Chapter 21
Hepatobiliary Cancer

Jennifer S. Chang and Mekhail Anwar

GENERAL PEARLS

- ~39,000 cases and 27,000 deaths for liver and intrahepatic bile duct cancers in 2016 in the USA.
- ~11,000 cases and 3700 deaths for gallbladder and other biliary cancers in 2016 in the USA.
- 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.
- Cirrhosis, chronic liver disease, hepatitis C, hereditary hemochromatosis, and aflatoxin B exposure are also risk factors.
- ~3–4× more common in men.
- Prevention: Hepatitis B vaccine, treatment of hepatitis B and C (reduces but does not eliminate risk).
- Milano/Mazzaferro criteria for liver transplantation: solitary tumor ≤5 cm or up to 3 tumors all ≤3 cm.
- UCSF criteria for liver transplanation: solitary tumor < or = 6.5 cm, or < or = 3 nodules with the largest lesion < or = 4.5 cm and total tumor diameter < or = 8 cm

Eric K. Hansen and M. Roach III (eds.), *Handbook of Evidence-Based Radiation Oncology*, https://doi.org/10.1007/978-3-319-62642-0_21

WORKUP

- Screening tools frequently used in high-risk patients every 6–12 months: serum alpha-fetoprotein, liver ultrasound.
- H&P: jaundice, diarrhea, bone pain or dyspnea (metastases), hepatosplenomegaly, ascites.
- Labs: CBC, LFTs (including bilirubin, transaminases, alk phos), chemistries, coagulation panel, albumin, serum AFP (10–15% false negative), hepatitis B/C panels.
- 3-phase liver protocol CT and/or MRI with IV contrast, including late arterial and portal venous phase.
- Chest CT; bone scan if clinically indicated.
- Assess liver reserve (Child-Pugh score, portal HTN).
- Consider indocyanine green clearance test to assess liver function, if resection is being considered.
- FNA can be performed but is not always needed, if radiographic characteristics are diagnostic.

STAGING: HEPATOCELLULAR

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2010 AJCC staging nomenclature unless otherwise noted, as the new system below was published after this chapter was written.

Table 21.1 (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

Table 21.1 (continued)

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

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media

Table 21.2 (AJCC 8TH ED., 2017)

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tl	Solitary tumor ≤ 2cm or >2 cm without vascular invasion
Tla	Solitary tumor ≤ 2 cm
Tib	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion or multiple tumors, not >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IVA
Any T	Any N	M1	IVB

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

TREATMENT RECOMMENDATIONS

Table 21.3 TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Resectable	Partial hepatectomy
Unresectable, medically operable	Liver transplant Bridging therapy can be used while awaiting transplant
Unresectable, medically inoperable	Ablation (radiofrequency, cryotherapy, percutaneous ethanol or acetic acid, microwave) Arterially directed (bland embolization, transarterial chemoembolization, radioembolization) Conformal RT +/– chemo SBRT Systemic therapy alone Supportive care

SURGERY

- Child-Pugh score is used to assess prognosis of chronic liver disease.
  - Score 1–3 each for total bilirubin, albumin, prothrombin time or INR, ascites, hepatic encephalopathy categories.
  - Class A = 5–6 points, good operative risk, 2-yr OS 85%.
  - Class B = 7–9 points, moderate operative risk, 2-yr OS 57%.
  - Class C = 10–15 points, poor operative risk, 2-yr OS 35%.
- Partial hepatectomy is a treatment of choice if tumor can be resected with negative margins and patient has enough functional reserve. Generally, Child-Pugh Class A without

portal hypertension; solitary mass without major vascular invasion; adequate future liver remnant.
  - Five-year overall survival ~35–40%.
- Total hepatectomy with liver transplant is an option for patients with advanced cirrhosis and either a single tumor <5 cm or up to 3 lesions up to 3 cm each, without vascular invasion.
  - Five-year overall survival as high as ~70% in selected patients.
- MELD score is used to assess severity of liver disease and prioritize allocation of liver transplants. Calculated based on bilirubin, creatinine, and INR to predict survival.

