepatic catheters. For LDR, a dose of 20 Gy to 30 Gy may be delivered with iridium-190 to a 1-cm radius.[160] With HDR, a dose of 16 Gy in 4 fractions to a 1-cm radius delivered twice daily over 2 days is calculated to have similar biologic effect to 20 Gy with LDR. Endoscopically placed two-catheter brachytherapy is depicted in Figure 49-6. With HDR placement, CT-based treatment planning may be used to limit dose to adjacent duodenum and stomach (Figure 49-7).

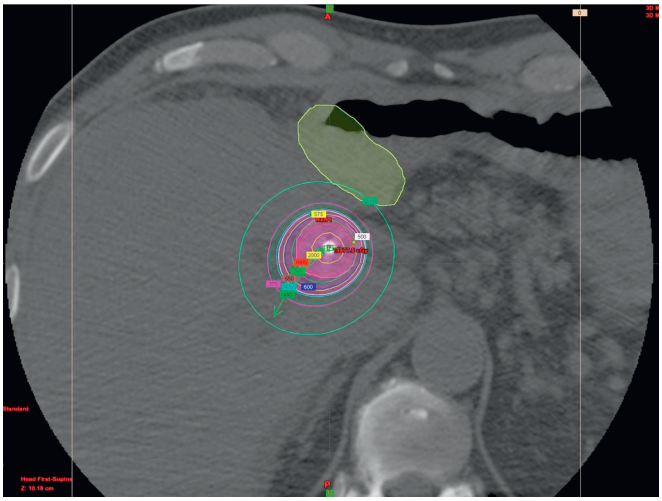


Figure 49-6 Endoscopically placed two-catheter brachytherapy. Low-dose rate iridium-190 lines loaded hot through endoscope inside nasobiliary catheter.

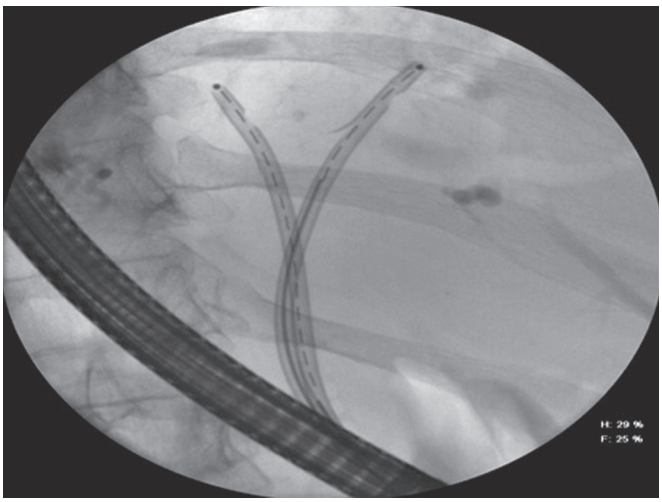
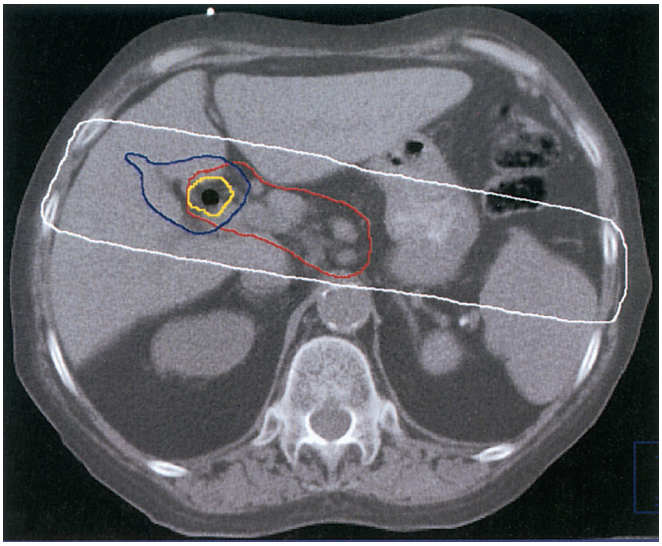


Figure 49-7 Isodose curves for high-dose rate biliary brachytherapy plan for single 5-Gy fraction. Fifteen-Gy in three fractions or 16 Gy in four fractions delivered over 2 days is typically delivered.

