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NCCN Clinical Practice Guidelines in Oncology™

Hepatobiliary Cancers

V.2.2010

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines Updates

The 2.2010 version of the Hepatobiliary Cancers guidelines represents the addition of the Discussion text correspondent to the changes in the algorithm (MS-1).

Summary of the changes in the 1.2010 version of the Hepatobiliary Cancer guidelines from the 2.2009 version include:

Hepatocellular Carcinoma:

(HCC-1)

- **Patients at risk for HCC; Without cirrhosis: "Non-alcoholic steatohepatitis" was removed.**
- **Footnote "b" regarding additional risk factors for hepatitis B carriers without cirrhosis is new to the algorithm.**
- **Footnote "e" regarding the use of CT with contrast is new to the algorithm.**

(HCC-2)

- **1-2 cm pathway; Non-classic enhancement: "Biopsy" changed to "Biopsy (preferred) or FNA".**
- **Footnote "i" regarding the absolute value of AFP cut-offs is new to the algorithm.**

(HCC-5)

- **Treatment; Options:**
  - **Sorafenib: The panel clarified that category 1 referred to Child-Pugh Class A.**
  - **RT (conformal or stereotactic) changed from category 2A to category 2B.**
- **Footnote "u": Changed to "Caution: There are limited safety data available for Child-Pugh Class B patients *and dosing is uncertain*. Use with extreme...".**
- **Footnote "v" regarding limited data and the use of RT is new to the algorithm.**

(HCC-B)

- **Second bullet; First arrow: "...Child-Pugh class A with mild or moderate portal hypertension" changed to "Child-Pugh Class A *without* portal hypertension".**

Gallbladder Cancer:

(GALL-1)

- **Footnote "d": The sentence "There are no randomized phase III clinical trial data to support the following combinations" was replaced with "A recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer."**
  (Also for GALL-2, INTRA-1, and EXTRA-1)

(GALL-2)

- **Workup for "Mass on imaging" and "Jaundice" pathways: "Consider staging laparoscopy" was added.**

(GALL-3)

- **Footnote "c": Changed to, "There are limited clinical trial data to define a standard regimen *or definitive benefit*."**
  (Also for INTRA-2 and EXTRA-2)

Intrahepatic Cholangiocarcinoma:

(INTRA-1)

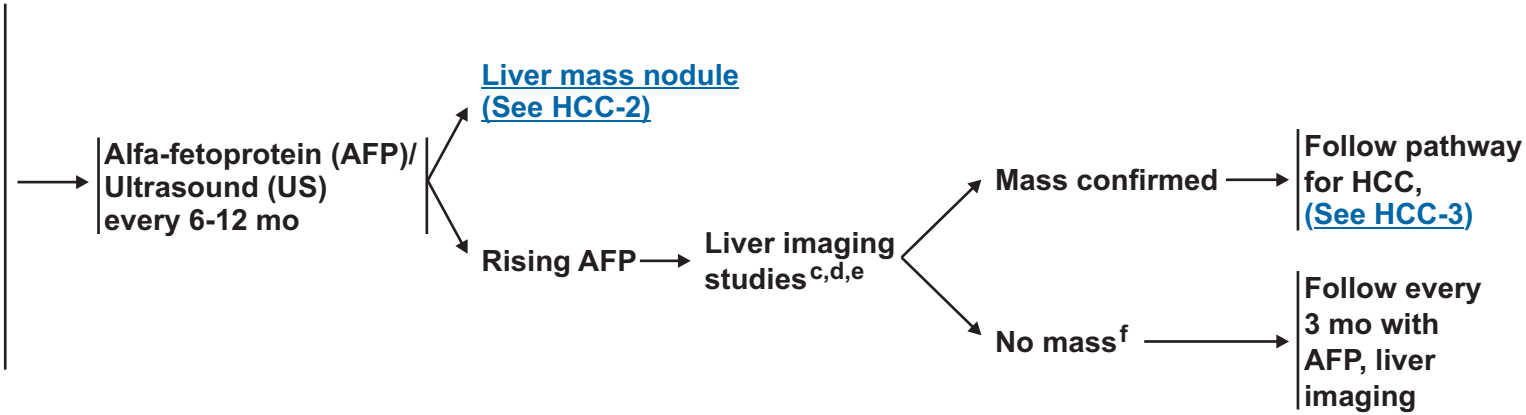
- **Primary Treatment for "Unresectable" and "Metastatic" disease: After "Clinical trial," footnote "d" that states, "Systemic or intra-arterial chemotherapy in a clinical trial" is new to the algorithm.**

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HEPATOCELLULAR CARCINOMA (HCC) SCREENING



[a] Adapted with permission from Bruix J and Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-1236.

[b] Additional risk factors include patients with active viral replication, high HBV DNA levels, family history of HCC, Asian males ≥ 40 y, Asian females ≥ 50 y, Africans ≥ 20 y.

[c] If ultrasound negative, CT/MRI should be performed.

[d] MRI/CT scan to define extent and number of primary lesions, vascular anatomy, involvement with tumor, and extrahepatic disease; triphasic helical CT or MRI to include early arterial phase enhancement.

[e] CT should be with contrast. PET/CT is not adequate.

[f] Rule out germ cell tumor if clinically indicated. MRI or triple phase CT scan may be helpful.

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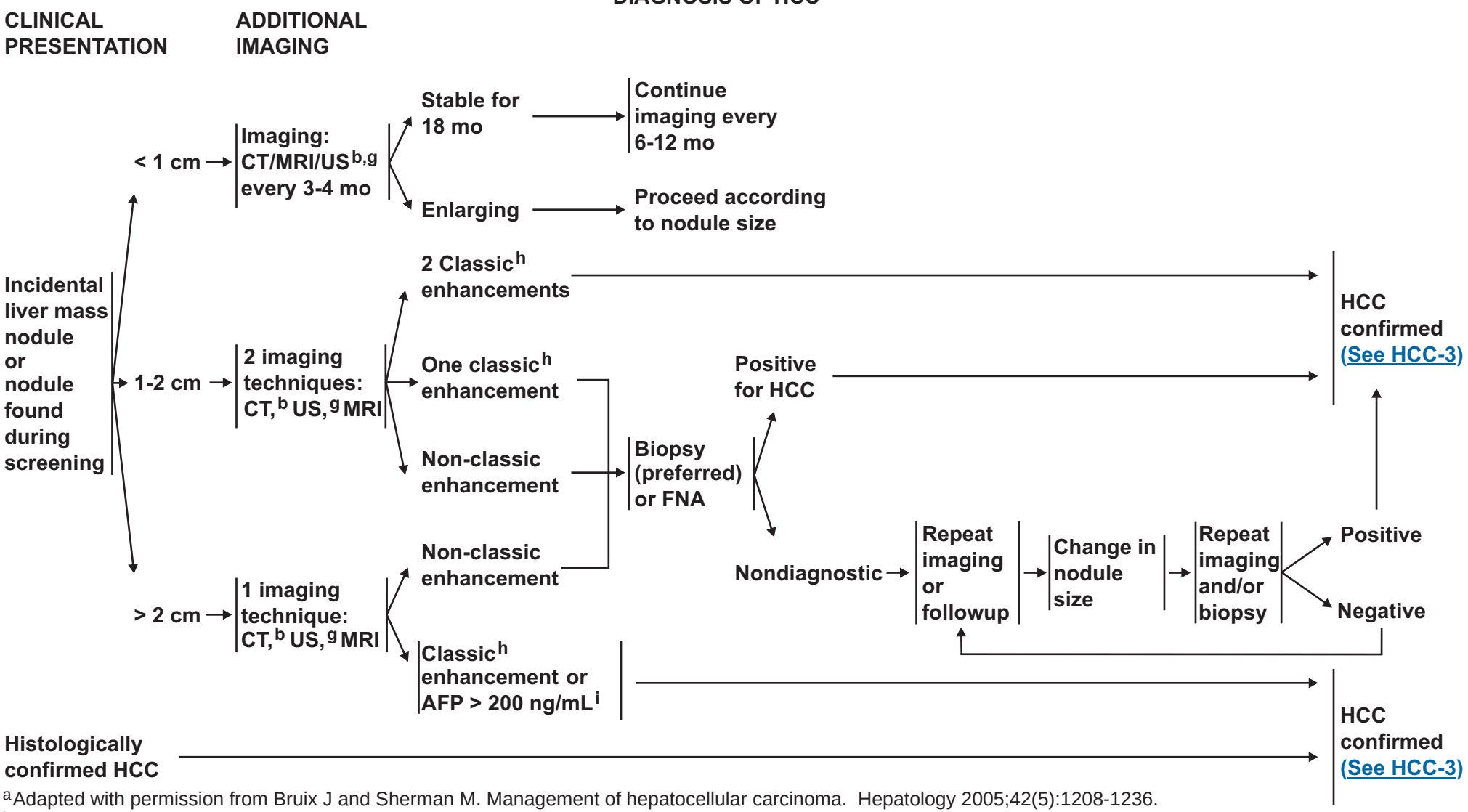
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DIAGNOSIS OF HCC[a]



[a] Adapted with permission from Bruix J and Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-1236.

[b] CT should be with contrast. PET/CT is not adequate.

[g] Contrast enhanced ultrasound where available.

[h] Classic imaging: Lesion shows arterial hyperenhancement and washes out in the venous phase. From Bruix J and Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-1236.

[i] There is no definitive evidence to support an absolute value of AFP cut-offs. AFP cut-offs among institutions may vary.

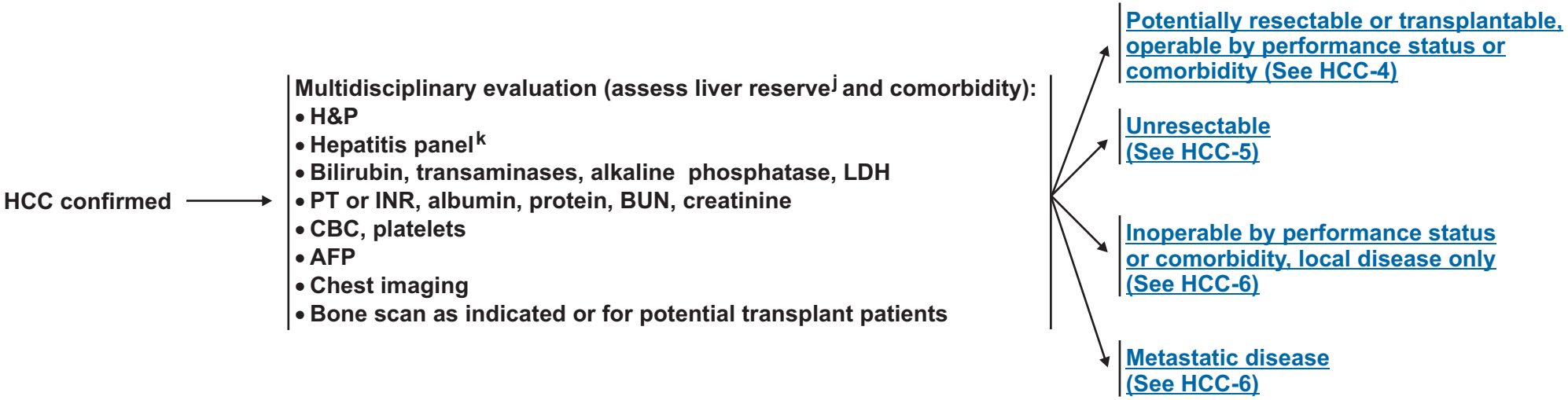
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CLINICAL PRESENTATION

WORKUP



[j] See Child-Pugh Score (HCC-A) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

[k] An appropriate hepatitis panel should preferably include:
- Hepatitis B surface antigen (HBsAg). HBe and anti-HBc (IgM) are included if HBsAg is positive
- Hepatitis B surface antibody (for HBIG or vaccine evaluation only)
- Hepatitis C virus antibodies. If low positive, recombinant immuno blot assay (RIBA) confirmation test is performed

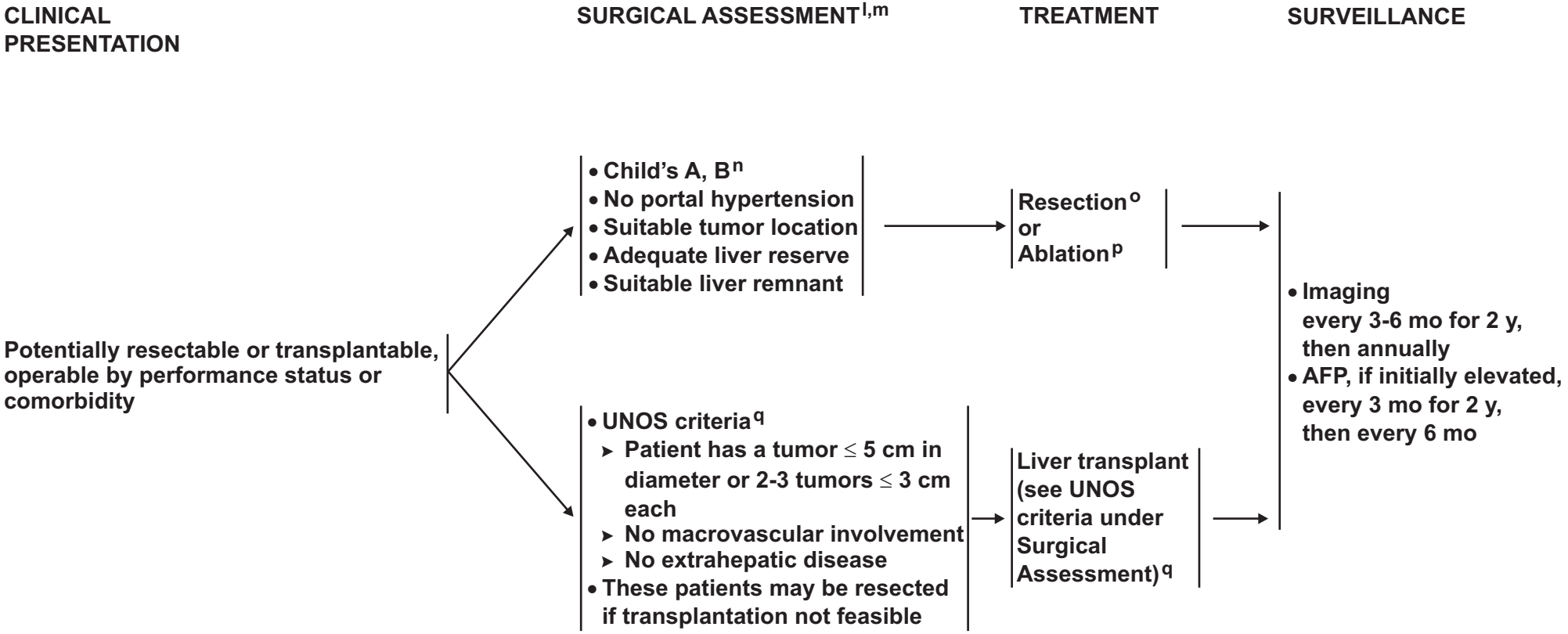
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[l]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

[m]Patients with Child's A liver function, who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

[n]In highly selected Child's B patients with limited resection.

[o]See Principles of Surgery (HCC-B).

[p]See Principles of Locoregional Therapy (HCC-C).

[q]Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.