ABLATIVE PROCEDURES

- Consider ablative therapy for pts who are not surgical candidates as it may cure tumors <3 cm and may prolong survival for tumors 3–5 cm. Lesions >5 cm should be considered for arterially directed or systemic therapy.
- Radiofrequency ablation (RFA) is typically used for tumors <4 cm. Usually performed percutaneously by US or CT guidance.
- Technically challenging areas for ablation include subdiaphragmatic location, subcapsular lesions, and proximity of major biliary or vascular structures that could cause biliary injury or heat-sink effect.
- 5-yr local progression after ablation is about 5–15%, but intrahepatic recurrence is 60–75%.

ARTERIALLY DIRECTED AND SYSTEMIC THERAPY

- Arterially directed therapy is potentially indicated if arterial blood supply to tumor may be isolated without excessive nontarget treatment.
  - Relatively contraindicated if bilirubin > 3 or if main portal vein thrombosis and Child-Pugh class C.
  - Transarterial chemoembolization (TACE) involves intraarterial injection of chemotherapy, often with lipiodol and/or chemotherapeutics.
  - Chemoembolization and intrahepatic artery chemotherapy have response rates of 40–50% but may not improve survival.

- Transarterial radioembolization (TARE) Y-90 microspheres have increased risk of radiation-induced liver disease in pts with bilirubin > 2. Randomized trials of TARE are ongoing.
- Sorafenib may have survival benefit over supportive care for advanced HCC, although response rates are low (SHARP trial, Llovet NEJM 2008).
- Antiviral therapy for patients with chronic hepatitis.

RADIATION THERAPY

- *Definitive EBRT (3D, IMRT, or preferably SBRT)*
  - Option for unresectable tumors or as an alternative to ablation/embolization techniques or when they have failed or are contraindicated. There must be sufficient uninvolved liver and liver radiation tolerance must be respected. There should be no or minimal extrahepatic disease. Most data includes Child-Pugh class A disease, with more limited data for Child-Pugh class B or poorer liver function.
  - Use highly conformal radiotherapy techniques for each lesion, typically with SBRT or protons with modern immobilization, respiratory motion management, and image guidance.
  - Higher doses may improve local control and survival.
  - Concurrent FUDR hepatic arterial chemotherapy may be considered with fractionated conformal radiotherapy.
  - SBRT may be an alternative or adjunct to RFA and TACE as a bridge for pts waiting for a liver transplant because delay to transplant contributes to about 20% of potentially curable pts being delisted before surgery.
- *Palliative EBRT*
  - Consider for lung, brain, node, and bone metastases with about 70–80% response rate. There is little published data on the role of low-dose palliative whole liver RT for patients with multiple small lesions and liver-related symptoms who are not candidates for other therapies.

STUDIES

- *Huo (JAMA Oncol 2015)*: Meta-analysis of unresectable HCC treated with TACE alone vs. TACE + RT (including SBRT). 25 trials with 2577 patients showed better

complete response (OR 2.73), 1-year OS (OR 1.36) with addition of RT, with survival benefit more pronounced with longer follow-up. Increased incidence of ulcers, transaminitis, elevated TBili with TACE + RT.

CONVENTIONALLY FRACTIONATED EBRT

- *Dawson (JCO 2000):* University of Michigan method for treating with high-dose 3DCRT, delivered 1.5 Gy BID. 68% response rate. Survival improved with tumor doses of 70 Gy or higher.
- *Dawson (IJROBP 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.
- *French RTF-1 trial (Mornex, IJROBP 2006):* Prospective phase II trial including 25 patients with small 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 (IJROBP 2007):* Retrospective analysis of 305 patients undergoing radiotherapy for HCC. Median survival was 11 months. 1-, 2-, and 5-year OS were 45%, 24%, and 6%, respectively.
- *Zeng (Cancer J 2004):* Retrospective analysis of 203 patients with unresectable hepatocellular carcinoma received transcatheter arterial chemoembolization (TACE) or combination therapy with external beam radiotherapy. 1-/2-/3-yr OS for RT and non-RT groups was 72%/60%/42% vs. 26%/24%/11%, respectively.

SBRT

- See excellent review by McPartlin and Dawson (The Cancer Journal 2016).
- *TRIAL 1/2 (Bujold, JCO 2013)*: Phase I (50 patients) and phase II (52 patients) trials of SBRT for Child-Pugh A HCC not suitable for resection, RFA, or TACE. Received 24–54 Gy in 6 fractions, based on RILD model and proximity to GI. 1-year local control 87%, median OS 17 months. Grade ≥ 3 toxicity in 30%. Tumor vascular thrombosis correlated with worse OS.

