Chapter 21
Hepatobiliary Cancer

Chien Peter Chen, Kim Huang, and Mack Roach III

GENERAL PEARLS

- ~22,000 cases and 17,000 deaths per year in the U.S.
- Frequency: hepatocellular carcinoma (most common) > gallbladder cancer > extrahepatic cholangiocarcinoma > intrahepatic cholangiocarcinoma (least common).

LIVER (HEPATOCELLULAR)

PEARLS

- 100–250× more common in patients with chronic Hepatitis B.
- 3–4× more common in men.
- Cirrhosis, Hepatitis C, and aflatoxin B exposure are also risk factors.
- Prevention: Hepatitis B vaccine.
- Screening tools frequently used in high-risk patients: serum alpha-fetoprotein, liver ultrasound.

WORKUP

- Labs: CBC, LFTs, chemistries, coagulation panel, serum AFP (10–15% false negative), Hepatitis B/C panels.
- Abdominal CT scan (special contrast protocol).
- FNA can be performed but is not always needed.

STAGING: HAPATOCELLULAR

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

(AJCC 6TH ED., 2002)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Solitary tumor without vascular invasion
T2: Solitary tumor with vascular invasion or multiple tumors not more than 5 cm
T3: Multiple tumors more than 5 cm or tumor 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 visceral peritoneum

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)

MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage grouping		~5-year OS by stage	
I:	T1N0M0	I:	50–60%
II:	T2N0M0	II:	30–40%
IIIA:	T3N0M0	III:	10–20%
IIIB:	T4N0M0		
IIIC:	Any T, N1, M0		
IV:	Any T, Any N, M1	IV:	<10%

(AJCC 7TH ED., 2010)

Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Solitary tumor without vascular invasion
T2: Solitary tumor with vascular invasion or multiple tumors not more than 5 cm
T3a: Multiple tumors more than 5 cm
T3b: Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
T4: Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)

M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups

I: T1 N0 M0
II: T2 N0 M0
IIIA: T3a N0 M0
IIIB: T3b N0 M0
IIIC: T4 N0 M0
IVA: Any T N1 M0
IVB: Any T Any N M1

continued

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TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Resectable	■ Partial hepatectomy
Unresectable, medically inoperable	■ Liver transplant ■ Ablation (radiofrequency, cryotherapy, alcohol) ■ chemoembolization ■ Conformal RT ■ RT with concurrent chemotherapy ■ SBRT ■ Chemotherapy alone ■ Supportive care

SURGERY

- Partial hepatectomy is a treatment of choice if tumor can be resected with negative margins and patient has enough functional reserve to tolerate procedure.
  - Five-year overall survival ~35–40%
- Total hepatectomy with liver transplant is an option for patients with advanced cirrhosis and tumors smaller than 5 cm without vascular invasion.
  - Five-year overall survival as high as ~70% in selected patients
- Local failure is common.
- Role of adjuvant and neoadjuvant therapy unclear.

ABLATIVE PROCEDURES/OTHER INTERVENTIONS

- Radiofrequency ablation best for deep tumors with a diameter of 3 cm or less.
- Cyroablation can treat tumors up to 6 cm in size but requires laparotomy.
- Alcohol injection is commonly used because it is inexpensive but is limited to small tumors and may require several injections to be effective.
- Cryoablation and alcohol injection no longer used in the US.
- Chemoembolization and intrahepatic artery chemotherapy have response rates of 40–50% but may not improve survival.
- Systemic chemotherapy not useful, response rates <20%, no survival benefit, what about sorafinib?
- Antiviral therapy for patients with chronic hepatitis.

RADIATION THERAPY

- *EBRT definitive*
  - Option for unresectable tumors.

- Use local field for each lesion.
- High doses may improve survival, use conformal techniques, SBRT.
- Consider addition of concurrent FUDR hepatic arterial chemotherapy.

- *EBRT palliative*
  - Whole liver.
  - Consider for patients with multiple small lesions and liver related symptoms who are not candidates for other therapies.
- ^{131}I Lipiodol
  - Intraarterial injection.
  - May decrease recurrences and improve overall survival.
- *Yttrium microspheres*