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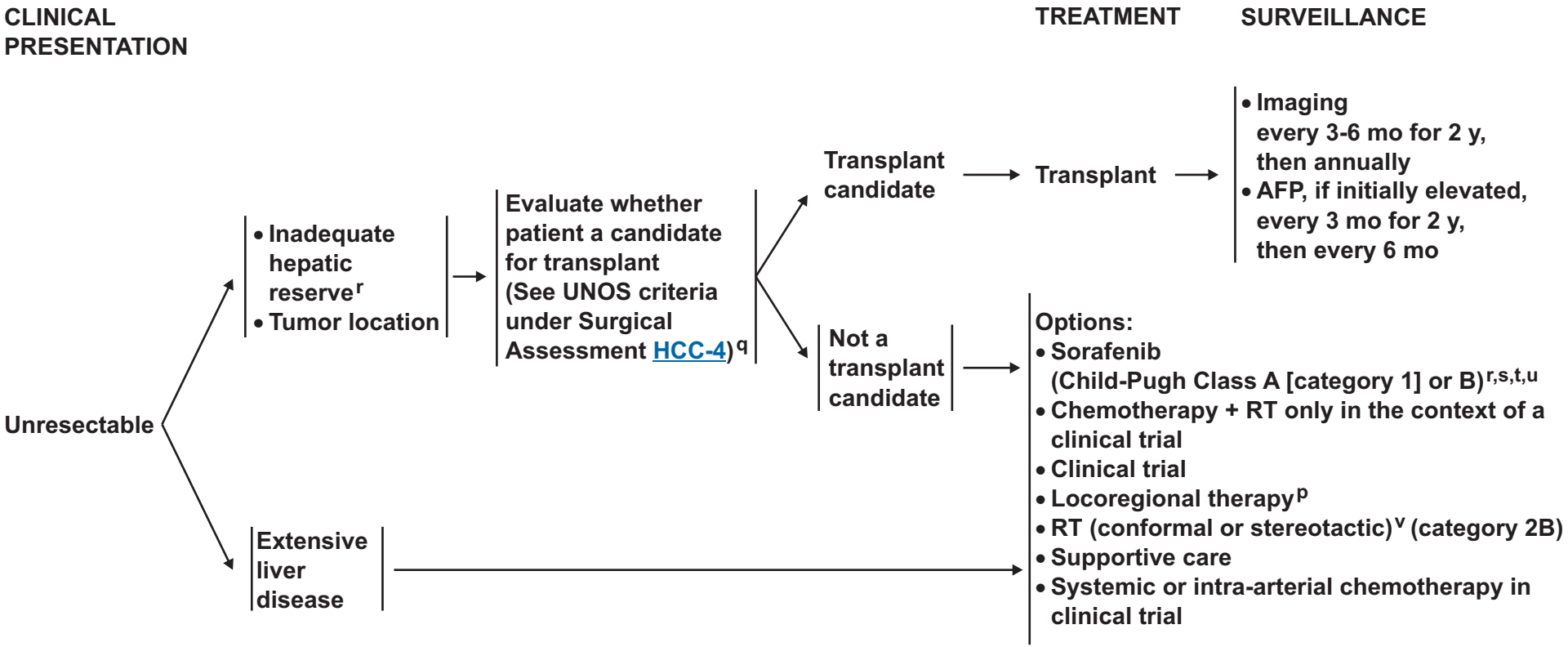
For relapse, see initial Workup (HCC-3)

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[p] See Principles of Locoregional Therapy (HCC-C).

[q] Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.

[r] See Child-Pugh Score (HCC-A).

[s] The impact of sorafenib on patients potentially eligible for transplant is unknown. Data are inadequate to define dosing for patients with abnormal liver function (Child-Pugh Class B or C).

[t] For selected patients, a randomized clinical trial has demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34. Epub 2008 Dec 16).

[u] Caution: There are limited safety data available for Child-Pugh Class B patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Pharmacokinetic (PK) phase I study of sorafenib (S) for solid tumors and hematologic malignancies with hepatic or renal dysfunction (HD or RD): CALGB 6031 2007 ASCO Annual Meeting Proceedings Part I. J Clin Onc 2007 Vol 25, No 18S (June 20 Supplement), 2007:3538).

[v] There are limited data to support the use of RT in this setting.

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CLINICAL PRESENTATION	TREATMENT
Inoperable by performance status or comorbidity, local disease only	Options: • Sorafenib (Child-Pugh Class A [category 1) or B)[r,s,t,u] • Clinical trial • Locoregional therapy[p] • RT (conformal or stereotactic)[v] (category 2B) • Supportive care
Metastatic disease	Sorafenib (Child-Pugh Class A [category 1] or B)[r,s,t,u] or Supportive care or Clinical trial

[p] See Principles of Locoregional Therapy (HCC-C).

[r] See Child-Pugh Score (HCC-A).

[s] The impact of sorafenib on patients potentially eligible for transplant is unknown. Data are inadequate to define dosing for patients with abnormal liver function (Child-Pugh Class B or C).

[t] For selected patients, a randomized clinical trial has demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34. Epub 2008 Dec 16).

[u] Caution: There are limited safety data available for Child-Pugh Class B patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Pharmacokinetic (PK) phase I study of sorafenib (S) for solid tumors and hematologic malignancies with hepatic or renal dysfunction (HD or RD): CALGB 6031 2007 ASCO Annual Meeting Proceedings Part I. J Clin Onc 2007, Vol 25, No 18S (June 20 Supplement), 2007:3538)

[v] There are limited data to support the use of RT in this setting.

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CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time prolonged (sec)[2]	1-4	4-6	> 6
Bilirubin (mg/dL) • For primary biliary cirrhosis	1-2 1-4	2-3 4-10	> 3 > 10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

[1]Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med 1966;274(9):473-481.
Source: Pugh R, Murray-Lyon I, Dawson J, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J of Surg 1973;60(8):646-649.
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[2]Corresponding International Normalized Ratio (INR) measurements are Score points 1: < 1.7; Score points 2: 1.8 - 2.3; Score points 3: > 2.3
(van Rijn JL, Schmidt NA, Rutten WP. Correction of instrument- and reagent-based differences in determination of the International Normalized Ratio (INR) for monitoring anticoagulant therapy. Clin Chem 1989;35(5):840-843).

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PRINCIPLES OF SURGERY

Hepatocellular Carcinoma:

- **Patients must be medically fit for a major operation.**
- **Hepatic resection is indicated as a potentially curative option in the following circumstances:**
  - **Adequate liver function (generally Child-Pugh class A without portal hypertension)**
  - **Solitary mass without major vascular invasion**
  - **Adequate future liver remnant (at least 20% without cirrhosis and at least 30% to 40% with Childs A cirrhosis, adequate vascular and biliary inflow/outflow)**
- **Hepatic resection is controversial in the following circumstances, but can be considered:**
  - **Multifocal disease**
  - **Major vascular invasion**
- **Patients with chronic liver disease being considered for major resection, pre-operative portal vein embolization should be considered.[1]**
- **Patients meeting the UNOS criteria ([single lesion ≤ 5 cm, or 2 or 3 lesions ≤ 3 cm], http://www.unos.org) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside the UNOS guidelines and may be considered at some institutions for living-related liver transplantation.**
- **Patients with Childs A liver function, who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.**

[1]Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237(2):208-217.

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PRINCIPLES OF LOCOREGIONAL THERAPY

All HCC patients should be evaluated for potential curative therapies (resection, transplantation). Those patients not candidates for curative treatments may be treated with locoregional approaches. These are broadly categorized into ablation and transarterial embolization.

Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):

- **All tumors should be amenable to ablation such that the tumor and margin of normal tissue is treated.**
- **Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.**
- **Tumors ≤ 3 cm are optimally treated with ablation. Lesions between 3-5 cm may be treated using combination embolization and ablation as long as tumor location is favorable. Unresectable/inoperable lesions > 5 cm should be treated using arterial embolic approaches. [1-2]**
- **Caution should be exercised when ablating lesions near major vessels, major bile ducts, and other intra-abdominal organs.**

Embolization:

- **All tumors irrespective of location may be amenable to embolization (chemoembolization, bland embolization, radioembolization) provided that the arterial blood supply to the tumor may be isolated without non-target embolization. [3-5]**
- **Chemoembolization/bland embolization are relatively contraindicated in patients with bilirubin > 3 mg/dL unless segmental injections can be performed.[6]**
- **Chemoembolization is contraindicated in cases of main portal vein thrombosis or Child-Pugh Class C.**
- **The angiographic endpoint may be chosen by the treating physician and is dependent on size of hepatic vessels, flow dynamics, tumor vascularity, patency of the portal vein and number of previous arterial treatments.**

[1] Yamakado, K., et al., Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008; 247(1):260-266.

[2] Maluccio, M., et al., Comparison of survival rates after bland arterial embolization and ablation versus surgical resection for treating solitary hepatocellular carcinoma up to 7 cm. J Vasc Interv Radiol 2005;16(7): 955-961.

[3] Maluccio, M.A., et al., Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol 2008; 19(6):862-869.

[4] Kulik, L.M., et al., Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47(1):71-81.

[5] Llovet, J.M., et al., Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359(9319):1734-1739.

[6] Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2002;13(9 Pt 2):S211-21.

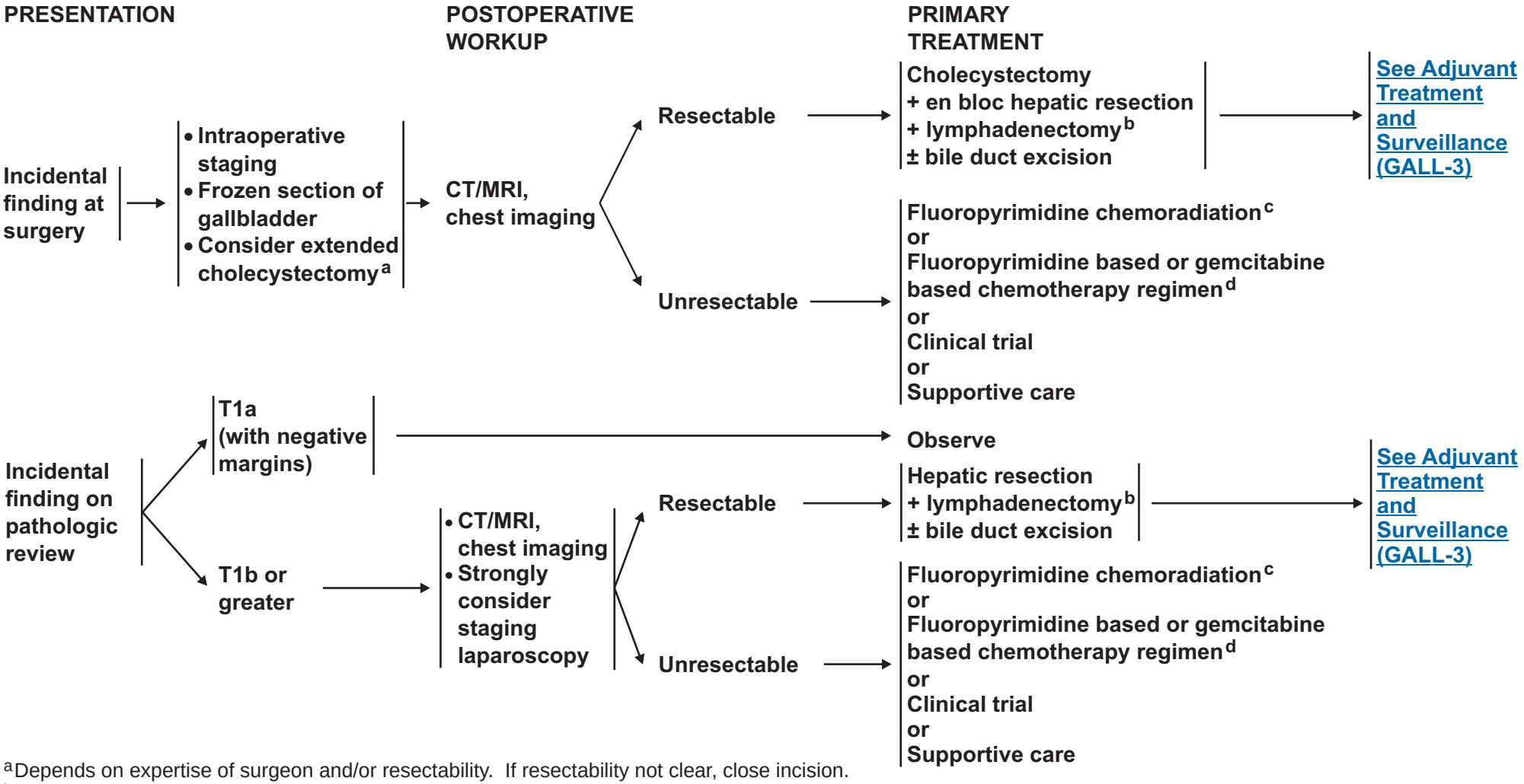
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[a] Depends on expertise of surgeon and/or resectability. If resectability not clear, close incision.

[b] Include porta hepatis, gastrohepatic ligament, retroduodenal. Patients with nodal disease outside this area are unresectable.

[c] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

[d] A recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. Valle JW, Wasan HS, Palmer DD, et al. Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial) J Clin Oncol 27:15s, 2009 [suppl; abstr 4503]) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

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Other Clinical Presentations (See GALL-2)

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PRESENTATION	WORKUP		PRIMARY TREATMENT	
Mass on imaging →	• H&P • CT/MRI • Liver function tests • Chest imaging • Surgical consultation • Assessment of hepatic reserve • Consider CEA • Consider CA 19-9 • Consider staging laparoscopy	Resectable →	Cholecystectomy + en bloc hepatic resection + lymphadenectomy[b] ± bile duct excision	→ See Adjuvant Treatment and Surveillance (GALL-3)
		Unresectable → Biopsy →	Fluoropyrimidine chemoradiation[c] or Fluoropyrimidine based or gemcitabine based chemotherapy regimen[d] or Clinical trial or Supportive care	
Jaundice →	• H&P • Liver function tests • Chest imaging • CT/MRI • Cholangiography[e] • Surgical consultation • Consider CEA • Consider CA 19-9 • Consider staging laparoscopy	Resectable →	Cholecystectomy + en bloc hepatic resection + lymphadenectomy[b] + bile duct excision	→ See Adjuvant Treatment and Surveillance (GALL-3)
		Unresectable → Biopsy →	Options: • Biliary drainage[f] • Fluoropyrimidine chemoradiation[c] • Gemcitabine based or fluoropyrimidine based chemotherapy regimen[d] • Clinical trial • Supportive care	
Metastases →			Options: • Biliary drainage[f] • Gemcitabine based or fluoropyrimidine based chemotherapy regimen[d] • Clinical trial • Supportive care	

[b] Include porta hepatis, gastrohepatic ligament, retroduodenal.

[c] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

[d] A recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. Valle JW, Wasan HS, Palmer DD, et al. Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial). J Clin Oncol 27:15s, 2009 [suppl; abstr 4503]) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

[e] Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic MR cholangiography (ERCP/PTC) are used more for therapeutic intervention.

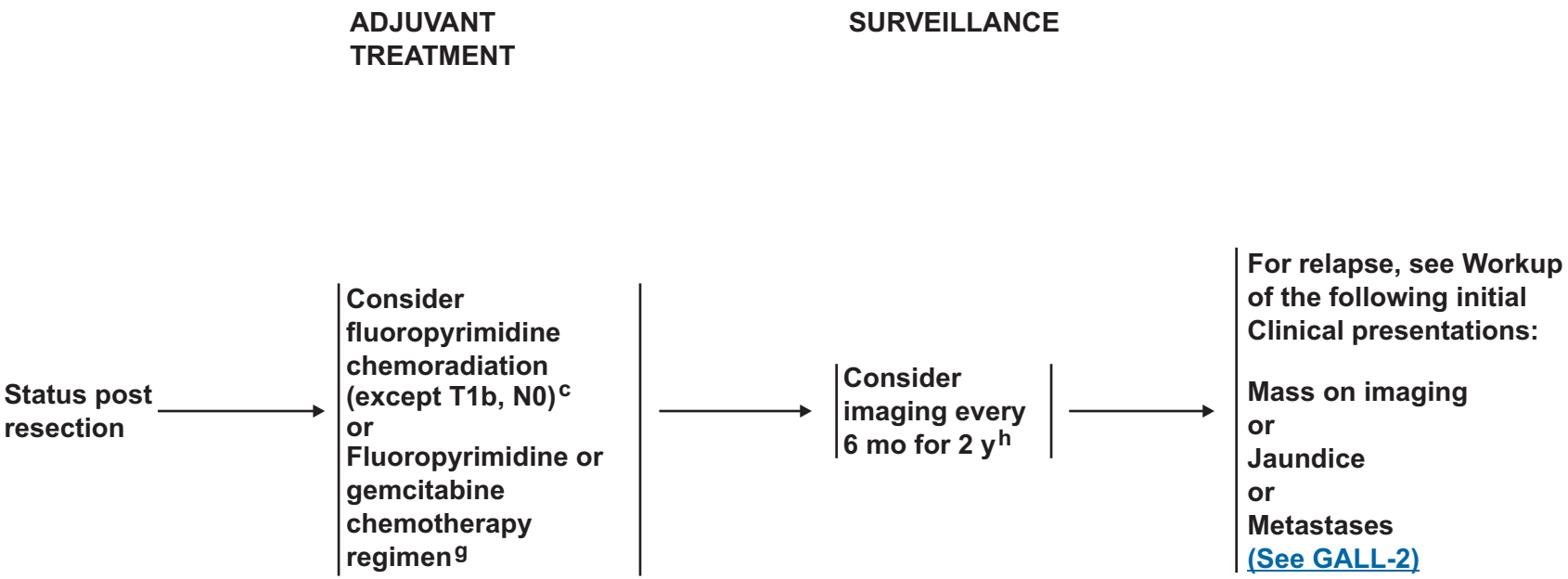
[f] It is expected that patients will have biliary drainage for jaundice prior to instituting chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Other Clinical Presentations (See GALL-1)

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[c]There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

[g]There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. Single agent fluoropyrimidine or gemcitabine is generally recommended in the adjuvant setting.