- *Lasley (Practic Radiat Oncol 2015)*. Phase I/II trial of 38 Child-Pugh A and 26 Child-Pugh B HCC pts treated with SBRT (48 Gy in 3 fx or 40 Gy in 5 fx). 3-yr LC/OS: Child-Pugh A 91%/61%, Child-Pugh B 82%/26%.
- *Wahl (JCO 2016)*: Prospective single-institution database of inoperable, nonmetastatic HCC treated with RFA (249 lesions, 161 patients) or SBRT (83 lesions, 63 patients). Larger tumor correlated with worse freedom from local progression for RFA but not SBRT. Lesions ≥2 cm had increased freedom from local progression with SBRT; no difference for smaller lesions. Similar acute grade 3+ complications and 1- and 2-yr overall survival.
- *Sanuki (Acta Oncol 2014)*. 185 pts with single HCC ≤5 cm treated with SBRT. 40 Gy/5 fx for Child-Pugh A, 35 Gy/5 fx for Child-Pugh B. 3-yr LC 89–91%, OS 66–72%. Acute grade ≥ 3 toxicity 13%.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms out of field.
- Use Vac-Lok or SBRT body fixation.
- 3D treatment planning. IV contrast with planning CT to visualize tumor. Consider MRI fusion.
- Recommend 4D-CT imaging and/or respiratory gating motion management.
- CTV is typically the gross tumor.
- PTV = CTV + 0.5–1 cm margin (Often 5mm axially, and 8mm joint).

DOSE PRESCRIPTIONS

Mean Liver Dose (Liver-GTV)	
50 Gy/5	13 Gy
45 Gy/5	15 Gy
40 Gy/5	15 Gy
35 Gy/5	15.5 Gy
30 Gy/5	16 Gy
27.5 Gy/5	17 Gy

DOSE LIMITATIONS

- QUANTEC (Pan, IJROBP 2010) estimates <5% risk of radiation-induced liver disease (RILD):
  - Palliative whole liver: <28 Gy at 2 Gy/fx or <21 Gy at 3 Gy/fx.

- Partial liver: mean dose (minus GTV) <28 Gy in 2 Gy fx.
- SBRT: mean dose (minus GTV) <13 Gy/3fx, <18 Gy/6 fx, <6 Gy Child-Pugh B at 4–6 Gy/fx; >700 ml normal liver should receive <15 Gy in 3–5 fx.

- Other SBRT dose constraints are evolving. Recommend following established constraints in published prospective or large retrospective studies.

COMPLICATIONS

- Fatigue, nausea/vomiting, gastritis/esophagitis, further decline in liver function, uncommonly GI bleeding or ulceration.
- RILD typically occurs 4–8 weeks after treatment but can be as early as 2 weeks or as late as 7 months later.
- Classical RILD (pts without underlying liver disease) may present with fatigue, abdominal pain, hepatomegaly, ascites, and elevated alkaline phosphatase out of proportion to liver enzymes.
- Nonclassical RILD (pts with underlying liver disease) present with elevated transaminase or jaundice.
- There is no specific RILD treatment. Supportive care with paracentesis for ascites and correction of coagulopathy, and consider steroids to reduce hepatic congestion.

FOLLOW-UP

- Office visit, MRI or multiphase CT, and labs (LFTs, AFP) every 3–4 months for 2 years, then every 6 months. Chest CT as clinically indicated.

GALLBLADDER

PEARLS

- <5000 cases per year in the USA.
- Most are asymptomatic and found incidentally during cholecystectomy.
- Chronic gallbladder inflammation is a risk factor, often from gallstones or chronic infection.

- Other risk factors: anomalous pancreaticobiliary duct junction, gallbladder polyps, primary sclerosing cholangitis, porcelain gallbladder.
- Resectable disease in ~30% of patients.
- Frequently advanced stage at presentation; generally poor prognosis.
- Jaundice is associated with more advanced disease and worse prognosis.

WORKUP

- Labs: CBC, LFTs, chemistries, coagulation panel.
- Consider baseline serum CEA, CA 19–9.
- Ultrasound (RUQ or endoscopic) and/or abdominal CT scan and/or MRI.
- If suspicious mass is present, a biopsy is not necessary and can lead to peritoneal spread.
- Consider staging laparoscopy, especially for ≥T3, poorly differentiated, or positive margin on cholecystectomy.
- CT chest.