STUDIES

- Borgelt et al. (1981): Whole liver RT can relieve symptoms of abdominal pain, nausea, vomiting, fever, night sweats, ascites, anorexia, abdominal distention, weakness, fatigue.
- Russell et al. (1993): RTOG whole liver fractionation paper. patients treated with 1.5 b.i.d with dose escalation 27 Gy → 30 Gy → 33 Gy. No liver injury at 27 and 30 Gy. 5/51 patients had toxicity at 33 Gy. Authors suggest that 21 Gy may be insufficient radiation dose.
- Dawson et al. (2000): University of Michigan method for treating with high dose 3DCRT. Sixty-eight percent response rate. Survival improved with tumor doses of 70 Gy or higher.
- Dawson et al. (2002): Liver tolerance histograms. No radiation induced liver disease (RILD) with mean liver dose <31 Gy. Whole organ TD_{50} for mets 45.8 Gy, for primary hepatobiliary 39.8 Gy.
- Mornex et al. (2006): Prospective phase II trial including 25 patients with small-size HCC (1 nodule ≤5 cm or 2 nodules ≤3 cm) received 66 Gy in 2 Gy/fraction 3DCRT. CR achieved in 80% and PR in 12%. Stable disease in 8%. Grade 4 toxicities occurred only in Child-Pugh B patients.
- Seong et al. (2007): Retrospective analysis of 305 patients undergoing radiotherapy for HCC. Median survival was 11 months. The 1-, 2-, and 5-year OS were 45%, 24%, and 6%, respectively.
- Tse et al. (2008): 41 patients (31 with HCC and 10 with intrahepatic cholangiocarcinoma) completed six-fraction SBRT. Median dose was 36 Gy. Median survival of HCC was 11.7 months.
- Lau et al. (2008): 43 patients underwent curative resection for HCC and randomly assigned to one 1,850 MBq dose of

^{131}I-lipiodol or no adjuvant therapy. The 5-, 7-, and 10-year DFS in treatment and control groups were 62% vs. 32% ($p = 0.04$), 52% vs. 32% ($p = 0.02$), and 48% vs. 27% ($p = 0.09$), respectively. The 5-, 7-, and 10-year OS in treatment and control groups were 67% vs. 36% ($p = 0.04$), 67% vs. 32% ($p = 0.02$), and 52% and 27% ($p = 0.09$), respectively. DFS and OS difference became statistically insignificant at 8 year.

- Zeng et al. (2004): Retrospective analysis of 203 patients with unresectable hepatocellular carcinoma received transcetheter arterial chemoembolization (TACE) or combination therapy with external beam radiotherapy. OS for radiotherapy and non-radiotherapy groups for 1, 2, and 3 years were 72% vs. 60%, 42 vs. 26%, and 24% vs. 11%, respectively.
- Abou-Alfa et al. (2006): Phase II study including 137 patients with inoperable HCC, Child-Pugh A or B, no prior systemic treatment received oral sorafenib. Median OS 9.2 months.
- Llovet et al. (2008): Phase III, multicenter RCT including 602 patients with advanced HCC randomized to either sorafenib or placebo. Median OS was 10.7 months vs. 7.9 months ($p < 0.001$) for treatment vs. placebo. One-year OS 44% vs. 33% ($p = 0.009$).

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms above head (out of field).
- Use wingboard to immobilize arms and alpha cradle to stabilize torso.
- Whole Liver (palliation only).
  - AP/PA, chose borders based on CT scan
  - 3DCRT reasonable because permits generation of kidney and lung DVHs
- Partial Liver (definitive option).
  - 3D treatment planning
  - Give contrast with planning CT scan to visualize tumor
  - CTV = gross tumor + 1 cm in all directions
  - PTV = CTV + 0.5 cm for setup error + 0.3–3 cm for organ motion error secondary to breathing (determined using fluoroscopy)
  - Stereotactic radiosurgery investigational

DOSE PRESCRIPTIONS

- Whole liver: 21 Gy/7 fx.
- Partial liver: determined individually.

- Prescribe dose that gives 10% risk of RILD based on NTCP model.
- Limit isocenter dose to 90 Gy even if risk of RILD is less than 10%.
- 1.5 Gy BID with at least 6 h between fractions.

DOSE LIMITATIONS

- Whole liver
  - TD 5/5: 30 Gy/15 fx
  - TD 50/5: 42 Gy/21fx
- 2/3 of liver TD 5/5: 50.4 Gy/28 fx
- 1/3 of liver TD 5/5: 68.4 Gy/38 fx

COMPLICATIONS

- Refer to Dawson paper (above) to estimate risk of RILD.
- RILD occurs 2–8 weeks after treatment.
- Signs/symptoms include fatigue, RUQ pain, ascites, hepatomegaly.
- Alkaline phosphatase and transaminase levels are frequently markedly elevated while bilirubin levels remain near normal.