[h]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

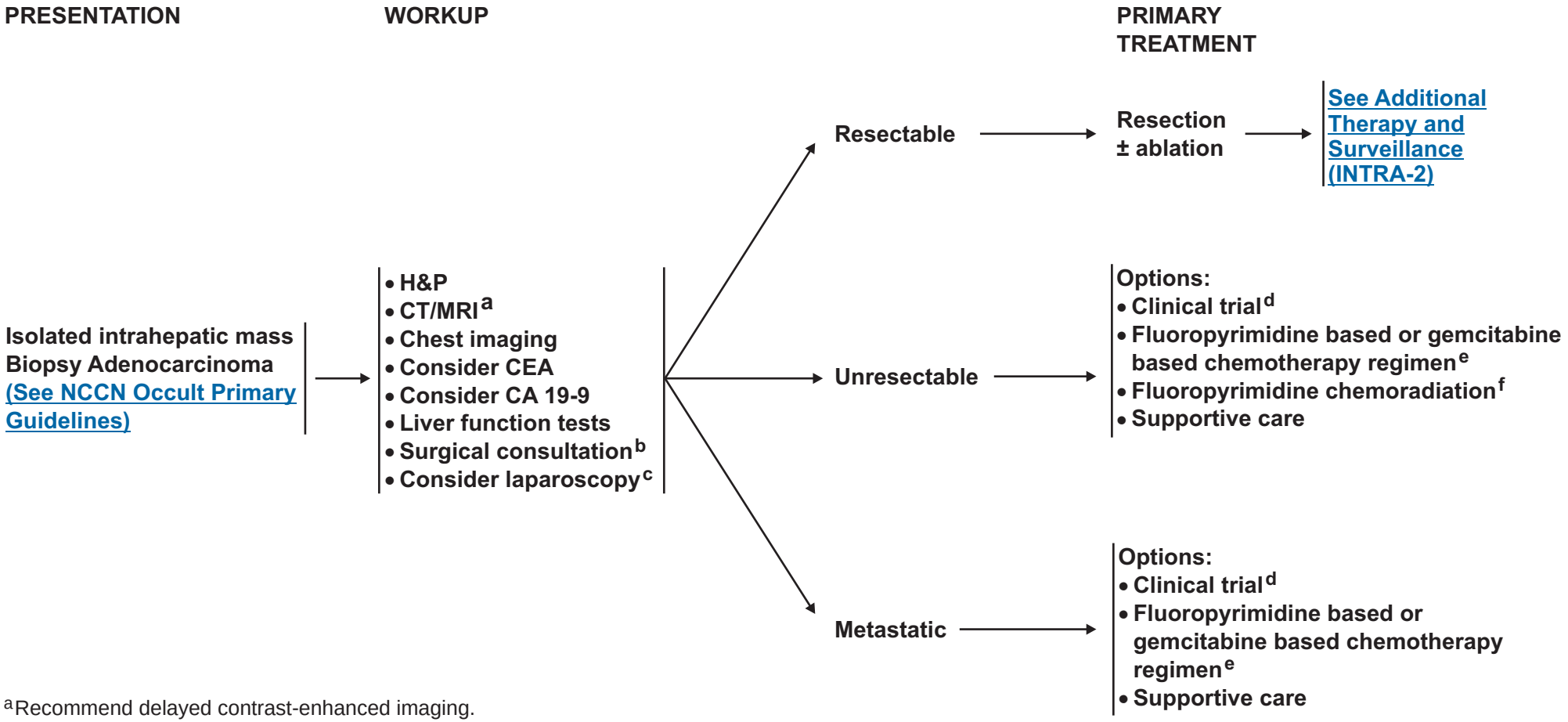
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Intrahepatic Cholangiocarcinoma

Guidelines Index
Hepatobilary Cancers TOC
Staging, Discussion, References



[a] Recommend delayed contrast-enhanced imaging.

[b] Consult with multidisciplinary team.

[c] Laparoscopy may be done in conjunction with surgery if no distant metastases are found.

[d] Systemic or intra-arterial chemotherapy may be used in a clinical trial.

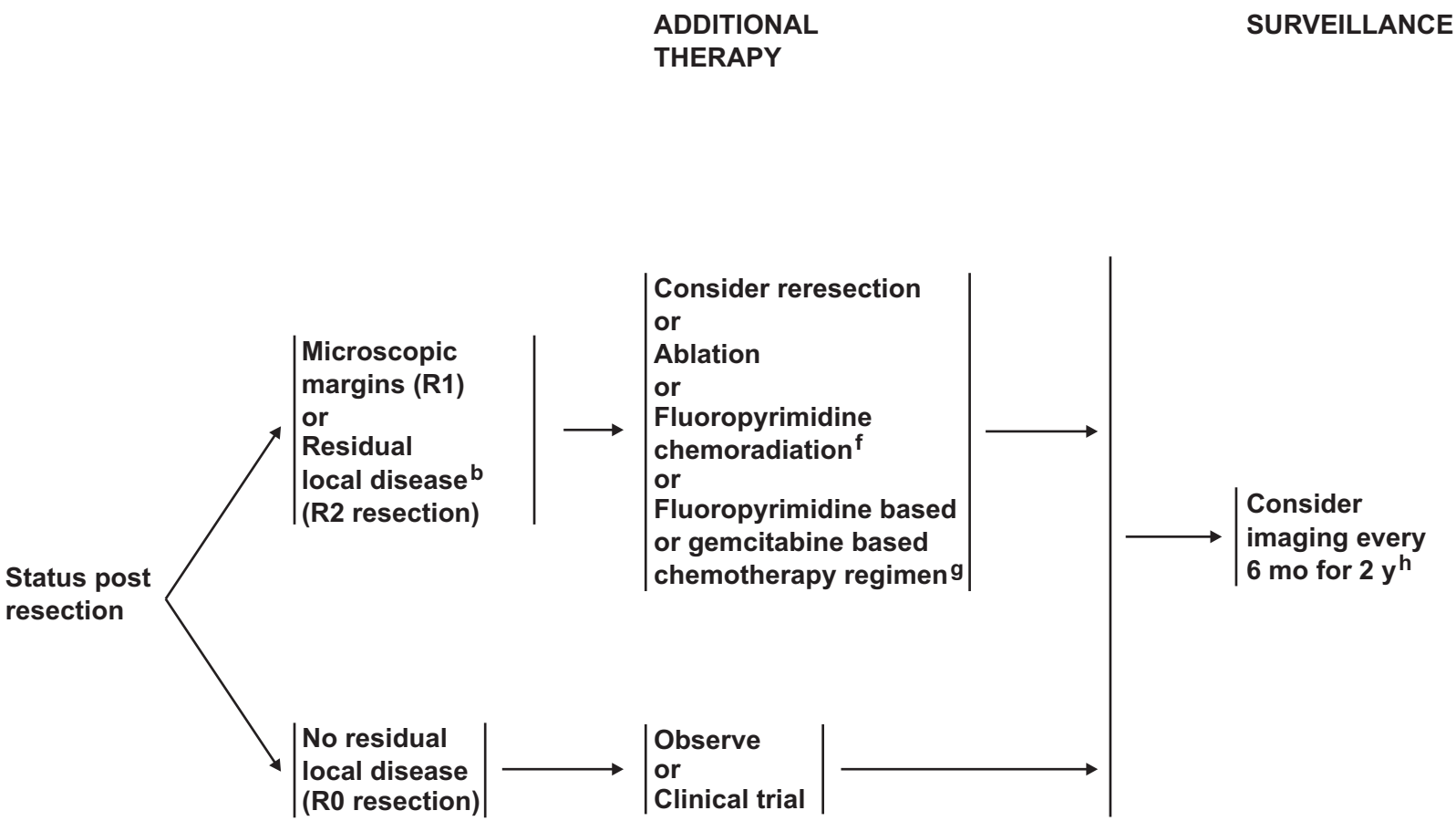
[e] A recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. Valle JW, Wasan HS, Palmer DD, et al. Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial) J Clin Oncol 27:15s, 2009 [suppl; abstr 4503]) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

[f] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

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[b] Consult with multidisciplinary team.

[f] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

[g] There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

[h] There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

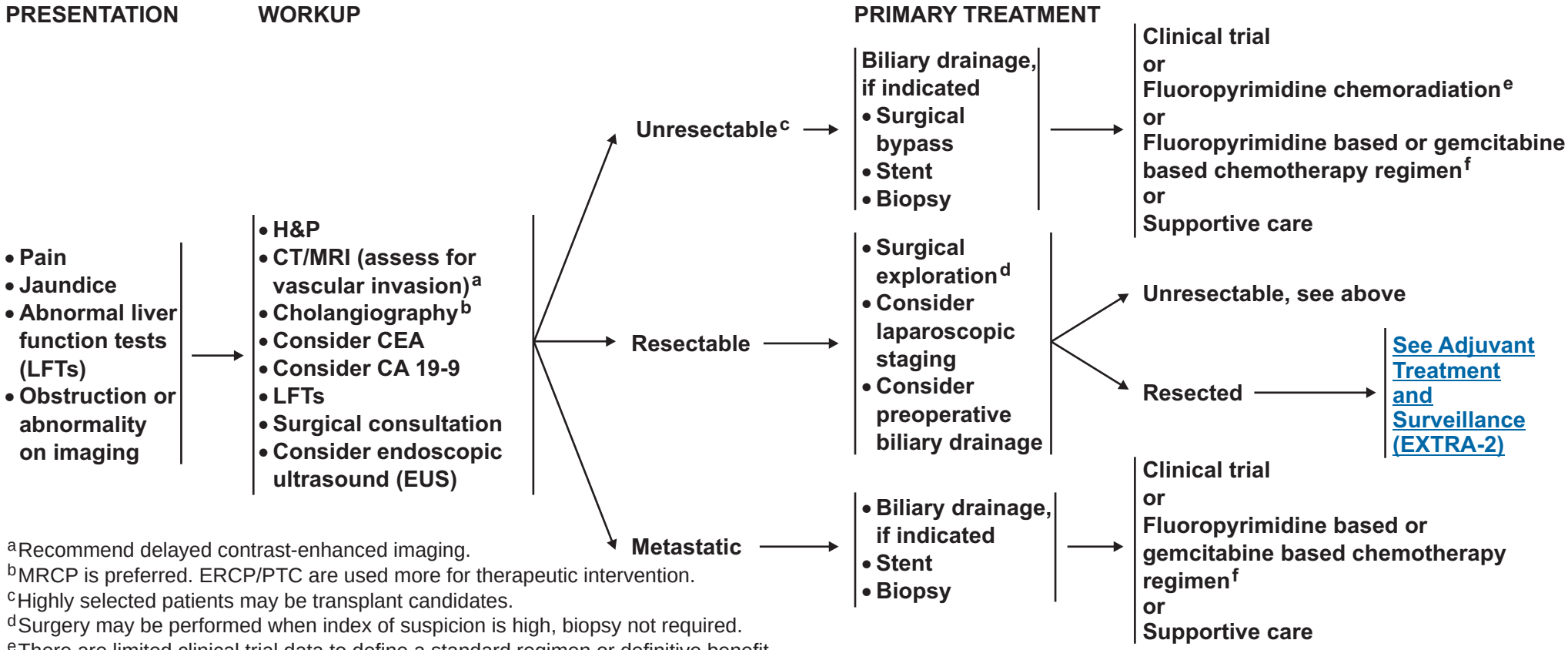
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Extrahepatic Cholangiocarcinoma

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Hepatobilary Cancers TOC
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[a] Recommend delayed contrast-enhanced imaging.

[b] MRCP is preferred. ERCP/PTC are used more for therapeutic intervention.

[c] Highly selected patients may be transplant candidates.

[d] Surgery may be performed when index of suspicion is high, biopsy not required.

[e] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002; 11(4):941-954)

[f] A recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. Valle JW, Wasan HS, Palmer DD, et al. Gemcitabine with or without cisplatin in patients (pts) with advanced or metastatic biliary tract cancer (ABC): Results of a multicenter, randomized phase III trial (the UK ABC-02 trial) J Clin Oncol 27:15s, 2009 [suppl; abstr 4503]) Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

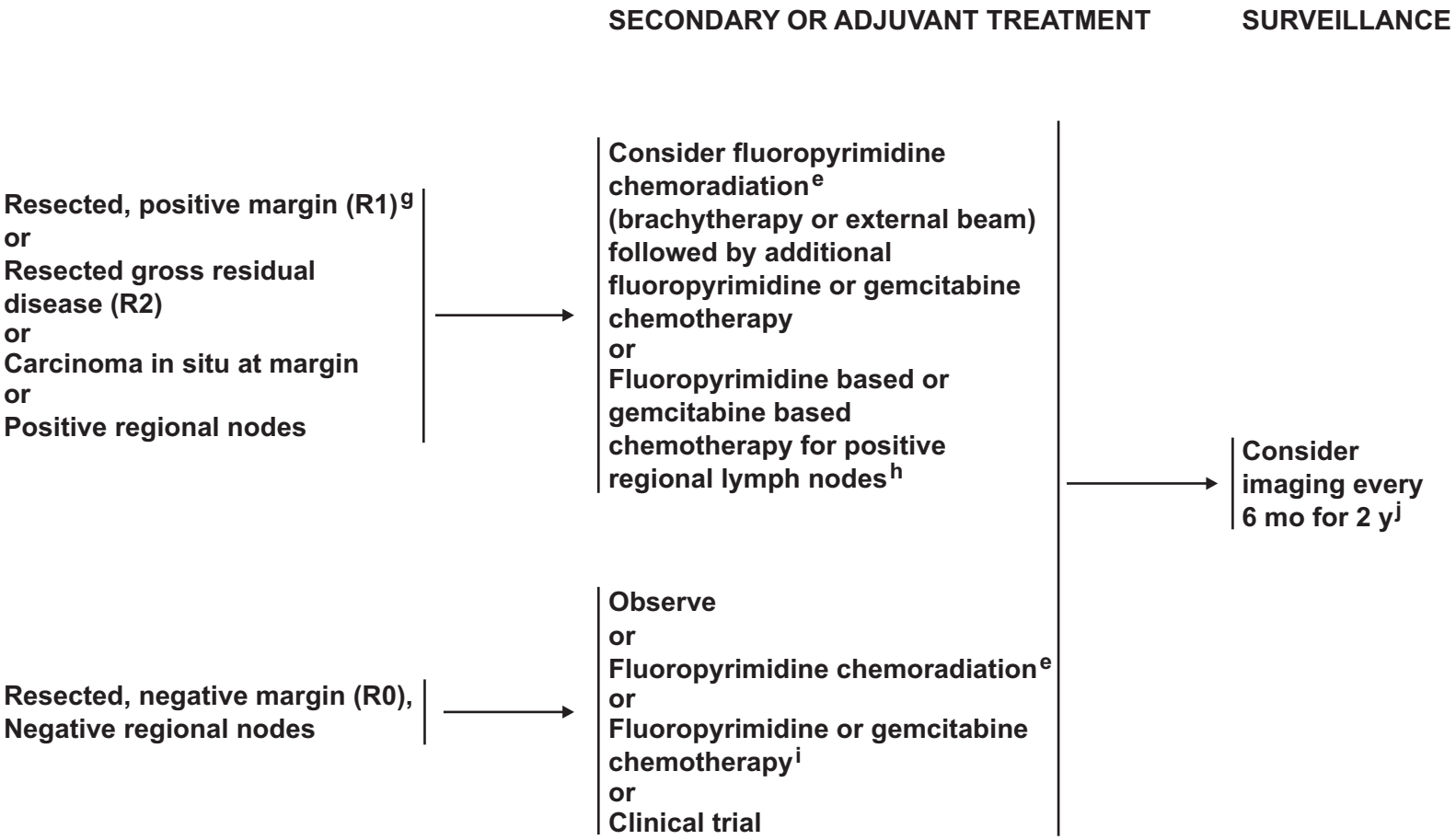
Surgical Procedures for Resectable Disease

- **Proximal Third: Hilar resection + lymphadenectomy + en bloc liver resection. Caudate resection strongly encouraged.**
- **Mid Third: Major bile duct excision with lymphadenectomy. Recommend frozen section assessment of bile duct margins.**
- **Distal Third: Pancreaticoduodenectomy with lymphadenectomy.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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[e] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11(4):941-954)

[g] Multidisciplinary team review.