STAGING: GALLBLADDER

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 2010 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

Table 21.4 (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

Table 21.4 (continued)

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
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

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media.

Table 21.5 (AJCC 8TH ED., 2017)

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or muscular layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscular layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/ or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When Tis...	And Nis...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2a	N0	M0	IIA
T2b	N0	M0	IIB
T3	N0	M0	IIIA
T1–3	N1	M0	IIIB
T4	N0–1	M0	IVA
Any T	N2	M0	IVB
Any T	Any N	M1	IVB

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

TREATMENT RECOMMENDATIONS

Table 21.6 TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Incidental finding on cholecystectomy, pT1a	If negative margins, observe
Incidental finding on cholecystectomy, pT1b or greater, resectable	Lymphadenectomy with hepatic resection ± bile duct excision to obtain clear margins No standard adjuvant regimen. Consider adjuvant RT and concurrent 5FU- based chemo, or adjuvant chemo alone
Jaundice or mass on imaging, resectable	Resection with lymphadenectomy No standard adjuvant regimen. Consider adjuvant RT and concurrent 5FU-based chemo, or adjuvant chemo alone

Table 21.6 (continued)

Presentation	Recommended treatment
Unresectable	Biliary drainage if needed Gemcitabine/cisplatin combination chemo Consider RT with concurrent 5FU based chemo Clinical trial Supportive care
Metastatic	Biliary drainage if needed Gemcitabine/cisplatin combination chemotherapy Clinical trial Best supportive care

SURGERY

- Radical cholecystectomy with partial hepatectomy for node-negative patients with invasion of perimuscular connective tissue.
- Before definitive resection, consider staging laparoscopy for poorly differentiated, T3, or positive margin to rule out disseminated disease.

ADJUVANT THERAPY

- Combination gemcitabine/cisplatin improved survival compared to single-agent chemo for locally advanced/metastatic disease.
- Role of chemoRT uncertain but generally recommended for T2 N1, T3/4, +margins, or residual disease after surgery.

STUDIES

- Cubertafond (Hepatogastroenterol 1999): Review of surgical data for 724 patients with gallbladder cancer, treated with simple cholecystectomy. Five-year survival for node negative: Tis 93%, T1 18%, T2 10%. No 3-year survivors with T3/4 disease.
- *SEER* (Wang, JCO 2008): 4180 patients with resected gallbladder cancer, 18% received adjuvant RT. Adjuvant RT improved MS for ≥T2 N+ disease from 8 to 15 months. Some patients with ≥T2 N0 disease may benefit, but to a smaller degree. Nomogram derived in paper.
- *SEER* (Pollom, Cancer Medicine 2016): 2343 patients with unresectable biliary tract cancer (444 with gallbladder cancer). Longer median survival with RT (10 vs. 9.3 months, $P = 0.02$). Among patients who received chemo, RT was associated with improved survival (HR 0.82). For patients

not receiving chemo, no RT benefit was seen. RT has declined since 1998.

- *NCDB* (Mantripragada, JNCI 2016): National Cancer Data Base analysis of 4775 patients with T2–3 or node-positive, nonmetastatic gallbladder cancer s/p resection with grossly negative margins. 29% received adjuvant chemo, 13.5% received adjuvant concurrent chemoRT. ChemoRT associated with a 6.7% improvement in 2-year OS for T3 or node-positive disease, but no difference by 5 years. No OS difference in overall cohort.
- Kim (Ann Surg Onc 2016): Retrospective multi-institutional analysis of 291 patients with gallbladder cancer undergoing R0 or R1 resection. 46% with T2 disease, 39% with T3, 38% with positive nodes. 21% with adjuvant chemo, 15% with adjuvant chemoRT. Improved OS with adjuvant chemo (HR 0.38) or chemoRT (HR 0.26). Only those with high-risk features (T3/T4, positive nodes, R1 resection) showed a benefit.
- Engineer (Ann Surg Onc 2016): Prospective study of 28 patients with stage III disease, treated with neoadjuvant chemoRT with 57 Gy in 25 fractions to gross disease and 45 Gy in 25 fractions to nodes with concurrent gemcitabine. 89% completed chemoRT, 71% with partial/complete response. 18 patients underwent surgery, and 14 patients had R0 resections. Median OS 20 months. 5-year OS 24% for entire group and 47% for those with R0 resection.
- *SWOG S0809* (Ben-Josef, JCO 2015): Phase II with 79 patients with resected gallbladder carcinoma or extrahepatic cholangiocarcinoma, stages pT2-4 or node positive. Received gemcitabine/capecitabine x 4 cycles, then chemoRT with 45 Gy to regional nodes and 54–59.4 Gy to tumor bed with concurrent capecitabine. 52% with grade 3 and 11% with grade 4 adverse effects. Overall 2-year survival 65%; median OS 35 months.
- *ABC-02* (Valle, NEJM 2010): Phase III RCT of 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder, or ampullary cancer. Randomized to cisplatin and gemcitabine vs. gemcitabine alone. Combination chemo with better median OS for (11.7 vs. 8.1 mo),