FOLLOW-UP

- Office visit, CT scan, and labs (LFTs, AFP) every 3 months for 2 years, then every 6 months.

GALLBLADDER

PEARLS

- Chronic gallbladder inflammation (usually from gallstones) increases risk of development of gallbladder cancer.
- Generally considered to have poor prognosis, frequently advanced stage at presentation.
- Usually undiagnosed before cholecystectomy.
- Can be found incidentally after simple cholecystectomy for benign etiology.

WORKUP

- Labs: CBC, LFTs, chemistries, coagulation panel, serum CEA, CA 19–9.
- Right upper quadrant US and/or abdominal CT scan and/or MRI.
- ERCP or percutaneous needle biopsy for diagnosis.

STAGING: GALLBLADDER

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(AJCC 6TH ED., 2002)

Primary tumor (T)
TX: Primary tumor cannot be assessed
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) and/or directly invades the liver and/or another adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extrahepatic bile ducts
T4: Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

(AJCC 7TH ED., 2010)

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor invades lamina propria or muscular layer
  T1a: Tumor invades lamina propria
  T1b: Tumor invades muscular layer
T2: Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3: Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or another 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 two or more extrahepatic organs or structures

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2: Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

continued

Stage grouping

0:	TisN0M0
IA:	T1N0M0
IB:	T2N0M0
IIA:	T3N0M0
IIB:	T1N1M0, T2N1M0, T3N1M0
III:	T4, Any N, M0
IV:	Any T, Any N, M1

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Anatomic stage/prognostic groups

0:	Tis N0 M0
I:	T1 N0 M0
II:	T2 N0 M0
IIIA:	T3 N0 M0
IIIB:	T1-3 N1 M0
IVA:	T4 N0-1 M0
IVB:	Any T N2 M0
	Any T Any N M1

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TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Incidental finding on cholecystectomy pathology, T1a	■ Cholecystectomy is adequate surgery. ■ No adjuvant therapy
Incidental finding on cholecystectomy pathology, T1b or more advanced	■ Additional resection with lymphadenectomy ■ Adjuvant treatment with RT and concurrent 5FU based chemo
Mass on imaging or jaundice, resectable	■ Surgery with lymphadenectomy ■ Adjuvant treatment with RT and concurrent 5FU based chemo
Mass on imaging or jaundice, unresectable	■ Biliary decompression if needed ■ RT with concurrent 5FU based chemo ■ Gemcitabine or 5FU based chemo alone ■ Supportive care

SURGERY

- Cholecystectomy possible in ~30% of patients.
- Radical cholecystectomy with partial hepatectomy for node negative patients with invasion of perimuscular connective tissue.
- Palliation.

ADJUVANT THERAPY

- Role of EBRT and chemo-RT unclear, but generally recommended for residual disease after surgery.

STUDIES

- Cubertafond et al. (1999): Review of surgical data for 724 patients. Five-year survival: Tis 93%, T1 18%, T2 10%. No 3-year survivors with T3/4 cancer.
- North et al. (1998): Review of surgical data for 162 patients. Median survival: complete resection 67 months, microscopic residual disease 9 months, gross residual disease 4 months. Some patients received chemo and/or RT.
- Mojica et al. (2007): Retrospective analysis of 3,187 cases of gallbladder cancer in SEER registry. Adjuvant RT was used in 17% of cases. Median survival for patients receiving adjuvant RT was 14 months compared to 8 months ($p \leq 0.001$) for those not receiving RT. Survival benefit only for those with regional spread and tumors infiltrating liver.

- Duffy et al. (2008): Retrospective analysis of 435 patients with gallbladder cancer. Median OS was 10 months with median survival of stage Ia-III of 12.9 months and stage IV of 6 months. Of those who received curative resections (123 patients), 20% received adjuvant therapy. Median survival for those who received adjuvant therapy was 23.4 months, but was not statistically significant.
- Czito et al. (2005): Retrospective analysis of 22 patients with primary and nonmetastatic gallbladder cancer treated with surgical resection followed by concurrent radiotherapy (median dose 45 Gy) and 5FU chemotherapy. Five-year LRC, DFS, and OS were 59%, 33%, and 37%, respectively. Median survival was 1.9 year.
- *SEER* (Wang 2008): 4,180 patients with resected gallbladder cancer, 18% received adjuvant RT. Adjuvant RT improved MS for ≥T2N+ disease from 8 to 15 months. Some patients with ≥T2N0 disease may benefit, but to a smaller degree. Nomogram derived in paper.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms above head (out of field).
- Use wingboard to immobilize arms and alpha cradle to stabilize torso.
- CT scan for treatment planning.
- Cover tumor bed and local regional lymph nodes including portahepatis, pericholechal, celiac, and pancreaticoduodenal.