[h] There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. There are phase II trials that support the following combinations: gemcitabine/cisplatin, gemcitabine/oxaliplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

[i] There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

[j] There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

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Staging

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging for Liver Tumors (Including Intrahepatic Bile Ducts)*

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 none 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

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

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Fibrosis Score (F)

The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

F0 Fibrosis score 0-4 (none to moderate fibrosis)
F1 Fibrosis score 5-6 (severe fibrosis or cirrhosis)

*Used with the 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, Sixth edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

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Table 2

American Joint Committee on Cancer (AJCC) TNM Staging for Gallbladder Cancer*

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 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

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

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

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Table 3

American Joint Committee on Cancer (AJCC) TNM Staging for Extrahepatic Bile Duct Tumors*

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 liver, gallbladder, pancreas, and/or ipsilateral 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

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Hepatobiliary cancers are highly lethal cancers. It has been estimated that approximately 24,120 and 9,760 persons will be diagnosed with liver or intrahepatic bile duct cancer and gallbladder cancer or other biliary tract cancer, respectively, in the United States during 2010 with approximately 18,910 deaths from liver or intrahepatic bile duct cancer, and 3,320 deaths due to gallbladder cancer or other biliary tract cancer occurring during that year.[1]

The Hepatobiliary Cancers Clinical Practice Guidelines presented here are the work of the members of the NCCN Hepatobiliary Cancers Clinical Practice Guidelines Panel. The types of hepatobiliary cancers covered in these guidelines include: hepatocellular carcinoma (HCC); gallbladder cancer; intrahepatic cholangiocarcinoma; and extrahepatic cholangiocarcinoma. By definition, the NCCN guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Although not explicitly stated at every decision point of the Guidelines, patient participation in prospective clinical trials is the preferred option for treatment of hepatobiliary cancers.

Hepatocellular Carcinoma

Risk Factors and Epidemiology

Risk factors for the development of HCC, the most common of the hepatobiliary malignancies, include hepatitis B and/or hepatitis C viral infection, particular comorbidities or conditions, and certain external sources.[2] For example, chronic hepatitis B viral infection is the leading cause of HCC in Asia and Africa, while hepatitis C viral infection is the leading cause of HCC in Europe, Japan, and North America.[3,4] A retrospective analysis of patients at liver transplantation centers in the U.S. found that nearly 50% and about 15% of patients were infected with the hepatitis C or B virus, respectively, with approximately 5% of patients having markers of both hepatitis B and hepatitis C infection.[5] Conditions associated with an increased risk of HCC include relatively rare, inherited errors of metabolism such as hereditary hemochromatosis, porphyria cutanea tarda, α1-antitrypsin deficiency, and Wilson's disease, as well as autoimmune hepatitis and primary biliary cirrhosis.[2,6] There is also growing evidence for an association between the sequelae of non-alcoholic fatty liver disease, such as non-alcoholic steatohepatitis [NASH] (ie, a spectrum of conditions characterized by histological findings of hepatic steatosis with inflammation in individuals who consume little or no alcohol) in the setting of metabolic syndrome or diabetes mellitus[7] and the development of HCC.[8] Excessive alcohol intake or environmental exposure to aflatoxin, a natural product of the *Aspergillus* fungus found in various grains, are other known risk factors for HCC.[2,4,9,10]

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In most cases, the risk factors for HCC are also risk factors for liver cirrhosis. It has been estimated that 60%-80% of persons with HCC have underlying cirrhosis,[9] possibly approaching 90% in the U.S.[11] Although most studies evaluating the risk of development of HCC in hepatitis C-infected individuals have focused on populations with cirrhosis, there are limited data showing that HCC can occur in some hepatitis C-infected patients with bridging fibrosis in the absence of overt cirrhosis.[12] Importantly, certain populations chronically infected with the hepatitis B virus (ie, hepatitis B carriers) have been identified as being at increased risk of HCC in the absence of cirrhosis, especially when other risk factors are present,[4] and it has been estimated that 30% to 50% of patients with chronic hepatitis B viral infection who develop HCC do not have underlying cirrhosis.[10] Some risk factors for development of HCC in hepatitis B viral carriers without evidence of liver cirrhosis include active viral replication, high hepatitis B viral DNA levels, a family history of HCC, Asian males ≥40 years, Asian females ≥ 50 years, and Africans >20 years.[4,13] The presence of liver cirrhosis is usually considered to be a prerequisite for development of HCC in individuals with inherited metabolic diseases of the liver or liver disease with an autoimmune etiology.[14,15] Although the mechanism of HCC development differs according to the underlying disease,[9] HCC typically occurs in the setting of a histologically abnormal liver. Hence, the presence of chronic liver disease represents a potential risk for development of HCC.[2]

The incidence of hepatocellular carcinoma is increasing in the United States, particularly in the population infected with the hepatitis C virus. Approximately 4 million individuals in the United States are chronically infected with the hepatitis C virus,[16] and the annual incidence rate of HCC among patients with hepatitis C-related cirrhosis has been estimated to be between 2% and 8%.[4] Although it has been reported that the number of cases of hepatitis C infection diagnosed per year in the United States is declining, it is likely that the observed increase in the number of cases of hepatitis C-related HCC is associated with the often prolonged period between viral infection and the manifestation of HCC.[17,18]

Approximately 1.5 million people in the United States are chronically infected with the hepatitis B virus.[16-20] Results from a prospective controlled study showed the annual incidence of HCC to be 0.5% in carriers of the virus without liver cirrhosis and 2.5% in those with known cirrhosis,[21] although studies have shown wide variation in the annual incidence rate of HCC among individuals with chronic hepatitis B infection.[4]

Estimations of the prevalence of NASH in the United States are in the range of 3%-5%, indicating that this sizable subpopulation is at risk for cirrhosis and development of HCC.[22] In one study, 12.8% of 195 patients with cirrhosis secondary to NASH developed HCC at a median follow-up of 3.2 years, with an annual incidence rate of HCC of 2.6%.[23] However, several studies suggest that HCC may be somewhat less likely to develop in the setting of NASH-associated cirrhosis compared with cirrhosis due to hepatitis C infection.[24,25]

Annual incidence rates of HCC associated with certain conditions (eg, hereditary hemochromatosis) or exposure to alcohol are not well characterized; in the former case, these conditions are uncommon; in the latter case, many of the studies evaluating the incidence rate of HCC in individuals with alcohol-induced cirrhosis have been confounded by the presence of other risk factors (eg, viral hepatitis infection), which can interact synergistically in the pathogenesis of HCC.[26,27]

Screening for HCC

The purpose of a cancer screening test is to identify the presence of a specific cancer in an asymptomatic individual in a situation where early detection has the potential to favorably impact patient outcome. The

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panel supports the recommendation by the American Association for the Study of Liver Disease (AASLD) that HCC screening should be "offered in the setting of a program or a process in which screening tests and recall procedures have been standardized and in which quality control procedures are in place." [4]

Support for enrolling individuals at high risk of HCC in a screening program comes from a large randomized controlled trial of 18,816 men and women with hepatitis B infection or a history of chronic hepatitis in China. In this study, screening with serum alpha-fetoprotein (AFP) testing and ultrasonography every 6 months was shown to result in a 37% reduction in HCC mortality, despite the fact that less than 60% of individuals in the screening arm completed the screening program.[28] In a recent prospective study of 638 patients with HCC in Singapore carried out over a 9 year period, patients 40 years or younger were more likely than older patients to be hepatitis B carriers and to have more advanced disease at diagnosis.[29] Although survival did not differ in the 2 groups overall, a significant survival benefit was observed for younger patients when the subgroup of patients with early-stage disease was considered. These results provide support for not restricting HCC screening to older patients.

AFP and liver ultrasonography are the most widely used methods of screening for HCC.[30] In a screening study involving a large population of patients in China infected with the hepatitis B virus or those with chronic hepatitis, the detection rate, false positive rate, and positive predictive value was 84%, 2.9%, and 6.6% for ultrasound alone; 69%, 5.0%, and 3.3% for AFP alone, and 92%, 7.5%, and 3.0% for the combination of AFP and ultrasound.[31] These results demonstrate that ultrasound imaging alone is a better HCC screening approach than AFP testing alone. Nevertheless, since ultrasonography is highly operator dependent, addition of AFP can increase the likelihood of detecting HCC in a screening setting. However, the utility of AFP as a screening biomarker is limited (eg, frequently not elevated in early-stage disease).[32-34]

In these guidelines, the populations considered to be "at risk" for HCC and likely to benefit from participation in an HCC screening program are defined on HCC-1 (see section on Risk factors and Epidemiology).

The panel recommends that patients at risk for HCC undergo periodic screening with ultrasonography and AFP testing every 6-12 months (see HCC-1). Additional imaging (eg, CT with contrast; PET/CT is not considered to be adequate) is recommended in the setting of a rising serum AFP or following identification of a liver mass nodule on ultrasound (see section on Diagnosis and Initial Workup, below).

Diagnosis and Initial Workup

HCC is asymptomatic for much of its natural history. Nonspecific symptoms associated with hepatocellular carcinoma can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites.[8] Paraneoplastic syndromes also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.[9]

Diagnosis

Imaging

Recommendations for additional imaging if clinical suspicion for HCC is high (eg, following identification of a liver nodule on ultrasonography or in the setting of rising a serum AFP level) are adapted from the guidelines outlined by the AASLD (see HCC-2).[4] HCC lesions are characterized by arterial hypervascularity, deriving most of their blood supply from the hepatic artery unlike the surrounding liver which receives most of its supply of blood from the portal vein.[35] Diagnostic HCC imaging involves use of one or more of the following modalities - triphasic helical computed tomography (CT); triphasic dynamic contrast

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enhanced magnetic resonance imaging (MRI); or contrast-enhanced ultrasonography, although the latter modality is not commonly available in the U.S.[4,36,37] The term "triphasic" refers to the three phases of scanning: an arterial phase, a portal venous phase, and the venous phase after a delay.[11] The classic imaging profile associated with an HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed venous phase.[4, 38,37,]

Patients with a liver mass on ultrasound should be evaluated using one or more imaging modalities with the number and type of imaging dependent on the size of the liver mass nodule (see HCC-2). It is recommended that liver nodules1-2 cm in size be evaluated using 2 different imaging techniques from the list above. A coincidental finding of classic arterial enhancement with both modalities is considered to be diagnostic of HCC, whereas additional confirmation through tissue sampling is recommended when a classic enhancement pattern is not seen or observed with only one imaging modality. Prospective validation of this diagnostic paradigm using contrast-enhanced ultrasonography and diagnostic MRI with biopsy confirmation for patients with a well-defined single, solid nodule between 0.5-2.0 cm observed on screening ultrasonography has recently been presented.[39] For lesions over 2 cm, however, only one imaging modality demonstrating classic arterial enhancement of the lesion is needed for a diagnosis of HCC. Finally, liver lesions <1 cm should be re-evaluated by triphasic CT or MRI or contrast-enhanced ultrasonography every 3-4 months, with enlarging lesions evaluated according to size as described on HCC-2. Patients with lesions stable in size over a period of 18 months should be followed with imaging every 6-12 months.

Biopsy

A diagnosis of HCC can be noninvasive in that biopsy confirmation may not be required. For example, in the evaluation of 1-2 cm liver nodules, classic arterial enhancement using 2 types of recommended imaging modalities, or classic arterial enhancement observed with a single recommended imaging technique for liver lesions >2 cm, is sufficient for a diagnosis of HCC (see HCC-2). However, a needle core biopsy (NCB) (preferred) or a fine needle aspiration biopsy (FNAB) is recommended in some cases when the diagnosis of HCC is uncertain. For example, a biopsy is recommended when classic arterial enhancement is not observed by any imaging method, or when the liver nodule is in the 1-2 cm range and classic arterial enhancement is seen on only one of the imaging tests performed. Of note, results from a recent study of a series of 64 patients with de novo liver nodules and liver cirrhosis, the majority of whom had 1-2 cm liver nodules, suggests that a finding of classical arterial enhancement using a single imaging technique is sufficient to diagnose HCC in this patient population.[40]

Both NCB and FNAB have advantages and disadvantages in this setting. For example, FNAB may be associated with a lower complication rate when sampling deeply situated lesions or those located near major blood vessels. In addition, the ability to rapidly stain and examine cytological samples can provide for immediate determinations of whether sufficient sample has been obtained, as well as the possibility of an upfront tentative diagnosis.[41] However, FNAB is highly dependent on the skill of the cytopathologist,[42] and there are reports of high false-negative rates[39,43] as well as the possibility of false-positive findings with this procedure.[44] Although a NCB is a more invasive procedure, it has the advantage of providing pathologic information on both cytology and tissue architecture. Further, additional histological and immunohistochemical tests cancer be performed on the paraffin wax embedded sample.[33,41,43] However, recent evidence indicates that a NCB does not provide an accurate determination of tumor grade.[45]

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Nevertheless, use of biopsy to diagnose HCC is limited by a number of factors including sampling error, particularly when lesions are between 1 and 2 cm.[4,11] Patients for whom a nondiagnostic biopsy result is obtained should be followed closely, and subsequent additional imaging and/or biopsy is recommended if a change in nodule size is observed.

Serum biomarkers

Serum AFP is not a sensitive or specific diagnostic test for HCC.[4,11] Other serum biomarkers being studied in this setting include des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence-II (PIVKA-II), and lens culinaris agglutinin-reactive AFP (AFP-L3), an isoform of AFP.[11,46,47] Although AFP was found to be more sensitive than DCP or AFP-L3 in detecting early-stage and very early-stage HCC in a recent retrospective case control study, none of these biomarkers were considered optimal in this setting.[48] A recent case-control study involving patients with hepatitis C enrolled in the large, randomized HALT-C trial who developed HCC showed that a combination of AFP and DCP is superior to either biomarker alone as a complementary assay to screening.[32]

Results of AFP testing can be useful in conjunction with other test results to guide management of patients for whom a diagnosis of HCC is suspected. For example, additional imaging studies (ie, CT/MRI) are recommended for patients with a rising serum AFP level in the absence of a liver mass (see HCC-1). If no liver mass is detected following measurement of an elevated AFP level, the patient should be followed with AFP testing and liver imaging on a more frequent basis (eg, every 3 months). In addition, an elevated AFP level in conjunction with imaging results showing the presence of a larger liver mass has been shown to have a high positive predictive value for HCC in 2 retrospective analyses involving small numbers of patients,[49,50] although the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institutions. Following the AASLD Guidelines, an AFP level >200 ng/mL or the presence of classic arterial enhancement on triphasic CT or MRI is considered to be diagnostic of HCC when liver lesions are > 2cm in size (see HCC-2). However, the panel considers an imaging finding of classic enhancement to be more definitive in this setting since the level of serum AFP may be elevated in those with certain nonmalignant conditions, as well as within normal limits in a substantial percentage of patients with HCC.[51]

Initial workup

The foundation of the initial workup of the patient diagnosed with HCC is a multidisciplinary evaluation involving investigations into the etiological origin of liver disease, including a hepatitis panel for detection of hepatitis B and/or C viral infection (see HCC-3) and an assessment of the presence of comorbidity; imaging studies to detect the presence of metastatic disease; and an evaluation of hepatic function, including a determination of whether portal hypertension is present.

Common sites of HCC metastasis include the lung, abdominal lymph nodes and the bone.[52,53] Hence, chest imaging, and a bone scan (if suspicious bone pain is present or if the patient is being considered for liver transplantation) are recommended as part of the initial workup. Triphasic CT or MR imaging results are also used in the evaluation of the HCC tumor burden, to detect the presence of metastatic disease, nodal disease, and vascular invasion, to assess whether evidence of portal hypertension is present, to provide an estimate of the size and location of HCC and the extent of chronic liver disease, and, in the case of patients being considered for resection, to provide an estimate of the future liver remnant in relation to the total liver volume (see section on Partial hepatectomy).[37]

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, aspartate

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transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AFP), measurement of prothrombin time (PT)/international normalized ratio (INR), albumin, and protein. Other recommended tests include tests of kidney function (ie, blood urea nitrogen [BUN] and creatinine) which are established prognostic markers in patients with liver disease,[54] as well as lactate dehydrogenase (LDH), and a complete blood count (CBC) (see HCC-3).