median PFS (8 vs. 5 months). More neutropenia with combination chemo but similar neutropenia-associated infection rate.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms up out of field.
- Use Vac-Lok or alpha cradle to stabilize torso.
- CT scan for treatment planning. Consider IV and/or oral contrast.
- Cover tumor bed and regional lymph nodes including porta hepatis, pericholedochal, celiac, and pancreaticoduodenal.
- Consider 4D-CT and/or respiratory gating.

DOSE PRESCRIPTION

- 45 Gy/25 fx followed by boost to reduced fields, 50.4–54 Gy to tumor bed/+margins, up to 54–55.8 Gy to gross disease (respecting normal tissue tolerance).

DOSE LIMITATIONS

- Small bowel <45–50.4 Gy/25–28 fx.
- Spinal cord <45 Gy/25 fx.
- Liver (see previous section).
- Kidney ≤1/3 receiving ≥20 Gy.

COMPLICATIONS

- Fatigue, nausea, vomiting, loose bowel movements, gastritis.
- Small risk of RILD.
- Uncommon: bowel ulceration or necrosis, small bowel obstruction, rarely fistula formation.

FOLLOW-UP

- Consider exam and imaging every 6 months for 2 years if clinically indicated, then annually up to 5 years, with CEA and CA 19-9 as clinically indicated.

BILE DUCT

PEARLS

- Divided into intrahepatic (IHCC, ~20%) and extrahepatic (EHCC) cholangiocarcinoma.
- Intrahepatic includes small or large ducts proximal to the bifurcation of the common hepatic duct.
- Extrahepatic includes perihilar (Klatskin) tumors and distal segments.
- Risk factors: primary sclerosing cholangitis (~10% lifetime risk), congenital biliary tree abnormalities, hepatolithiasis, chronic tapeworm infection, Thorotrast. Possible association with cholecystitis.
- Cholecystectomy decreases risk of cholangiocarcinoma.
- Can present concurrently with hepatocellular carcinoma.
- ~55% of patients are lymph node positive at diagnosis.

WORKUP

- H&P: For extrahepatic – jaundice, hepatomegaly, pruritis, dark urine, clay-colored stool, pain, weight loss, fever. Intrahepatic may have RUQ pain, weight loss, may be asymptomatic.
- Labs: CBC, LFTs, chemistries, coagulation panel, CA 19–9, CEA, AFP (rule out HCC), hepatitis B/C.
- Right upper quadrant US and/or abdominal multiphasic CT and possibly MRI/MRCP.
- EUS/ERCP with biopsy.
- EGD and colonoscopy.
- Chest CT.
- Consider staging laparoscopy before or in conjunction with resection to rule out disseminated disease.
- Biopsy not necessary for suspicious mass on imaging.
- If potential transplant candidate, refer to transplant center prior to biopsy.