TREATMENT ALGORITHM AND FUTURE DIRECTIONS

Treatment algorithms for hepatobiliary cancer are shown in Figures 49-3 and 49-8. Figure 49-3 displays a treatment algorithm for hepatocellular carcinoma, based on the BCLC classification system, with the last rows indicating where RT has the potential to be used.[224] Figure 49-8 reflects a treatment algorithm for EHCC.

The use of state of the art imaging for target delineation, breathing motion management, conformal and IMRT planning, and soft-tissue IGRT have permitted the delivery of much higher doses of RT for hepatobiliary cancers than would have been possible using standard techniques. The addition of brachytherapy to EBRT has done the same for EHCC. However there are many unanswered questions and research opportunities. The potential for liver toxicity in patients with underlying cirrhosis is high; functional liver imaging, novel treatments for liver toxicity, and regenerative medicine are



eFigure 49-1 Treatment plan for a patient with resected carcinoma of the gallbladder. The cystic duct margin was positive and a cystic lymph node contained metastatic disease. The clinical target volumes included the draining regional lymph nodes in the celiac axis *(red)* and the common hepatic and common bile ducts *(yellow)*. Opposed oblique fields were used to deliver an initial dose of 50.4 Gy *(white)*, and an anterior wedge pair was used to deliver a boost to the positive margin to a total dose of 63 Gy *(blue)*.

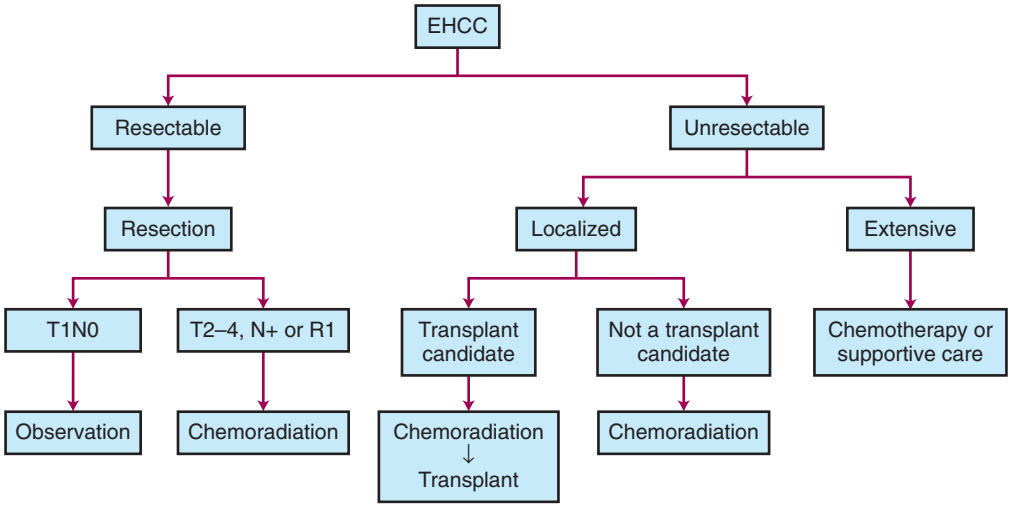


Figure 49-8 Treatment algorithm for extrahepatic cholangiocarcinoma (EHCC).

exciting areas of research that will benefit from collaborations of radiation oncologists with basic and imaging scientists and hepatologists.

Striving for the minimum RT doses required for a local control with a low chance of toxicity is a goal. Although it is becoming apparent that HCC is a relatively RT-sensitive tumor, the most appropriate doses and dose fractionations are not well defined. Collaborative efforts will be required to obtain evidence demonstrating the ideal patients, risk factors for relapse and toxicity, optimal doses and fractionation schedules and how to most appropriately combine RT with other regional and systemic therapies. Despite the growing literature on the use of RT for hepatobiliary cancer, there is a lack of level-1 evidence. At least two Phase III studies are planned for locally advanced HCC (NCT01910909, RTOG1112, PI Dawson) and intrahepatic cholangiocarcinoma (NRGGI001, PI Hong).

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