Further assessment of hepatic function or reserve in patients with chronic liver disease has traditionally been performed using the Child-Pugh score which places patients into one of 3 classes (A-C) according to likelihood of survival (see HCC-A).[55,56] The Child-Pugh classification provides a rough estimate of liver function by classifying patients as having compensated (class A) or decompensated (class B and C) cirrhosis. The Child-Pugh score is an empirical score which incorporates laboratory measurements (ie, serum albumin, bilirubin, and PT) as well as more subjective clinical assessments of encephalopathy and ascites. More recently, a version of the Child-Pugh score which includes INR has come into use (see HCC-A). Advantages of the Child-Pugh score include ease of performance (ie, can be done at the bedside) and the inclusion of clinical parameters. An important additional assessment of liver function not included in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension (ie, esophagogastric varices, splenomegaly, abdominal collaterals, thrombocytopenia). Evidence of portal hypertension may also be evident on CT/MR imaging.[37] Measurement of hepatic venous pressure gradient (HVPG) is an evolving tool for the assessment of portal hypertension.[57-60]

Another system for evaluation of hepatic reserve is the Model for End-Stage Liver Disease (MELD) score which is a numerical scale ranging from 6 (less ill) to 40 (gravely ill) for individuals 12 years or older. It is derived from an equation using three laboratory values (ie, serum bilirubin, creatinine, and INR), and was originally devised to provide an assessment of mortality for patients undergoing transjugular intrahepatic portosystemic shunts.[61] The MELD score has since been adopted by the United Network for Organ Sharing (UNOS) to stratify patients on the liver transplantation waiting list according to their risk of death within 3 months[62] (see section on Liver Transplantation). More recently, the MELD score has sometimes been used in place of the Child-Pugh score to assess prognosis in patients with cirrhosis. Advantages of the MELD score include the inclusion of a measurement of renal function and an objective scoring system based on widely available laboratory tests, although clinical assessments of ascites and encephalopathy are not included. It is currently unclear whether the MELD score is superior to the Child-Pugh score as a predictor of survival in patients with liver cirrhosis. The MELD score has not been validated as a predictor of survival in patients with cirrhosis who are not on a liver transplantation waiting list.[56]

Pathology and Staging

Pathology

Three gross morphologic types of HCC have been identified: nodular, massive and diffuse.[63-65] Nodular HCC is often associated with cirrhosis and is characterized by well circumscribed nodules. The massive type of HCC, usually associated with a noncirrhotic liver, occupies a large area with or without satellite nodules in the surrounding liver. The less common diffuse type is characterized by diffuse involvement of many small indistinct tumor nodules throughout the liver.

Staging

Clinical staging systems for the cancer patient can provide a more accurate prognostic assessment before and after a particular treatment intervention, and may be used to guide treatment decision-making. Therefore, staging can have a critical impact on treatment outcome by facilitating appropriate patient selection for specific therapeutic

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interventions, and by providing risk stratification information following treatment.

There are 4 main parameters affecting prognosis in patients with HCC: the stage, aggressiveness and growth rate of the tumor; the general health of the patient; the liver function of the patient; and the HCC treatments administered.[36] A number of staging systems for patients with HCC have been devised.[66,67] Each of the HCC staging systems includes variables which evaluate one or more of the first 3 factors listed above. For example, the Child-Pugh[55] and MELD scores[68] can be considered to be staging systems which evaluate aspects of liver function only. The American Joint Committee on Cancer (AJCC) TNM staging system (see Table 1) provides information on tumor characteristics only,[69] whereas the Okuda system incorporates aspects of liver function and tumor characteristics.[70] The French classification (GRETCH) system incorporates the Karnofsky performance score as well as measurements of liver function and serum AFP.[71] Several staging systems include all parameters from other staging systems as well as additional parameters. For example, the Chinese University Prognostic Index (CUPI) system[72] and the Japanese Integrated Staging (JIS)[73] scores incorporate the TNM staging system and the Cancer of the Liver Italian Program (CLIP),[74] Barcelona Clinic Liver Cancer (BCLC),[75] SLiDe,[76] and JIS systems include the Child-Pugh score (with modified versions of CLIP and JIS substituting the MELD score for the Child-Pugh score.[77-79] In addition, the BCLC system also incorporates the Okuda system, as well other tumor characteristics, measurements of liver function, and patient performance status.[4]

Although some of these systems have been found to have use in all stages of HCC (eg, BCLC),[4,11,80] limitations of all of these systems have been identified. For example, the AJCC TNM classification system has limited usefulness since most patients with HCC do not undergo surgery. A number of studies have shown that particular staging systems perform well for specific patient populations. Furthermore, staging systems may be used to direct treatment and/or to predict survival outcomes following a particular type of therapeutic intervention. For example, the AJCC TNM system has recently been shown to accurately predict survival for patients who underwent orthotopic liver transplantation.[81] The CLIP and GRETCH staging systems have been shown to perform well in predicting morbidity and mortality in patient populations with advanced disease,[82] and the CLIP system has been specifically identified as being useful for staging patients who underwent transarterial chemoembolization[83] and those treated in a palliative setting.[84] The utility of the BCLC staging system with respect to stratifying patients with HCC according to the natural history of the disease has been demonstrated in a meta-analysis of untreated patients with HCC enrolled in randomized clinical trials.[85] In addition, an advantage of the BCLC system is that it stratifies patients into treatment groups, although the type of treatment is not included as a staging variable.[67] Furthermore, the BCLC staging system was recently shown to be very useful for predicting outcome in patients following radiofrequency ablation therapy.[86] A recently developed novel staging system based on a nomogram of particular clinicopathologic variables, including patient age, tumor size and margin status, postoperative blood loss, the presence of satellite lesions and vascular invasion, and serum AFP level, has been shown to perform well in predicting postoperative outcome for patients undergoing liver resection for HCC.[87] In addition, another study showed tumor size > 2 cm, multifocal tumors, and vascular invasion to be independent predictors of poor survival in patients with early HCC following liver resection or liver transplantation,[88] and this staging system has been retrospectively validated in a population of patients with early HCC.[89]

Although a particular staging system (with the exception of the Child-Pugh score, and TNM system) is not currently used in these guidelines, following an initial workup (see HCC-3) patients are stratified into one of

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4 categories: potentially resectable or transplantable, operable by performance status or comorbidity; those who are unresectable; those who are inoperable by performance status or comorbidity with local disease only; or those with metastatic disease. The selection characteristics of these patient populations are described in more detail on HCC-4 - HCC-6 , and HCC-B, HCC-C and in the section on Management, below.

Management

The patient with HCC should be carefully evaluated for HCC treatment consideration. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, it is possible that the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome.[90] The treatment of patients with HCC often necessitates the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care.[11]

Surgery

Partial Hepatectomy

Partial hepatectomy (ie, liver resection) is a potentially curative therapy for patients with early-stage HCC who are eligible to undergo the procedure.[91, 92] Partial hepatectomy for selected patients with HCC can now be performed with low operative morbidity and mortality (in the range of 5% or less).[93,94] Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC, [94-96] and some studies suggest that for selected patients with preserved liver function and early stage HCC, liver resection can achieve a 5-year survival rate of about 70%.[96-98] However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.[4,95]

Since risks of liver resection for patients with HCC include surgical removal of functional liver parenchyma in the setting of underlying liver disease, careful patient selection, based on patient characteristics as well as characteristics of the liver and the HCC tumor(s), is essential. Assessments of patient performance status must be considered; the presence of comorbidity has been shown to be an independent predictor of perioperative mortality.[99] Likewise, estimates of overall liver function and the size and function of the putative future liver remnant, as well as technical considerations related to tumor and liver anatomy must be taken into account before a patient is determined to have potentially resectable disease (see HCC-4).

Resection is recommended only in the setting of preserved liver function. The Child-Pugh score provides an estimate of liver function, although it has recently been suggested that it is more useful as a tool to rule out patients for liver resection (ie, serving as a means to identify patients with substantially decompensated liver disease).[100] An evaluation of the presence of significant portal hypertension is also an important part of the presurgical assessment (see section on Initial workup). In general, evidence of optimal liver function in the setting of liver resection is characterized by a Child-Pugh class A score and no evidence of portal hypertension (see HCC-4). However, in highly selected cases, patients with a Child-Pugh class B score may be considered for limited liver resection, particularly if liver function tests are normal and clinical signs of portal hypertension are absent.

With respect to tumor characteristics and estimates of the future liver remnant following resection, preoperative imaging is essential for surgical planning.[37] CT/ MR imaging can be used to facilitate characterization of the number and size of the HCC lesions, to detect the presence of satellite nodules, extrahepatic metastasis, and tumor invasion of the portal vein or the inferior vena cava, and to help

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establish the location of the tumors with respect to vascular and biliary structures.

Optimal tumor characteristics for liver resection are solitary tumors without major vascular invasion. Although no limitation on the size of the tumor is specified for liver resection, the risk of vascular invasion and dissemination increases with size.[93,101] However, in one study, no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors of 10 cm or larger.[93] Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence.[93,102,103] The role of liver resection for patients with multifocal disease and/or signs of major vascular invasion is controversial,[92,102,104] although results of a recent retrospective analysis showed a 5-year overall survival rate of 81% for selected patients with 1 tumor of 5 cm or less or 3 or fewer tumors of 3 cm or less undergoing liver resection.[105] The consensus of the panel is that resection can be considered in selected patients with these disease characteristics. The presence of extrahepatic metastasis is considered to be a contraindication for resection.

Another critical preoperative assessment includes evaluation of the postoperative future liver remnant (FLR) as an indicator of postoperative liver function. CT is used to measure the FLR directly and estimates of the total liver volume can be calculated. The ratio of future remnant/total liver volume (subtracting tumor volume) is then determined.[106] The panel recommends that this ratio be at least 20% in patients without cirrhosis and least 30% to 40% in patients with a Child-Pugh A score.[107] For patients with an estimated FLR/total liver volume ratio below recommended values who are otherwise suitable candidates for liver resection, pre-operative portal vein embolization (PVE) should be considered. PVE is a safe and effective procedure for redirecting blood flow toward the portion of the liver which will remain following surgery. Hypertrophy is induced in these segments of the liver while the embolized portion of the liver undergoes atrophy.[108]

Liver Transplantation

Liver transplantation is an attractive, potentially curative therapeutic option for patients with early HCC.[91] It removes both detectable and undetectable tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small FLR. In a landmark study published in 1996, Mazzaferro et al. showed that 4-year overall and recurrence-free survival rates of 85% and 92%, respectively, were obtained when liver transplantation was restricted to a subgroup of patients with unresectable HCC meeting specific selection criteria (ie, Milan criteria),[109] and these results have been supported by more recent studies in which patient selection for liver transplantation was based on these criteria.[110] These selection criteria were adopted by UNOS (and include radiologic evidence of a single tumor ≤ 5 cm in diameter, or 2-3 tumors ≤ 3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease)[111] because they identify a subgroup of patients with HCC for whom liver transplantation results are similar to those in patients who underwent liver transplantation for end-stage cirrhosis without HCC.

The UNOS criteria also specify that patients eligible for liver transplantation should not be candidates for liver resection.[111] Therefore, liver transplantation has been generally considered to be the initial treatment of choice for patients with early-stage HCC and moderate to severe cirrhosis (ie, patients with Child-Pugh class B and C scores), with partial hepatectomy generally accepted as the best option for the first-line treatment of patients with early-stage HCC and Child-Pugh class A scores when tumor location is amenable to resection. However, there are no studies comparing the effectiveness of liver resection and liver transplantation for the latter group of patients; hence, the optimal initial strategy for this population is

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controversial.[112-115] The consensus of the NCCN panel is that initial treatment with either partial hepatectomy or transplantation can be considered for patients with liver function characterized by a Child-Pugh class A score who fit UNOS criteria. In addition, patients must have operable disease on the basis of performance status and comorbidity (see HCC-B).[116]

The MELD score as a measure of liver function (see section Initial Workup) is also used as measure of pre-transplant mortality. In 2002 it was adopted by UNOS to provide an estimate of risk of death within 3 months for patients on the waiting list for cadaveric liver transplant. According to the current UNOS policy, patients with T2 HCC tumors (defined by UNOS as 1 nodule 2-5 cm or 2 or 3 nodules all less than 3 cm) receive an additional 22 priority MELD points (also called a "MELD-exception").[62,111] In a retrospective analysis of data provided by UNOS of 15,906 patients undergoing first-time liver transplantation during 1997-2002 and 19,404 patients undergoing the procedure during 2002-2007, 4.6% of liver transplant recipients had HCC compared with 26% in 2002-2007, with most of patients in the latter group receiving an "HCC MELD exception".[117] In 2002-2007, patients with an "HCC MELD – exception" had similar survival to patients without HCC. Important predictors of poor posttransplantation survival for patients with HCC were MELD score ≥20, and serum AFP level ≥ 455 ng/mL,[117] although the reliability of the MELD score as a measure of posttransplantation mortality is controversial. Survival was also significantly lower for the subgroup of patients with HCC tumors in the size range of 3-5 cm.

Expansion of the Milan/UNOS criteria to provide patients who have marginally larger HCC tumors with liver transplant eligibility is an active area of debate.[4,110,118,119] An expanded set of criteria including patients with a single HCC tumor ≤ 6.5 cm, with a maximum of 3 total tumors with no tumor > 4.5 cm (and cumulative tumor size <8 cm) as liver transplant candidates has been proposed by a group at the University of California at San Francisco (UCSF).[120] Studies evaluating the posttransplantation survival of patients who exceed the Milan criteria but meet the UCSF criteria show wide variation in 5-year survival rates (range of 38% to 93%).[118,119,121-123] An argument in favor of expanding the Milan/UNOS criteria includes the general recognition that many patients with HCC tumors exceeding the Milan criteria can be cured by liver transplant.[119] Opponents of an expansion of the Milan/UNOS criteria cite the increased risk of vascular invasion and tumor recurrence associated with larger tumors and higher HCC stage, and the shortage of donor organs.[110,118,121] Some support for the former objection comes from a large retrospective analysis of the UNOS database showing significantly lower survival for the subgroup of patients with tumors 3-5 cm in size compared with those who had smaller tumors.[117]

Bridge therapy

A number of studies have investigated the role of locoregional treatment of HCC as a bridge to liver transplantation in patients on a waiting list for such a procedure.[4,124] These studies include use of radiofrequency ablation (RFA),[125,126] chemoembolization,[127] and sorafenib[128] as "bridge" therapies. However, the small size of these studies and the heterogeneous nature of the study populations, as well as the absence of randomized clinical trials evaluating the utility of bridge therapy for reducing the liver transplantation waiting list drop-out rate, limit the conclusions that can be drawn.[129,130] Nevertheless, use of bridge therapy in this setting is increasing, and it is administered at some NCCN centers.

Local Regional Therapy

Local approaches to the treatment of HCC are directed toward inducing selective tumor necrosis, and fall into one of 2 categories: ablation or embolization. The effectiveness of local regional approaches in the treatment of HCC has not been established to be comparable to that of

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liver resection or transplantation.[100, 131] The consensus of the panel is that these methods should not be used in place of liver resection or liver transplantation for patients who meet surgical selection criteria (see HCC-5; HCC-6; HCC-C).