Table 21.7 STAGING (AJCC 7TH ED., 2010): INTRAHEPATIC BILE DUCT

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

Used with the permission from the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media

Table 21.8 STAGING (AJCC 7TH ED., 2010): PERIHILAR BILE DUCT

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

continued

Table 21.8 (continued)

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science + Business Media

Table 21.9 STAGING (AJCC 7TH ED., 2010): DISTAL BILE DUCT

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
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

Table 21.9 (continued)

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science + Business Media

Table 21.10 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 the 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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science + Business Media

STAGING (AJCC 8TH ED., 2017)

Table 21.11 INTRAHEPATIC BILE DUCT

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis present

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIB
Any T	Any N	M1	IV

Table 21.12 PERIHILAR BILE DUCT

Definition of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue or tumor invades adjacent hepatic parenchyma
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 the main portal vein or its branches bilaterally, the common hepatic artery, or the unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	I
T2a–b	N0	M0	II
T3	N0	M0	IIIA
T4	N0	M0	IIIB
Any T	N1	M0	IIIC
Any T	N2	M0	IVA
Any T	Any N	M1	IVB

Table 21.13 DISTAL BILE DUCT

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
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 or tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T1a	Tumor limited to ampulla of Vater or sphincter of Oddi
T1b	Tumor invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa
T2	Tumor invades into the muscularis propria of the duodenum
T3	Tumor directly invades the pancreas (up to 0.5 cm) or the tumor extends more than 0.5 cm into the pancreas or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T3a	Tumor directly invades pancreas (up to 0.5 cm)
T3b	Tumor extends more than 0.5 cm into the pancreas or extends into peripancreatic tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, irrespective of size

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to one to three regional lymph nodes
N2	Metastasis to four or more regional lymph nodes

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1a	N0	M0	IA
T1a	N1	M0	IIIA
T1b	N0	M0	IB
T1b	N1	M0	IIIA
T2	N0	M0	IB
T2	N1	M0	IIIA
T3a	N0	M0	IIA
T3a	N1	M0	IIIA
T3b	N0	M0	IIB
T3b	N1	M0	IIIA
T4	Any N	M0	IIIB
Any T	N2	M0	IIIB
Any T	Any N	M1	IV

Table 21.14 AMPULLA OF VATER

Definitions of AJCC TNM

Definition of primary tumor (T)

T category	T criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T category	**T criteria**
T4	Tumor involves celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

DEFINITION OF REGIONAL LYMPH NODE (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

DEFINITION OF DISTANT METASTASIS (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	M0	III
Any T	Any N	M1	IV

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

TREATMENT RECOMMENDATIONS

Table 21.15 TREATMENT RECOMMENDATIONS

Presentation	Recommended treatment
Intrahepatic cholangiocarcinoma	
Resectable, no residual disease	Surgery alone Consider adjuvant chemo

Table 21.15 (continued)

Presentation	Recommended treatment
Resectable, microscopic positive margins (R1) or node positive	No standard adjuvant therapy Consider RT with concurrent 5FU-based chemo Consider gemcitabine- or cisplatin-based chemo
Resectable, gross residual disease (R2)	No standard adjuvant therapy Consider repeat resection if possible Consider ablative procedure Consider adjuvant gemcitabine/cisplatin chemo Consider RT with concurrent 5FU-based chemo
Unresectable	No standard treatment regimen Gemcitabine/cisplatin chemo Consider locoregional therapy Supportive care
Extrahepatic cholangiocarcinoma	
Resectable, no residual disease	Surgery Consider adjuvant 5FU-based chemoRT Consider adjuvant 5FU/gemcitabine-based chemo
Resectable, residual disease or positive nodes	Surgery followed by RT with concurrent 5FU-based chemo, then adjuvant chemo Or surgery with adjuvant 5FU-/gemcitabine-based chemo for positive nodes
Unresectable	Biliary drainage, if needed Consider for transplant Consider gemcitabine/cisplatin chemo Consider RT with concurrent 5FU-based chemo Supportive care

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.
- Include portal lymphadenectomy.
- Contraindications to resection: lymph nodes beyond porta hepatis, distant metastases. Highly selected cases of multifocal disease can be considered for resection.
- Palliative options – biliary enteric bypass, percutaneous transhepatic biliary drainage, stents.

ADJUVANT THERAPY

- Limited data; no standard adjuvant regimen.
- Risk factors for local recurrence: lymphovascular invasion, perineural invasion, positive node(s), primary ≥5 cm.