DOSE PRESCRIPTION

- 45 Gy/25 fx followed by boost to reduced fields.

DOSE LIMITATIONS

- Small bowel <45–50.4 Gy/25–28 fx
- Spinal cord <45 Gy/25 fx
- Liver (see previous sections, use NTCP model)
- Kidney 1/3 ≤ 20 Gy

COMPLICATIONS

- RILD
- Small bowel obstruction
- Fistula formation

FOLLOW-UP

- See liver section above

BILE DUCT

PEARLS

- Divided into intrahepatic (IHCC) and extrahepatic (EHCC) cholangiocarcinoma.
- Klatskin (hilar) tumor is located at birufication of common hepatic duct and is classified as extrahepatic.
- History of primary sclerosing cholangitis gives 10% lifetime risk of developing cholangiocarcinoma.
- Chronic inflammation from tape worm infection increases risk of developing cholangiocarcinma.
- Cholecystectomy decreases risk of cholangiocarcinoma.
- ~55% of patients are lymph node positive at diagnosis.

WORKUP

- Labs: CBC, LFTs, chemistries, coagulation panel, CA 19–9, CEA, Hepatitis B/C.
- Right upper quadrant US and/or abdominal CT scan and/or MRI.
- ERCP with biopsy.

STAGING: INTRAHEPATIC BILE DUCT

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(AJCC 6TH ED., 2002)

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor confined to bile duct histologically
T2: Tumor invades beyond wall of bile duct
T3: Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4: Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage grouping
0: TisN0M0
IA: T1N0M0
IB: T2N0M0
IIA: T3N0M0
IIB: T1N1M0, T2N1M0, T3N1M0

(AJCC 7TH ED., 2010)

Primary tumor (T)
TX: Primary tumor cannot be assessed
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 extra hepatic structures by direct invasion
T4: Tumor with periductal invasion

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis present

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis present

Anatomic stage/prognostic groups
0: Tis N0 M0
I: T1 N0 M0
II: T2 N0 M0
III: T3 N0 M0
IVA: T4 N0 M0
Any T N1 M0
IVB: Any T any N M1

continued

III: T4, any N, M0
IV: Any T, any N, M1

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STAGING (AJCC 7TH ED., 2010): PERIHILAR BILE DUCT

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Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
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; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)

NX: Regional lymph nodes cannot be assessed
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, and/or celiac artery lymph nodes

Distant metastasis (M)

M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups

0: Tis N0 M0
I: T1 N0 M0
II: T2a-b N0 M0
IIIA: T3 N0 M0
IIIB: T1-3 N1 M0
IVA: T4 N0-1
IVB: Any T N2 M0
Any T any N M1

STAGING (AJCC 7TH ED., 2010): DISTAL BILE DUCT

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Primary tumor (T)

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor confined to the bile duct histologically
T2: Tumor invades beyond the wall of the bile duct

continued

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

Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Anatomic stage/prognostic groups
0: Tis N0 M0
IA: T1 N0 M0
IB: T2 N0 M0
IIA: T3 N0 M0
IIB: T1-T3 N1 M0
III: T4 Any N M0
IV: Any T any N M1

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STAGING (AJCC 7TH ED., 2010): AMPULLA OF VATER

Primary Tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor limited to ampulla of Vater or sphincter of Oddi
T2: Tumor invades duodenal wall
T3: Tumor invades pancreas
T4: Tumor invades peripancreatic soft tissues or other adjacent organs or structures other than pancreas

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant Metastasis (M)
M0: No distant metastasis
M1: Distant metastasis

Anatomic Stage/Prognostic Groups
0: Tis N0 M0
IA: T1 N0 M0
IB: T2 N0 M0
IIA: T3 N0 M0
IIB: T1-T3 N1 M0
III: T4 Any N M0
IV: Any T Any N M1

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TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Intrahepatic cholangiocarcinoma	
Resectable No residual disease	■ Surgery followed by observation
Resectable Residual disease (MS 10–20 months; 5-year OS 20–35%)	■ Surgical resection, repeat resection if possible ■ Ablative procedure ■ RT with concurrent 5FU based chemo ■ Consider SBRT ■ Gemcitabine based chemo alone
Unresectable (MS 7 months; 5-year OS 0%)	■ Ablative procedure ■ RT with concurrent 5FU based chemo ■ Consider SBRT ■ 5FU or gemcitabine based chemo alone ■ Supportive care
Extrahepatic cholangiocarcinoma	
Resectable No residual disease (MS 20–25 months; 5-year OS 30%)	■ Surgery followed by observation
Resectable Residual disease (MS 13 months)	■ Surgery followed RT with concurrent 5FU based chemo
Unresectable (MS 6–12 months)	■ RT with concurrent 5FU based chemo (consider brachytherapy boost) ■ RT with concurrent 5FU based chemo followed by transplant ■ 5FU or gemcitabine based chemo alone ■ Supportive care