Ablation

Induction of HCC tumor necrosis can be achieved by direct exposure of the tumor to a particular chemical substance (eg, ethanol, acetic acid) or an alteration in temperature (radiofrequency ablation [RFA], microwave ablation, cryoablation).[30,91] Any ablative therapy can be performed by laparoscopic, percutaneous or open approaches. The 2 most commonly used methods of ablation therapy are RFA and percutaneous ethanol injection (PEI) therapy. Selection criteria for ablative therapy include patients with local disease only characterized as being completely amenable to ablative therapy according to the size and location of the tumor(s). The complication rate associated with ablative therapy in the treatment of HCC has been reported to be relatively low. For example, in a randomized controlled trial comparing treatment of patients with HCC using RFA or percutaneous ethanol injection (PEI), the major complication and mortality rates were 4.8% and 0%, respectively.[132]

The extent of tumor necrosis induced by ablative therapy is typically approximated by dynamic CT/MRI at a specified time following treatment (as opposed to a histologic assessment).[11,133] The absence of contrast uptake within the tumor as compared with imaging findings prior to treatment is interpreted as indicative of no residual vascularity and complete tumor necrosis. Nevertheless, a number of factors are involved in measuring the effectiveness of locoregional therapies, and the criteria for evaluating tumor response are evolving.[124,134-138]

Studies have shown that ablative therapy is most effective on smaller HCC tumors.[125,126,139,140] The consensus of the panel is that ablation therapy alone for the treatment of HCC performs optimally when tumors are ≤ 3 cm, and that lesions between 3 and 5 cm may be treated using a combination of ablation and embolization methods (see sections on Transarterial Embolization/Chemoembolization, and Combinations of local therapies). Furthermore, the panel considers percutaneous ablation to be a very good option for well selected patients with small tumors who are not candidates for surgery.

In a retrospective analysis, 40 mostly Child-Pugh class A or B patients with HCC liver nodules were treated with RFA, percutaneous ethanol injection (PEI), or a combination of both methods while awaiting liver transplantation. The results of this study showed complete and partial necrosis rates of 46.7% and 53.3%, respectively, when RFA therapy was used, and 23.1% and 46.1%, respectively, following PEI therapy with 30.8% of tumors showing no evidence of necrosis with PEI therapy. The overall rate of complete necrosis was 53.1% for HCC tumors < 3 cm and 14.3% for tumors ≥ 3 cm (P=0.033). However, this rate increased to 61.9% when the subset of tumors <3 cm treated by RFA was evaluated.[125] The study of Mazzaferro et al. provides additional support for the conclusion that tumor size is a critical factor in determining the effectiveness of ablation therapy in the treatment of HCC.[126] In this prospective study of 50 consecutive patients with liver cirrhosis undergoing RFA while awaiting liver transplantation, the rate of complete tumor necrosis was 55% overall and 63% when only tumors ≤ 3 cm were considered.

The effectiveness of RFA and PEI therapy in the treatment of Child-Pugh class A patients with HCC has also been compared in a number of randomized controlled trials.[141-143] RFA was shown to be superior to PEI with respect to complete response rate (65.7% vs. 36.2% for RFA vs. PEI [P=0.0005]),[142] and rate of local recurrence.[141,143] In addition, in one study patients in the RFA treatment arm were shown to require fewer treatment sessions.[143] However, the benefit of RFA compared with PEI on overall survival was demonstrated in 2 of these

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studies,[141,143] but not in a third which showed no significant overall survival differences between the 2 treatment arms.[142] RFA has also been compared with liver resection in a prospective randomized controlled study.[133] No differences in recurrence-free survival or overall survival were found when treatment arms were compared, although limitations of the study include the small number of patients and the lack of a noninferiority design.

There is a wide range of reported rates of local recurrence following ablative therapy for HCC which may reflect differences in patient selection criteria and treatment protocols. For example, in the study of Shiina et al. estimated 4-year recurrence rates were 70% and 85% in the RFA and PEI arms, respectively, for patients with 3 or fewer small tumors (≤3 cm).[143] However, another study found <3% of patients with single HCC tumors ≤ 2 cm who underwent repeated applications of RFA therapy to have a recurrence of disease at 31 months.[140]

Results of some long-term studies show survival rates of over 50% at 5 years for patients with successful HCC tumor necrosis following ablative therapy.[144,145] Nevertheless reported rates of overall survival vary widely across studies of patients with HCC treated with ablation.[133,141-146] This is likely to reflect differences in specific disease characteristics (eg, size and number of tumors) and, perhaps more importantly, the extent of underlying liver function in the patient populations studied.[145,146]

With respect to tumor location, lesions in certain portions of the liver (eg, dome) may not be accessible to a percutaneous approach, ablative treatment of tumors associated with the liver capsule may cause organ rupture, and major vessels in close proximity to the tumor can absorb large amounts of heat when methods such as radiofrequency ablation is performed.[11] The panel emphasizes that caution should be exercised when ablating lesions near major blood vessels, major bile ducts, and other intra-abdominal organs (see HCC-C).

Embolization

Arterial embolization therapy (chemoembolization, bland embolization, radioembolization) in the treatment of HCC is based on selective catheter-based infusion of particles targeted to the arterial branch of the hepatic artery feeding the portion of the liver in which the tumor is located.[147] Embolization therapy is made possible by the dual blood supply to the liver; whereas the majority of the blood supply to normal liver tissue comes from the portal vein, blood flow to liver tumors is mainly from the hepatic artery.[35] Furthermore, HCC tumors are characterized by hypervascularity resulting in increased blood flow to tumor relative to normal liver tissue.

Prior to performance of the embolization procedure, a careful evaluation of the arterial anatomy of the liver of each patient is necessary. Because non-target embolization of the liver can result in serious injury, arterial embolization is limited to a segment, subsegment, or lobe of the liver. All HCC tumors, irrespective of location in the liver, may be amenable to embolization therapy provided that the arterial blood supply to the tumor may be isolated.[148-151] Tumor necrosis induced by embolic therapy is typically estimated by the extent to which contrast uptake on dynamic CT/MRI is diminished at some specified point following treatment when compared with pre-treatment imaging findings. Nevertheless, a number of factors are involved in measuring the effectiveness of locoregional therapies, and the criteria for evaluating tumor response are evolving.[124,134-138]

General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of extrahepatic disease (see HCC-5; HCC-6; HCC-C). An evaluation of performance status and liver function (ie, Child-Pugh score) should also be performed. In addition, more individualized patient selection that is specific to the particular embolization procedure being considered is necessary to avoid

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significant treatment-related toxicity (see sections on Bland embolization and chemoembolization and Radioembolization, below).

The panel recommends that patients with unresectable/inoperable disease who are eligible to undergo embolization therapy and have tumor lesions > 5 cm should be treated using arterial embolic approaches, whereas those patients with lesions 3-5 cm can be considered for combination therapy with ablation and arterial embolization (see HCC-C; section on Combinations of local therapies).

Bland embolization and chemoembolization

The principle of bland embolization, also called transarterial embolization (TAE), and transarterial chemoembolization (TACE) is a reduction in blood flow to the tumor, resulting in tumor ischemia followed by tumor necrosis. Gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres have been used to block arterial flow.[149,152,153] TACE is distinguished from TAE by the catheter-based administration of a concentrated dose of chemotherapy (eg, doxorubicin or cisplatin) combined with an emulsifying agent, usually administered prior to the embolic particles.[152] Results of 2 randomized clinical trials have shown a survival benefit for use of TACE therapy vs. supportive care in patients with unresectable HCC.[151,154] In one study patients were randomly assigned to TAE, TACE, and supportive care treatment arms.[151] One- and 2-year survival rates were 82%, and 63%, 75% and 50%, and 63% and 27% for patients in the TACE, TAE, and supportive care arms, respectively. The majority of the patients in the study had liver function classified as Child-Pugh A, a performance status of 0 and main tumor nodule size of about 5 cm. For the group of evaluable patients receiving either TACE or TAE therapy, partial and complete response rates sustained for at least 6 months of approximately 30% and 1%, respectively, were observed. Limitations of this study include its early termination, and lack of power to detect a difference between TACE and TAE treatment arms.[149]

Many of the clinical studies evaluating the effectiveness of TAE and/or TACE therapies in the treatment of patients with HCC are confounded by use of a wide range of treatment strategies, including type of embolic particles, type of chemotherapy and type of emulsifying agent (for studies involving TACE), and number of treatment sessions.[149,153] In a recent retrospective analysis of patients undergoing TAE therapy for the treatment of HCC in which a standardized technique was used, 1-, 2- and 3-year overall survival rates of 66%, 46%, and 33%, respectively, were observed. These 1-, 2-, and 3-year survival rates were increased to 84%, 66%, and 51%, respectively, when only the subgroup of patients without extrahepatic spread or portal vein involvement by tumor was considered.[149]

In the study of Maluccio et al., predictors of poor prognosis on multivariate analysis following TAE therapy were tumor size ≥5 cm, 5 or more tumors and extrahepatic disease; portal vein occlusion was not found to be an independent predictor of survival.[149] However, there is evidence showing portal vein obstruction,[155,156] liver function categorized as Child-Pugh class C,[156] and total serum bilirubin level of > 3 mg/mL[157] to be significant predictors of poor prognosis in patients treated with TACE therapy. Hence, the panel considers main portal vein thrombosis to be a contraindication for TACE therapy, and recommends against its use in those with liver function characterized as Child-Pugh class C. Because transarterial embolization therapy can increase the risk of hepatic necrosis and liver abscess formation in patients with biliary obstruction,[152] the panel recommends that a total bilirubin level > 3 mg/mL should be considered as a relative contraindication for TACE or TAE therapy unless segmental injections can be performed (see HCC-C). Furthermore, patients with previous biliary-enteric bypass have an increased risk of intrahepatic abscess following TACE therapy.[152]

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Complications of TAE and TACE therapy can include acute portal vein thrombosis, cholecystitis, and bone marrow suppression, in addition to other toxicities,[30,158] although the reported frequencies of serious adverse events vary across studies. A post-embolization syndrome involving fever, abdominal pain, and intestinal ileus has been reported to be relatively common in patients undergoing these procedures.[30,158] Reported rates of TAE and TACE treatment-associated mortality for are usually < 5%.[30,149,151,158]

A recent multicenter, randomized study comparing doxorubicin-eluting embolic beads to conventional TACE with doxorubicin in 212 patients with Child-Pugh A/B cirrhosis and localized, unresectable HCC without nodal involvement showed comparable effectiveness for the 2 methods although toxicity was significantly decreased with the former approach.[159]

Radioembolization

Radioembolization is a newer embolization method that provides for the internal delivery of high-dose radiation to the tumor-associated capillary bed.[147,160] This is accomplished through the catheter-based administration of microspheres in which yttrium-90, an emitter of beta radiation, is embedded. This method allows for limited penetration of radiation, thereby sparing the normal liver tissue. The microspheres are available in 2 formulations: TheraSpheres (glass microspheres) and SIR-Spheres (resin microspheres). Although radioembolization, like TAE and TACE, involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia.[150]

A partial response rate of 42.2% was observed in phase 2 study of 108 patients with unresectable HCC with and without portal vein thrombosis treated with radioembolization therapy and followed for up to 6 months.[150] Grade 3/4 adverse events were more common in patients with main portal vein thrombosis. However, patients with branch portal vein thrombosis experienced a similar frequency of adverse events related to elevated bilirubin levels as patients without portal vein thrombosis. Results from a recent single-center, prospective longitudinal cohort study of 291 patients with HCC treated with radioembolization therapy showed a significant difference in median survival times based on liver function level (Child-Pugh A [17.2 months]; Child-Pugh B [7.7 months]; P=0.002).[161] Median survival for patients with disease characterized by Child-Pugh class B liver function and portal vein thrombosis was 5.6 months. Reported complications of radioembolization therapy include cholecystitis/bilirubin toxicity and abscess formation.[150,161,162] Randomized controlled studies of the use of radioembolization therapy in the treatment of patients with HCC are needed.

Combinations of local therapies

Recently, a number of studies have evaluated the effectiveness of using a combination of local therapies in the treatment of patients with unresectable/inoperable HCC. For example, the principle behind the combination of RFA and transarterial embolization is that the focused heat delivery of RFA may be enhanced by vessel occlusion through transarterial embolization since blood circulation inside the tumor may interfere with the transfer of heat to the tumor.

A retrospective review of selected patients with a single HCC tumor up to 7 cm treated with either the combination of TAE and ablation or liver resection showed 1-, 3-, and 5-year actuarial survival rates of 97%, 77%, and 56% for patients receiving combination therapy and 81%, 70%, and 58% for the patients undergoing surgery.[148] In another study of similar design the 1-, 3-, and 5-year survival rates of patients with tumors meeting UNOS criteria with respect to number and size were 98%, 94%, and 75% for the combination group and 97%, 93%, and 81% for the surgery group.[105]

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The consensus of the panel is that patients with 3-5 cm HCC tumors who are not eligible for liver resection or transplantation may be treated with a combination of RFA and embolization.

Conformal or stereotactic radiation therapy

External-beam radiotherapy (3-D conformal or stereotactic) allows focal administration of high dose radiation to HCC tumors while sparing surrounding liver tissue, thereby limiting the risk of radiation-induced liver damage in patients with unresectable/inoperable liver disease.[163]

Limited data support the use of conformal or stereotactic radiation therapy for patients with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation, and those with local disease only who are not operable due to performance status or comorbidity[164] (see HCC-5; HCC-6). In these settings, it is listed as a category 2B treatment option. It is not included in the Guidelines as an option for patients with metastatic disease (see HCC-6).

Systemic therapy

The majority of patients diagnosed with HCC have advanced disease, and many are not eligible for potentially curative therapies. Furthermore, with the wide range of ablative and embolization techniques available to treat patients with unresectable HCC confined to the liver, it has often been only those patient with very advanced disease who are referred for systemic therapy

Clinical studies evaluating the use of chemotherapy (eg, doxorubicin) in the treatment of patients with advanced HCC have typically reported low response rates to therapy, and evidence for a favorable impact of chemotherapy on overall survival in patients with HCC is lacking.[165-167] The panel recommends that systemic single agent or combination chemotherapy, intra-arterial chemotherapy, as well as the combination of chemotherapy and radiation therapy be given to patients with unresectable HCC only in the context of a clinical trial (see HCC-5).

Sorafenib, an oral multikinase inhibitor which suppresses tumor cell proliferation and angiogenesis, has been evaluated in one phase 2 trial and two randomized, placebo-controlled phase 3 trials for the treatment of patients with advanced or metastatic hepatocellular carcinoma.[90,124,153,168-170,177]

In the phase 3 Sorafenib in Advanced Hepatocellular Carcinoma (SHARP) trial, 602 patients with advanced HCC were randomly assigned to sorafenib or best supportive care. In this study, advanced HCC was defined as patients not eligible for or those who had disease progression after surgical or locoregional therapies.[168] Approximately 70% of patients in the study had macroscopic vascular invasion, extrahepatic spread or both. Nevertheless, the majority of the patients had preserved liver function (ie, ≥ 95% of patients classified as Child-Pugh A) and good performance status (ie, > 90% of patients had ECOG performance status of 0 or 1) in order to limit confounding causes of death. Disease etiology for the enrolled patients was varied with hepatitis C, alcohol, and hepatitis B determined to be the cause of HCC in 29%, 26%, and 19% of patients, respectively. Median overall survival was significantly longer in the sorafenib arm (10.7 months in the sorafenib arm vs. 7.9 months in the placebo group; hazard ratio=0.69; 95% CI, 0.55 to 0.87; P<0.001).

In the Asia-Pacific study, another phase 3 trial with a similar design to the SHARP study, 226 patients were randomly assigned to sorafenib or placebo arms (150 and 76 in sorafenib and placebo arms, respectively).[169] Although inclusion/exclusion criteria were similar in the Asia-Pacific and SHARP trials as was the percentage of patients with Child-Pugh A liver function (97%), there were significant differences in patient and disease characteristics between the 2 trials. Only Asian patients were enrolled in the Asia-Pacific study and these patients were more likely to be younger, to have hepatitis B-related disease (ie, over 70%), symptomatic disease, and a higher number of tumor sites than

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patients in the SHARP study. The hazard ratio for the sorafenib arm compared with the placebo arm (0.68; CI, 0.50-0.93; P=0.014) was nearly identical to that reported for the SHARP study, although median overall survival was lower in both treatment and placebo groups in the Asia-Pacific study (6.5 months vs. 4.2 months).