STUDIES

- Todoroki (IJROBP 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 (Ann Surg 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 (IJROBP 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 (IJROBP 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 (Ann Surg Oncol 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 (IJROBP 2009): Retrospective analysis of 45 patients undergoing resection followed by concurrent chemoradiation. Thirty-three patients underwent adjuvant radiotherapy and 12 neoadjuvant radiotherapy. Five-year OS, DFS, and 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.
- Tse (JCO 2008): Phase I trial with 41 patients (31 with HCC and 10 with intrahepatic cholangiocarcinoma), unresectable Child-Pugh class A treated with 6-fraction SBRT. Median dose 36 Gy. 12% with grade 3 liver enzymes, no grade 4/5 toxicity. Median survival of IHC was 15 months.
- Ben-David (IJROBP 2006): Retrospective single-institution experience of 81 patients with extrahepatic cholangiocarcinoma or gallbladder cancer, all treated with surgery (35% R0/R1) and adjuvant 3D RT to mean dose 58.4 Gy. 54% with concurrent chemo. Median OS 14.7 months, median PFS 11 months. R0 resection was only predictive factor; R1 and R2 outcomes similar. 69% of failures were locoregional.
- Wang (JCO 2013): Nomogram for intrahepatic cholangiocarcinoma treated with partial hepatectomy. Independent factors for survival: CEA, CA 19-9, tumor diameter and number, vascular invasion, lymph node involvement, direct invasion, local extrahepatic metastasis.
- Al-Adra (Eur J Surg Oncol 2015): Systematic review of 12 retrospective studies involving 298 patients treated with Y-90 microspheres for unresectable intrahepatic cholangiocarcinoma. Most had undergone prior treatment. Median overall survival 15.5 months. Stable disease in 54%, partial response in 28%.
- Tao (JCO 2015): Single-institution retrospective analysis of 79 patients with inoperable intrahepatic cholangiocarcinoma, treated with RT +/– chemo. Median OS 30 months, no significant treatment-related toxicities. RT dose correlated with 3-year OS: 73% for BED >80.5 Gy vs. 38% with lower doses.
- Horgan (JCO 2012): Analysis of 20 studies including 6712 patients with gallbladder and bile duct tumors who

underwent surgery with curative intent. Nonsignificant improvement in overall survival with any adjuvant therapy compared to surgery (pooled odds ratio 0.74, P = 0.06). Chemo or chemoRT with more benefit than RT alone (OR 0.39, 0.61, and 0.98, respectively). Greatest benefit of adjuvant therapy in node-positive disease (OR 0.49).

- *SWOG S0809* (Ben-Josef JCO 2015): Phase II with 79 patients with resected gallbladder carcinoma or extrahepatic cholangiocarcinoma, stages pT2-4 or node positive. Received gemcitabine/capecitabine x 4 cycles, then chemoRT with 45 Gy to regional nodes and 54–59.4 Gy to tumor bed with concurrent capecitabine. 52% with grade 3 and 11% with grade 4 adverse effects. Overall 2-year survival 65%; median OS 35 months.
- ACTICCA-1: Ongoing phase III trial of adjuvant gemcitabine and cisplatin vs. observation for resected colangiocarcinoma or muscle-invasive gallbladder carcinoma.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine with arms up out of field.
- Use Vac-Lok or alpha cradle to stabilize torso.
- CT scan for treatment planning. Consider IV and/or oral contrast.
- Cover tumor bed, porta hepatis, celiac axis + 1–2 cm margin.
- Consider extending field up to 3–5 cm into liver to cover additional intrahepatic bile duct length for margin as indicated, respecting liver tolerance.
- Add additional margins as needed to account for organ motion secondary to breathing, or perform 4D CT to define ITV. Consider respiratory gating.

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 up to 54–60 Gy total; ^{192}Ir intraluminal brachytherapy (20–25 Gy); IORT at time of surgery.

DOSE LIMITATIONS

- See liver section.

COMPLICATIONS

- Fatigue, nausea, vomiting, loose bowel movements, gastritis.
- RILD uncommon as much of the liver can be excluded from the field.
- Cholangitis after brachytherapy.
- Small bowel damage (ulcer, bleeding, obstruction).

FOLLOW-UP

- No data to support aggressive surveillance imaging.
- Consider imaging every 6 months for 2 years if clinically indicated, then annually up to 5 years.

Acknowledgment We thank Chien Peter Chen MD, Kim Huang MD, and Mack Roach III MD, for their work on the prior edition of this chapter.

REFERENCES

Al-Adra DP, Gill RS, Axford SJ, et al. Treatment of Unresectable intrahepatic cholangiocarcinoma with yttrium-90 Radioembolization: a Systematic review and pooled analysis. Eur J Surg Oncol. 2015;41(1):120–7.