VI

SURGERY

- Complete surgical resection is the most effective treatment.
- Surgical procedure depends on tumor location and extent of disease.
  - Partial hepatectomy or lobectomy for intrahepatic tumors.
  - Roux-en-y hepaticojejunostomy for hilar tumors.
  - Pancreaticoduodenectomy for distal lesions.
  - Liver transplant.
- Palliative Options - biliary enteric bypass, percutaneous transhepatic biliary drainage, stents.

ADJUVANT THERAPY

- Not studied prospective.
- Adjuvant RT and chemotherapy may improve overall survival.

STUDIES

- Todoroki et al. (2000): 63 patients. Treatment: surgical resection. RT given to 28/47 with microscopic disease and 13/14 with gross residual disease. 5-year OS with RT 32 months vs. surgery alone 13.5 months. RT group OS: IORT+EBRT 39%, IORT alone 17%, EBRT alone 0%. LRC with RT 79% vs. with surgery alone 31.2%. IORT dose recommendations - 20 Gy, 8 MeV electrons, 6 cm cone.
- Schoenthaler et al. (1994): UCSF experience. 129 patients, retrospective, extrahepatic ducts only. Treatment: 62 patients surgery alone, 45 patients surgery + conventional RT (46 Gy median), 22 patients surgery + charged particles (60 GyE median). MS: 6.5 months with surgery, 11 months with surgery + EBRT, 14 months with surgery + particles, 7 months with gross residual disease, 19 months with microscopic residual disease, and 39 months with negative margins.
- Alden and Mohiuddin (1994): Unresectable disease. Higher RT doses improve survival. MS: 44 Gy = 4.5 months, 45–54 Gy = 18 months, >54 Gy = 24 months. Recommended dose is 45 Gy EBRT with a 25-Gy intraluminal brachytherapy boost.
- Crane et al. (2002): 52 patients, locally advanced, unresectable treated with RT + chemo (73% of patients, PVI 5FU). Median time to local progression: 9 months after 30 Gy, 11 months after 36–50.4 Gy, 15 months after 54–85 Gy (p = ns). MS 10 months. Grade 3 toxicity similar in all groups.
- Borghero et al. (2008): Retrospective analysis of 65 patients with extrahepatic bile duct adenocarcinoma treated with curative-intent resection (S). For those with high-risk of local regional recurrence (42 patients), adjuvant chemoradiation (S-CRT) was implemented. Five-year OS and LRR for S- vs. S-CRT groups were 36% vs. 42% and 38% vs. 37%, respectively.
- Nelson et al. (2009): Retrospective analysis of 45 patients underwent resection followed by concurrent chemoradiation. Thirty-three patients underwent adjuvant radiotherapy and 12 neoadjuvant radiotherapy. Five-year OS, DFS, LRC were 33%, 37%, and 78%, respectively. Median survival was 34 months. Patients treated neoadjuvantly showed a trend toward longer 5-year OS (53% vs. 23%) but was not statistically significant.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms above head (out of field).
- Use wingboard to immobilize arms and alpha cradle to stabilize torso.
- CT scan for treatment planning.
- Cover tumor bed, porta hepatis, celiac axis + 1.5 cm margins.
- Consider extending field 3–5 cm into liver to cover additional intrahepatic bile duct length for margin.
- Add additional margins as needed to account for organ motion secondary to breathing, determined using fluoroscopy or perform 4D CT to define ITV.

DOSE PRESCRIPTION

- 45 Gy/25 fx to large field described above.
- Additional boost dose should be given. Options include: EBRT with conedown to tumor bed to 60 Gy total; ^{192}Ir intraluminal brachytherapy (20–25 Gy); IORT at time of surgery.

VI

DOSE LIMITATIONS

- See liver and gallbladder sections.

COMPLICATIONS

- RILD rare, as much of the liver can be excluded from the field.
- Cholangitis after brachytherapy.
- Small bowel damage (ulcer, bleeding, obstruction).

FOLLOW-UP

- See liver section above.

REFERENCES

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