Using data from the SHARP trial, a number of analyses have been performed to investigate the efficacy of sorafenib in particular patient subgroups. Results of these analyses suggest that sorafenib has a survival benefit in patients with ECOG performance status of 1-2,[171] and those with alcohol-related,[172] and hepatitis C viral-related HCC.[173] Sorafenib was well tolerated in both randomized clinical trials. Adverse sorafenib-related events in the SHARP trial included diarrhea, weight loss, and hand-foot skin reaction.[168]

Data on the efficacy of sorafenib in patients with Child-Pugh class B liver function are limited since almost all patients in the randomized trials were characterized as having preserved liver function (Child-Pugh class A).[177] However, approximately 28% of the 137 patients enrolled in a phase 2 trial evaluating sorafenib in the treatment of HCC had Child-Pugh class B liver function.[170] A subgroup analysis of data from this study showed lower overall survival for patients in the Child-Pugh class B group compared with those in the Child-Pugh class A group (14 weeks vs. 41 weeks).[174] In addition, liver function impairment may impact sorafenib dosing and toxicity. Abou-Alfa et al. found higher levels of hyperbilirubinemia, encephalopathy, and ascites in the group with Child-Pugh class B liver function, although it is difficult to separate the extent to which treatment drug and underlying liver function contributed to these disease manifestations.[90,174] A pharmacokinetic and phase I study of sorafenib in patients with hepatic and renal dysfunction showed an association between elevated bilirubin levels and possible hepatic toxicity.[175] Furthermore, a grade 3/4 toxicity rate of 34% was seen in a study of sorafenib in a poor-risk patient population characterized by Child-Pugh class B or higher liver function and extensive portal vein thrombosis in 26% and 50% of patients, respectively.[176] Finally, it is important to mention that validated criteria to evaluate tumor response to sorafenib are needed since true objective responses are rare.[177]

Based on the results of these trials, sorafenib is recommended as a category 1 option (for selected patients with Child-Pugh class A liver function) and as a category 2A option (for selected patients with Child-Pugh class B liver function) with disease characterized as: unresectable and extensive/not suitable for liver transplantation; local disease only in patients who are not operable due to performance status or comorbidity; or metastatic. Nevertheless, the panel considers the data on safety and dosing of sorafenib to be inadequate in patients with liver function characterized as Child-Pugh class B, and recommends extreme caution when considering use of sorafenib in patients with elevated bilirubin levels (see HCC-5; HCC-6).

Best supportive care

The panel recommends that best supportive care measures be administered to patients with unresectable/inoperable disease who are not candidates for other therapies (see HCC-5; HCC-6).

Surveillance

Although data on the role of surveillance in patients with resected HCC are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends high-quality cross-sectional imaging every 3 to 6 months for 2 years, then annually. AFP levels, if initially elevated, should be measured every 3 months for 2 years, then every 6 months. Re-evaluation according to the initial work-up should be considered in the event of disease progression (see HCC-4; HCC-5).

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Gallbladder Cancer

Risk Factors

Risk factors for gallbladder cancer, of which cholelithiasis is the most prevalent, are associated with the presence of chronic inflammation. Calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been associated with gallbladder cancer.[178,179]

Diagnosis and Initial Workup

Gallbladder cancer is often diagnosed at an advanced stage due to the aggressive nature of the tumor which can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation which mimics that of biliary colic or chronic cholecystitis.[178] Hence, it is not uncommon for a diagnosis of gallbladder cancer to be an incidental finding at surgery or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis. (See section on Management of Gallbladder Cancer for recommendations on surgical assessment and postoperative workup of patients diagnosed at or following the time of surgery.)

Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound or jaundice. The initial workup of these patients should include liver function tests, and an assessment of hepatic reserve. CEA and CA 19-9 testing can be considered although these markers are not specific for gallbladder cancer.[178] High-quality imaging is recommended to evaluate tumor penetration within the wall of the gallbladder, to detect direct tumor invasion of other organs/biliary system, to determine whether major vascular invasion is present, and to evaluate for the presence of nodal and distant metastases.[37] In addition, chest imaging should be performed. Staging laparoscopy should be considered if no distant metastases are found on imaging since the risk of peritoneal metastases is high in this disease.[179,180] For patients presenting with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor.[37] Noninvasive magnetic resonance cholangiography (MRCP) is preferred over endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), unless a therapeutic intervention is planned. Although the role of positron emission tomography (PET) scanning has not been established in the evaluation of patients with gallbladder cancer, emerging evidence indicates that it is useful for detecting the presence of distant metastatic disease in patients with otherwise potentially resectable disease.[181,182]

Pathology and Staging

Approximately 80% of gallbladder cancers are adenocarcinomas.[178,183] Gallbladder cancer is often characterized by early spread to lymph tissue and the bloodstream.[178,184]

The AJCC TNM staging criteria for gallbladder cancer are shown in Table 2. A review of about 2500 patients with gallbladder cancer from hospital cancer registries throughout the U.S. showed tumor stage to be closely associated with survival; 5-year survival rates were 60%, 39%, 15%, 5% and 1% for patients with stage 0 - stage IV disease, respectively.[185] Results from a recent retrospective single-center analysis showed a 10.3 month median survival for the overall population of patients diagnosed with gallbladder cancer.[183] Median survival was 12.0 months and 5.8 months for those with stage Ia-III and stage IV disease, respectively.[183]

Management of Gallbladder Cancer

Surgery remains the only curative modality for gallbladder cancer. In a retrospective review covering the period of 1995-2005, 123 patients of 435 patients treated for gallbladder cancer at a single center underwent curative resection, and 47% were diagnosed with gallbladder cancer as an incidental finding during laparoscopic cholecystectomy.[183]

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Although the initial management of patients discovered to have gallbladder cancer at the time of cholecystectomy or on pathologic review following cholecystectomy differs from the initial management of patients with a diagnosis of gallbladder cancer prior to surgery (see below), the surgical approach for patients found to have resectable gallbladder cancer is the same, with the exception that the gallbladder has been removed in the case of an incidental finding of cancer on pathologic review; In all cases, surgery to treat gallbladder cancer should be performed by a surgeon who is prepared to do a cancer operation. Factors determining gallbladder tumor resectability include the stage of the tumor according to AJCC TNM staging criteria (see Table 2) as well as tumor location.[178] All patients should undergo CT/MRI imaging and chest imaging prior to surgery to evaluate for the presence of distant metastases. Furthermore, since staging laparoscopy has a high yield in this disease, it should be considered before laparotomy for a potentially curative resection of gallbladder cancer.

An analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990-2002 showed that while major hepatectomy and common bile duct excision significantly increased the surgical complication rate, they were not independently associated with survival, leading the authors to conclude that these procedures should be performed only when necessary to remove disease.[186] Another study which retrospectively evaluated data from 115 patients who underwent re-resection for incidental gallbladder cancer showed achievement of R0 resection margins to strongly correlate with long-term survival.[187] The panel recommends that those patients deemed as having resectable gallbladder cancer undergo treatment with cholecystectomy, en bloc hepatic resection, and lymphadenectomy with or without bile duct excision.[178,188] Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal regions. Nodal disease outside of this area (most commonly, celiac, retropancreatic or in the interaortocaval groove) should be considered unresectable.

In a retrospective analysis of patients with gallbladder cancer treated at a single institution, 74% of patients who underwent surgical re-exploration following an incidental diagnosis of gallbladder cancer following laparoscopic cholecystectomy were found to have residual cancer.[183] In the event that gallbladder cancer is found at the time of surgery, the panel recommends intraoperative staging, and procurement of a frozen section of gallbladder. An extended cholecystectomy, as described above, can be considered depending on the expertise of the surgeon and the establishment of disease resectability. Among patients with an incidental finding of gallbladder cancer on pathologic review, those with T1a lesions may be observed if the tumor margins are negative since these tumors have not penetrated the muscle layer.[179] For patients with T1b or greater lesions, surgery is recommended for resectable lesions, after CT/MRI, chest imaging, and laparoscopy confirm the absence of metastatic disease. This recommendation is supported by findings of residual disease within the liver in a high percentage of these patients and an association between increasing risk of metastasis to locoregional lymph nodes and increasing T stage.[187] Therefore, if resectable, patients should undergo hepatic resection and lymphadenectomy with or without bile duct excision.[189] The consensus of the panel is that surgery should not be performed in situations where the resectability of disease has not been established nor should it be performed by surgeons untrained in this operation (see GALL-1). There is evidence that a delayed open laparotomy due to referral following an incidental diagnosis of gallbladder is not associated with a survival deficit compared with immediate resection.[190,191] Nevertheless, given the option, upfront surgical resection of gallbladder cancer by a surgeon experienced in this procedure is the approach preferred by the panel. Although the optimal adjuvant treatment strategy for patients with resected

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gallbladder cancer has not been determined, options include consideration of fluoropyrimidine chemoradiation (except T1b,N0) and fluoropyrimidine or gemcitabine chemotherapy (see GALL-3 and section on Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma).

For patients with unresectable disease after preoperative evaluation, a biopsy should be performed to confirm the diagnosis. In patients with unresectable or metastatic gallbladder cancer and jaundice, biliary drainage is an appropriate palliative procedure and should be done before instituting chemotherapy if technically feasible (see GALL-2). Biliary drainage followed by chemotherapy can result in improved quality of life.[192] Other options for these patients include chemoradiation (in patients with localized disease) and chemotherapy (See section on Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma), participation in a clinical trial or best supportive care.

Surveillance

There are no data to support aggressive surveillance following resection of gallbladder cancer; determination of appropriate follow-up schedule/imaging should include a careful patient/physician discussion. It is recommended that follow-up of patients undergoing an extended cholecystectomy for gallbladder cancer should include consideration of imaging studies every 6 months for 2 years. Re-evaluation according to the initial work-up should be considered in the event of disease progression (see GALL-3).

Cholangiocarcinomas

The term cholangiocarcinoma encompasses all tumors originating in the epithelium of the bile duct.[193,194] Although cholangiocarcinomas are diagnosed throughout the biliary tree, they are distinguished by anatomic site and typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinomas have also been called “peripheral cholangiocarcinomas” and are located within the hepatic parenchyma (see Figure 1). In these Guidelines, extrahepatic cholangiocarcinomas include hilar cholangiocarcinomas (also called Klatskin tumors) which occur at or near the junction of the right and left hepatic ducts. Therefore, cholangiocarcinomas occurring anywhere within the common hepatic duct, the region of the junction of the right and left hepatic ducts, or the common bile duct (including the intrapancreatic portion of the common bile duct) are classified as extrahepatic (see Figure 1). Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas and hilar cholangiocarcinoma is most common type of extrahepatic cholangiocarcinoma.[195]

Risk Factors

No predisposing factors have been identified in most patients diagnosed with cholangiocarcinoma,[196] although there is evidence that particular risk factors may be associated with the disease in some patients. These risk factors, like those for gallbladder cancer, are associated with the presence of chronic inflammation, and include chronic calculi of the bile duct, choledochal cysts, and liver fluke infections.[194, 197] Unlike gallbladder cancer, however, cholelithiasis is not thought to be closely linked with the etiology of cholangiocarcinoma.[178] Recently, however, intrahepatic cholangiocarcinoma has been associated with hepatitis C viral infection,[198] and this may be responsible for the increased incidence of intrahepatic cholangiocarcinoma recently observed at some centers.[199] Nevertheless, future studies are needed to further explore this putative association.[200]

Diagnosis and Initial Workup

Early stage cholangiocarcinomas are typically asymptomatic. The patient with intrahepatic cholangiocarcinoma is more likely to present

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with nonspecific symptoms such as fever, weight loss, and/or abdominal pain; symptoms of biliary obstruction are uncommon. Alternatively, intrahepatic cholangiocarcinoma may be detected incidentally as an isolated intrahepatic mass on imaging.[37] In contrast, the patient with extrahepatic cholangiocarcinoma is likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.[178]

The initial workup of these patients should include liver function tests. CEA and CA 19-9 testing can be considered although these markers are not specific for cholangiocarcinoma,[178] and are also associated with other malignancies and benign conditions.[201] Early surgical consultation with a multidisciplinary team is recommended as part of the initial workup for assessment of resectability in both types of cholangiocarcinomas (see section on Management of Cholangiocarcinoma).

Delayed contrast CT/MR imaging is recommended as part of the workup of patients with intrahepatic cholangiocarcinoma. Although there are no pathognomonic CT/MR imaging features associated with intrahepatic cholangiocarcinoma, CT/MR imaging is used to help determine tumor resectability by characterizing the primary tumor, its relationship to nearby major vessels and the biliary tree, the presence of satellite lesions and distant metastases in the liver, as well as lymph node involvement, if present.[37] In addition, chest imaging should be performed, and laparoscopy may be done in conjunction with surgery if no distant metastasis is found. The panel emphasized that a multidisciplinary review of imaging studies involving experienced radiologists and surgeons is necessary to stage the disease and determine potential treatment options (ie, resection or other approach).

Delayed contrast CT/MR imaging to assess disease involvement of the liver, major vessels, nearby lymph nodes, and distant sites is also recommended in the initial workup of patients for whom there is a suspicion of extrahepatic cholangiocarcinoma.[37] Since many of these patients present with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor.[37] Because magnetic resonance cholangiography (MRCP) is noninvasive it is considered to be a safer alternative to direct cholangiography; hence, it is preferred over endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), unless a therapeutic intervention is planned. Although the role of positron emission tomography (PET) scanning has not been established in the evaluation of patients with cholangiocarcinoma, emerging evidence indicates that it is useful for detecting the presence of lymph node involvement and distant metastatic disease in patients with otherwise potentially resectable disease.[181,182,202,203]

Pathology and Staging

More than 90% of cholangiocarcinomas are adenocarcinomas.[204] Cholangiocarcinomas can be divided into 3 types depending on macroscopic appearance: mass-forming; periductal; and intraductal.[193,205]

The AJCC has developed staging systems for cholangiocarcinomas (see Table 1 and Table 3), and the AJCC staging system for intrahepatic cholangiocarcinoma is the same one used for the staging of HCC (Table 1). However, this staging system does not include predictive clinicopathologic features that are specific to intrahepatic cholangiocarcinoma.[37] Other more practical staging systems for intrahepatic cholangiocarcinoma have been used.[206,207] The AJCC staging system for extrahepatic cholangiocarcinoma (Table 3) is based on pathologic criteria but it is not useful for determining resectability or predicting outcome.[37] Jarnagin and colleagues have developed a useful preoperative staging system for hilar cholangiocarcinoma that predicts resectability, likelihood of metastatic disease, and survival.[208]

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Management of Cholangiocarcinoma

Intrahepatic Cholangiocarcinoma.

Complete resection is the only potentially curative therapy for patients with intrahepatic cholangiocarcinoma, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis. Surgery involves removal of the involved hepatic lobe or segment along the bile duct in which the tumor is located.[209] Patient selection for surgery is facilitated by careful pre-operative staging which may include laparoscopy to identify patients with unresectable or metastatic disease. There is evidence that an R0 resection is associated with significantly longer survival rates in patients undergoing surgery for intrahepatic cholangiocarcinoma.[210] Five-year survival rates in the range of 20% to 43% have been reported. [210-214]

Although the optimal treatment strategy for patients with resected intrahepatic cholangiocarcinoma has not been determined, patients who have undergone an R0 resection with or without ablation may be followed with observation alone. Adjuvant chemotherapy can be administered if appropriate clinical trials are available.

For patients found to have microscopic positive tumor margins (R1) or residual local disease (R2) after resection, it is essential for a multidisciplinary team to review the available options on a case-by-case basis. Although the optimal treatment strategy has not been determined, options include (1) consideration of additional resection; (2) ablative therapy; (3) fluoropyrimidine chemoradiation; or (4) fluoropyrimidine-based or gemcitabine-based chemotherapy (see INTRA-2). (See section on Chemoradiation/Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma.)

For patients with unresectable disease, the options include (1) clinical trial; (2) fluoropyrimidine-based or gemcitabine-based chemotherapy; (3) fluoropyrimidine chemoradiation; or (4) best supportive care (see INTRA-1). The same primary treatment options are recommended for patients with metastatic disease with the exception of chemoradiation. (See section on Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma.)

Extrahepatic Cholangiocarcinoma

Complete resection is the main curative therapy for patients with extrahepatic cholangiocarcinoma. The surgical procedures for resectable disease are based on the portion of the extrahepatic biliary tree in which the lesion resides. Hilar resection with lymphadenectomy and en bloc liver resection is recommended for lesions in the proximal third or the extrahepatic biliary tree. In this situation, caudate resection is strongly encouraged. The recommendation for concomitant liver resection is supported by retrospective analyses showing an association between partial hepatectomy and improved outcomes.[208, 215] Since this association was maintained when only those patients undergoing an R0 resection were considered, it cannot be solely attributed to the increased likelihood of an R0 resection when concomitant liver resection was performed. Major bile duct excision with lymphadenectomy with frozen section assessment of bile duct margins, and pancreaticoduodenectomy with lymphadenectomy are recommended for lesions in the mid third and distal third of the extrahepatic biliary tree, respectively.[178] Very rare cases of small mid bile duct tumors can be resected with an isolated bile duct resection and lymphadenopathy. Five-year survival rates in the range of 20% to 40% have been reported for patients treated for hilar cholangiocarcinoma[208,216,217] and 37% for bile duct cancers in the distal third of the extrahepatic biliary tree.[193]

Patient selection for surgery is facilitated by careful pre-operative staging which may include surgical exploration and laparoscopy to identify patients with unresectable or metastatic disease. However, the consensus of the panel is that surgery may be performed without a

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biopsy if the index of suspicion is high. The consensus of the panel is that biliary drainage should be considered prior to surgery, although there is controversy regarding the risks and benefits of such an approach.[218,219] Pre-operative biliary drainage is accomplished by ERCP or PTC.