Alden ME, Mohiuddin M. The impact of radiation dose in combined external beam and intraluminal Ir-192 brachytherapy for bile duct cancer. Int J Radiat Oncol Biol Phys. 1994;28:945–51.

Ben-David MA, Griffith KA, Abu-Isa E, et al. External-beam radiotherapy for localized extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2006;66(3):772.

Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol. 2015;33(24):2617–22.

Borghero Y, Crane CH, Szklaruk J, et al. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. Ann Surg Oncol. 2008;15:3147–56.

Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631–9.

Crane CH, MacDonald KO, Vauthey JN, et al. Limitations of conventional doses of chemoradiation for unresectable biliary cancer. Int J Radiat Oncol Biol Phys. 2002;53:969–74.

Cubertafond P, Mathonnet M, Gainant A, et al. Radical surgery for gallbladder cancer. Results of the French surgical association survey. Hepatogastroenterology. 1999;46:1567–71.

Dawson LA, McGinn CJ, Normolle D, et al. Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol. 2000;18:2210–8.

Dawson LA, Normolle D, Balter JM, et al. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys. 2002;53:810–21.

Engineer R, Goel M, Chopra S, et al. Neoadjuvant chemoradiation followed by surgery for locally advanced gallbladder cancers : a new paradigm. Ann Surg Onc. 2016;23(9):3009–15.

Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer : a systematic review and meta-analysis. J Clin Oncol. 2012;30(16):1934–40.

Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma: a systematic review and meta-analysis. JAMA Oncol. 2015;1(6):756–65.

Kim Y, Amini N, Wilson A, et al. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer : a multi-institutional analysis. Ann Surg Onc. 2016;23(9):2998–3008.

Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotacti body radiation therapy. Pract Radiat Oncol. 2015;5(5):e443–9.

Mantripragada KC, Hamid F, Shafgat H, Olszewski AJ. Adjuvant therapy for resected gallbladder cancer: analysis of the national cancer data base. J Natl Cancer Inst. 2016;109(2):pii. djw202

McPartlin AJ, Dawson LA. Stereotactic body radiotherapy for hepatocellular carcinoma. Cancer J. 2016;22(4):296–301.

Mornex F, Girarda N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies – mature results of the French phase II RTF-1 trial. Int J Radiat Oncol Biol Phys. 2006;66:1152–8.

National Comprehensive Cancer Network. Clinical practice guidelines in oncology: hepatobiliary cancers. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. Accessed on 25 Jan 2017.

Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys. 2009;73:148–53.

Pan CC, Kavanagh BD, Dawson LA, et al. Radiation-associated liver injury. Int J Radiat Oncol Biol Phys. 2010;76(3):S94–S100.

Pollom EL, Alagappan M, Park LS, et al. Does radiotherapy still have a role in Unresected biliary tract cancer? Cancer Med. 2016. https://doi.org/10.1002/cam4.975.

Sanuki N, Takeda A, Oku Y, et al. Stereotactic body radiotherapy for small hepatocellular carcinoma: a retrospective outcome analysis in 185 patients. Acta Oncol. 2014;53(3):399–404.

Seong J, Shim SJ, Lee IJ, et al. Evaluation of the prognostic value of Okuda, cancer of the liver Italian program, and Japan integrated staging systems for hepatocellular carcinoma patients undergoing radiotherapy. Int J Radiat Oncol Biol Phys. 2007;67:1037–42.

Schoenthaler R, Phillips TL, Efrid JT, et al. Carcinoma of the extrahepatic bile ducts, the University of California at San Francisco experience. Ann Surg. 1994;219:267–74.

Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol. 2015;34(3):219–26.

Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized Stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008;26:657–64.

Todoroki T, Ohara K, Kawamoto T, et al. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. Int J Radiat Oncol Biol Phys. 2000;46:581–7.

Valle JW, Hasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81.

Wahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol. 2016;34(5):452–9.

Wang SJ, Fuller CD, Kim JS, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. J Clin Oncol. 2008;26:2116–7.

Wang Y, Li J, Xia Y, et al. Prognostic Nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol. 2013;31(9):1188–95.

Zeng ZC, Tang ZY, Fan J, et al. A comparison of chemoembolization combination with and without radiotherapy for unresectable hepatocellular carcinoma. Cancer J. 2004;10:307–16.