Patients who have undergone an R0 resection and who have negative regional nodes may be followed with observation alone, receive fluoropyrimidine chemoradiation, or fluoropyrimidine or gemcitabine chemotherapy. However, there are limited clinical trial data to define a standard regimen, and patient enrollment in a clinical trial is encouraged. For patients found to have microscopic positive tumor margins (R1), residual local disease (R2), carcinoma in situ, or positive regional lymph nodes after resection, it is essential for a multidisciplinary team to review the available options on a case-by-case basis. Although the optimal treatment strategy has not been determined, options include: (1) fluoropyrimidine chemoradiation (brachytherapy or external beam) followed by additional fluoropyrimidine or gemcitabine chemotherapy; (2) fluoropyrimidine-based or gemcitabine-based chemotherapy for patients with positive regional nodes (see EXTRA-2). Data to support particular chemoradiation and chemotherapy regimens are limited. (See section on Chemoradiation and Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma.)

Liver transplantation is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma.[220,221] This option is only recommended for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. There is retrospective evidence showing selected patients with hilar cholangiocarcinoma receiving preoperative chemoradiation therapy followed by liver transplantation to have significantly improved overall survival compared with patients undergoing resection.[222] Nevertheless, there were substantial differences in the characteristics of patients in the 2 treatment groups in this study. The panel encourages continuation of clinical research in this area.

For distal strictures in which a diagnosis is needed or where palliation is indicated, an ERCP is performed which allows for complete imaging of the duct and stenting of the obstruction. In addition, brushes of the duct can be obtained for pathologic evaluation. Hilar strictures can be managed with a PTC approach. Endoscopic ultrasound may be useful for distal common bile duct cancers for defining a mass or abnormal thickening, which can direct biopsies. Direct visualization of the duct with directed biopsies is the ideal technique for the workup of cholangiocarcinoma.

Patients with unresectable disease should undergo biliary drainage using either surgical bypass or an endoscopic (ie, ERCP) or percutaneous approach (ie, PTC), most often involving biliary stent placement.[178,223-225] A biopsy is also recommended to confirm diagnosis before initiation of further treatment. Additional treatment options include (1) a clinical trial; (2) fluoropyrimidine chemoradiation; (3) fluoropyrimidine-based or gemcitabine-based chemotherapy (4) best supportive care (see EXTRA-1). Data to support particular chemoradiation and chemotherapy regimens are limited. (See section on Chemoradiation and Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma, below).

Those with metastatic disease should undergo biliary drainage by stent placement using an endoscopic or percutaneous approach. A biopsy is also recommended to confirm diagnosis before initiation of further treatment. Additional treatment options include clinical trial, best supportive care, fluoropyrimidine-based or gemcitabine-based chemotherapy, or best supportive care (see EXTRA-1). Data to support particular chemoradiation and chemotherapy regimens are limited. (See

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section on Chemoradiation and Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma, below).

Photodynamic therapy is a relatively new therapy for the local treatment of cholangiocarcinoma. It is an ablative method involving intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation, and has been used for palliation of cholangiocarcinoma.[226,227] The combination of photodynamic therapy (PDT) with biliary stenting was reported to improve the overall survival of patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.[228,229]

Surveillance

There are no data to support aggressive surveillance in patients undergoing resection of cholangiocarcinoma; determination of appropriate follow-up schedule/imaging should include a careful patient/physician discussion. It is recommended that follow-up of patients undergoing resection of cholangiocarcinoma should include consideration of imaging studies every 6 months for 2 years. Re-evaluation according to the initial work-up should be considered in the event of disease progression (see INTRA-2; EXTRA-2).

Chemoradiation and Chemotherapy for Treatment of Gallbladder Cancer and Cholangiocarcioma

Due to the low incidence of biliary tract cancers (ie, gallbladder cancer and cholangiocarcinomas), most trials evaluating the efficacy and safety of chemotherapeutic agents administered either alone or concurrently with radiation therapy in these cancers, with a few exceptions, represent single institution phase 2 trials. Most of these studies are not randomized, often combine gallbladder cancers with intrahepatic and extrahepatic cholangiocarcinoma, and involve small numbers of patients, making it difficult to draw definitive conclusions. Some of the recommendations included in the Guidelines, particularly those relating to the use of chemoradiation, are primarily based on practice patterns at NCCN member institutions and retrospective studies from single center experiences. Despite the challenges associated with accruing large numbers of patients with biliary tract cancer for randomized phase 3 trials, it is widely recognized that efforts should be made to conduct such studies in which the individual disease entities are evaluated separately.[230] Nevertheless, due to the limited data and the heterogenous patient populations in many of the published studies, in most cases, recommendations in these Guidelines on use of chemotherapy or chemoradiation therapy are not specific to the particular type of biliary tract cancer.

Chemotherapy and Chemoradiation in the Adjuvant Setting

The role of adjuvant chemotherapy/chemoradiation in patients with resected biliary cancer is poorly defined.. In a recent retrospective review covering the period of 1995-2005 at a single institution, of the patients treated for biliary tract cancer, only 6.5% of patients received adjuvant chemotherapy alone, 6.5% received adjuvant chemoradiation alone, and 6.5% received both adjuvant chemoradiation and systemic chemotherapy.[183] In another retrospective analysis which used the Surveillance Epidemiology and End Results (SEER) database to investigate patients diagnosed with gallbladder cancer during 1992-2002, only 17% of the 2325 patients in the surgical cohort received adjuvant chemoradiation.[231]

Studies evaluating the use of adjuvant chemotherapy alone in patients with biliary tract cancer are few; hence, there are limited clinical trial data to define a standard regimen or definitive clinical benefit of such therapy. No clear benefit of adjuvant chemotherapy alone was seen in 2 large retrospective analyses of patients with biliary tract cancer,[183,232] although the number of patients who received such therapy was very limited in one study,[183] and chemotherapy did not include newer agents in the latter study which covered the period from1988-1997.[232] A phase

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3 trial evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer.[233] About 50% of the eligible patients in this study had a diagnosis of either gallbladder cancer or cholangiocarcinoma. Patients were randomly assigned to adjuvant chemotherapy with 5-fluorouracil (5-FU)/mitomycin C or to a control arm. Subgroup analyses showed a significantly better 5-year survival in the chemotherapy group for patients with gallbladder cancer although no significant differences in the 2 treatment arms were observed when the subgroup of patients with biliary tract cancer was considered. A retrospective analysis of 177 patients with resected biliary tract cancer showed that initial recurrence involving a distant site occurred in 85% and 41% of patients with gallbladder cancer and hilar cholangiocarcinoma, respectively, arguing for the development of active adjuvant systemic therapy in gallbladder cancer.[184] Due to very limited data on use of chemotherapy in the adjuvant setting, specific recommendations for fluoropyrimidine-based or gemcitabine-based chemotherapy listed in the Guidelines primarily represent an extrapolation from studies of patients with advanced disease (see GALL-3; INTRA-2; EXTRA-2).

A primary limitation for cure in patients with biliary tract cancer following surgery is local failure, thereby providing an important justification for use of adjuvant radiation therapy. Useful reviews on the use of radiation therapy in biliary tract cancers are available and include specific citations to a number of relevant studies.[234-236] In a retrospective study of 2325 patients who had undergone surgery for gallbladder cancer from the SEER database during the period 1992-2002, median survival was 14 months and 8 months in the groups receiving adjuvant chemoradiation versus not, respectively (P<0.0001). The survival benefit of adjuvant chemoradiation was even more pronounced (16 months vs 5 months; P<0.0001) when only the group of patients with positive regional lymph nodes was considered.[231] Retrospective analyses from single center experiences for patients with resected extrahepatic cholangiocarcinoma who received fluoropyrimidine-based chemoradiation therapy also suggested that chemoradiation may offer a local control benefit, although distant failure was commonly observed.[237,238] Results from a recent population-based analysis of patients with locoregional extrahepatic cholangiocarcinoma included in the SEER database covering the period from 1973 to 2005 suggested that while adjuvant radiotherapy was associated with an initial improvement in survival within 1-2 years following surgery, this benefit was no longer evident at long-term (ie, > 5 years) follow-up.[239]

A multivariate Cox proportional hazards model developed to make individualized predictions of survival from the addition of radiation therapy following gallbladder cancer resection, showed that the greatest benefit of radiation therapy was seen in patients with T2 or higher stage tumors and node positive disease.[240] Results of these studies provide support for omitting adjuvant chemoradiation in the post-surgical treatment of patients with gallbladder cancer characterized asT1b, N0 (GALL-3).

Some support for use of adjuvant chemoradiation in the treatment of patients with intrahepatic cholangiocarcinoma comes from a retrospective analysis of patients in the SEER database.[241] In this study, overall survival was significantly improved when patients received chemoradiation in addition to surgery (P=0.014), In a retrospective study of patients with extrahepatic cholangiocarcinoma, no significant survival differences when seen when patients with R0 margins following surgery who did not undergo adjuvant therapy were compared with patients with R1 margins following surgery who received chemoradiation, suggesting that chemoradiation may have a survival benefit in the latter group.[242] In another retrospective analysis of patients with extrahepatic cholangiocarcinoma, the addition of maintenance chemotherapy following adjuvant chemoradiation was found to have a survival benefit (ie, 3-year overall survival of 75.6%

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with addition of maintenance chemotherapy vs. 34.8% with no maintenance chemotherapy; P=0.001).[243] These results provide support for the recommendation of consideration of fluoropyrimidine chemoradiation followed by additional fluoropyrimidine or gemcitabine chemotherapy for patients with extrahepatic cholangiocarcinoma with either positive margins or positive regional lymph nodes (see EXTRA-2).

Most of the collective experience of chemoradiation in biliary tract cancer involves concurrent chemoradiation and 5-FU.[234,235] More recently, concurrent chemoradiation with capecitabine has also been used. [242,244] Concurrent chemoradiation with gemcitabine is it not recommended due to the limited experience and toxicity associated with this treatment.[245]

Chemotherapy and Chemoradiation in the Advanced Setting

The prognosis of patients with advanced biliary tract cancers is poor, and the median survival time for those undergoing supportive care alone is short. [246] Following publication of a recent phase III trial of patients with advanced or metastatic biliary tract cancers, the combination of gemcitabine/cisplatin is considered to be the standard of care as first-line chemotherapy for this population of patients. [247] In that study, the survival of the group receiving the combination of gemcitabine/cisplatin was shown to be significantly increased compared with those in the gemcitabine alone arm. (Further details of this study are discussed below). Many of the other studies addressing this issue are summarized in a recent review.[230]

The survival benefit of chemotherapy in patients with advanced biliary tract cancer was suggested in a trial comparing the regimen of 5-FU/leucovorin/etoposide versus best supportive care.[248] A subsequent phase 3 trial evaluating patients with advanced biliary tract cancer randomly assigned to receive either 5-FU/leucovorin/etoposide or 5-FU/cisplatin/epirubicin did not show one regimen to be significantly superior with respect to overall survival (12.03 months vs. 9.02 months, respectively), although the trial was underpowered to detect such a difference.[249]

A number of other chemotherapy combinations as well as single agents have been evaluated in clinical studies for the treatment of advanced biliary tract cancers.[230] (See Hezel and Zhu[230] and references therein.) Examples of chemotherapy combinations demonstrated in phase 2 trials to have activity in the treatment of advanced biliary tract cancers include: gemcitabine/cisplatin[250-254] gemcitabine/capecitabine[255,256]; gemcitabine/oxaliplatin[257,258]; capecitabine/oxaliplatin[259]; capecitabine/cisplatin[250]; and 5-FU/cisplatin,[260] as well as others. Results of a recent pooled analysis of 104 trials of patients with advanced biliary tract cancers showed that the subgroup of patients receiving a combination of gemcitabine and platinum-based agents had the greatest benefit.[261] Additional support for gemcitabine as an anchor drug for the treatment of advanced biliary tract cancers comes from a retrospective review of 304 patients with advanced biliary tract cancer who received gemcitabine, a cisplatin-based regimen, or a fluoropyrimidine-based regimen.[262] In that study, patients receiving a gemcitabine-based regimen were shown to have a lower risk of death.

Most importantly, the recently published randomized, controlled phase 3 ABC-02 study which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer demonstrated that the combination of gemcitabine and cisplatin improved overall survival and progression-free survival by 30% over gemcitabine alone.[247] Median overall survival was 11.7 months and 8.1 months (hazard ratio=0.64; 95% CI, 0.52-0.80; P<0.001), and median progression-free survival was 8.0 months vs. 5.0 months (hazard ratio=0.63; 95% CI, 0.51-0.77; P<0.001), both in favor of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine/cisplatin, there was no significant

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difference in the rate of neutropenia-associated infections between the 2 arms. Based on the experiences from phase 2 studies and the randomized phase 3 ABC-02 study, the following gemcitabine-based and fluoropyrimidine-based chemotherapy options are recommended for the treatment of advanced biliary tract cancer: combination regimens of gemcitabine/cisplatin; gemcitabine/oxaliplatin; gemcitabine/capecitabine, capecitabine/cisplatin; capecitabine/oxaliplatin; 5-FU/cisplatin; and 5-FU/oxaliplatin, as well as single agent 5-FU, capecitabine, and gemcitabine. The combination of gemcitabine/5-FU is not included due to the increased toxicity and decreased efficacy observed with this regimen[263] when compared with results of studies of the gemcitabine/capecitabine regimen in the setting of advanced biliary tract cancer.[230]

Chemoradiation in the setting of advanced biliary tract cancer can provide control of symptoms due to local tumor effects, and may prolong overall survival, although there are limited clinical trial data to define a standard regimen or definitive benefit. Useful reviews on the use of radiation therapy in biliary tract cancers are available and include specific citations to a number of relevant studies.[234,235] In a retrospective analysis of 37 patients with inoperable extrahepatic cholangiocarcinoma who received chemoradiation, actuarial overall survival at 1 and 2 years was 59% and 22%, respectively, although effective local control was observed in the majority of patients during this time period (actuarial local control rates of 90% and 61% at 1- and 2-years, respectively).[264] The most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers has been 5-FU,[234,235] although capecitabine has been substituted for 5-FU in some studies.[244] The panel recommends that chemotherapy administered concurrently with radiation should be limited to either 5-FU or capecitabine, and that such treatment should be restricted to patients without evidence of metastatic disease. Concurrent chemoradiation with gemcitabine is it not recommended due to the limited experience and toxicity associated with this treatment.

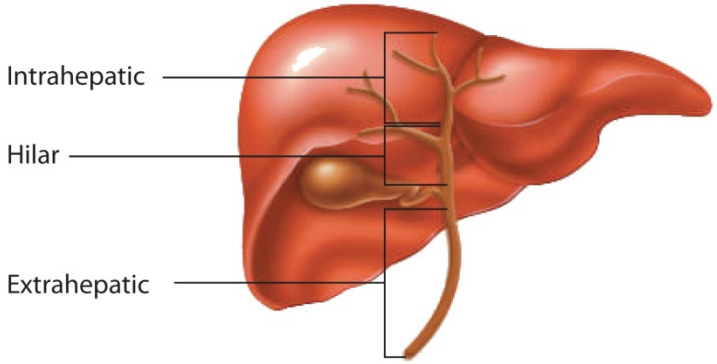
Summary

Although many patients with hepatobiliary cancers are diagnosed at an advanced stage, all patients should be evaluated for treatment. Nevertheless, careful patient selection for treatment and active multidisciplinary cooperation are essential. There are very few high-quality randomized clinical trials of patients with hepatobiliary cancers, and patient participation in prospective clinical trials is the preferred option for the treatment of patients with all stages of disease.

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Figure 1: Classification of Cholangiocarcinoma.



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