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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Hepatobiliary Cancers

Version 2.2011

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NCCN Guidelines™ Version 2.2011 Panel Members

Hepatobiliary Cancers

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[Summary of the Guidelines Updates](#)

Hepatocellular Carcinoma (HCC):

- [HCC Screening \(HCC-1\)](#)
- [Diagnosis of HCC \(HCC-2\)](#)
- [Histologically confirmed HCC, Workup \(HCC-4\)](#)
- [Potentially resectable or transplantable, operable \(HCC-5\)](#)
- [Unresectable \(HCC-6\)](#)
- [Inoperable, local disease, Metastatic disease \(HCC-7\)](#)

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[Principles of Surgery \(HCC-B\)](#)

[Principles of Locoregional Therapy \(HCC-C\)](#)

Gallbladder Cancer:

- [Incidental finding at surgery \(GALL-1\)](#)
- [Incidental finding on pathologic review \(GALL-1\)](#)
- [Mass on imaging \(GALL-2\)](#)
- [Jaundice \(GALL-3\)](#)
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Intrahepatic Cholangiocarcinoma

- [Presentation, Workup, Primary Treatment \(INTRA-1\)](#)
- [Additional Therapy, Surveillance \(INTRA-2\)](#)

Extrahepatic Cholangiocarcinoma

- [Presentation, Workup, Primary Treatment \(EXTRA-1\)](#)
- [Secondary or Adjuvant Treatment, Surveillance \(EXTRA-2\)](#)

[Staging \(ST-1\)](#)

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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](#)

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2011.



The 2.2011 version of the NCCN Hepatobiliary Guidelines represents the addition of the Discussion text to reflect the algorithm changes. [\(MS-1\)](#)

Updates in version 1.2011 of the NCCN Guidelines for Hepatobiliary Cancer from version 2.2010 include:

Global Changes:

The staging tables were updated to reflect the 7th edition (2010) AJCC Staging Manual ([ST-1](#) through [ST-5](#)).

Hepatocellular Carcinoma:

[HCC-1](#)

- Under Patients at risk for HCC: Autoimmune hepatitis was removed
- Footnote d was revised.

[HCC-2](#)

- Page was revised to reflect the updated 2010 American Association for the Study of Liver Diseases (AASLD) Guidelines.

[HCC-4](#)

- Workup; Third bullet: LDH was removed
- Footnote k; first bullet: The following sentence was added, “If sAg, eAg, and/or viral load are positive, patients should be evaluated by hepatology for appropriate antiviral therapy”.

[HCC-5](#)

- Under Treatment for Child-Pugh Class A,B: “Resection or Ablation” changed to “Resection, if feasible (preferred) or Locoregional therapy”.

[HCC-6](#)

- Footnotes “t” and “x” are new to the algorithm.

[HCC-7](#)

- Clinical Presentation: “Inoperable by performance status or comorbidity, local disease only” changed to, “Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only”.

[HCC-B--Principles of Surgery](#)

- Third bullet; First arrow: “Multifocal disease” changed to “Limited and resectable multifocal disease”.

[HCC-C--Principles of Locoregional therapy](#)

- Under Ablation: A new bullet was added regarding the use of sorafenib and post transcatheter arterial chemoembolization (TACE)/ablation therapy.
- Under Embolization: Third bullet was revised.
- A new section was added on stereotactic body radiotherapy (SBRT) and external-beam radiotherapy.

Gallbladder Cancer:

[GALL-1](#) and [GALL-2](#)

- Primary Treatment for Unresectable disease: “Gemcitabine/cisplatin combination therapy” was added as a category 1 recommendation.”

[GALL-3](#)

- Primary Treatment for Unresectable and Metastatic disease: “Gemcitabine/cisplatin combination therapy” was added as a category 1 recommendation.”
- Footnote “f” regarding consult with a multidisciplinary team is new to the algorithm.
- Footnote g: “Consider baseline CA 19-9 after biliary decompression” was added.

Intrahepatic Cholangiocarcinoma:

[INTRA-1](#)

- Workup: “Consider esophagogastroduodenoscopy and colonoscopy” with corresponding footnote “d” were added.
- Primary treatment for Unresectable or Metastatic disease: “Gemcitabine/cisplatin combination therapy” was added as a category 1 recommendation.”

[INTRA-2](#)

- Footnote “h” that states, “R1 or R2 resections should be evaluated by an experienced hepatobiliary surgeon for the uncommon scenario where re-resection may be considered” is new to the algorithm.

Extrahepatic Cholangiocarcinoma:

[EXTRA-1](#)

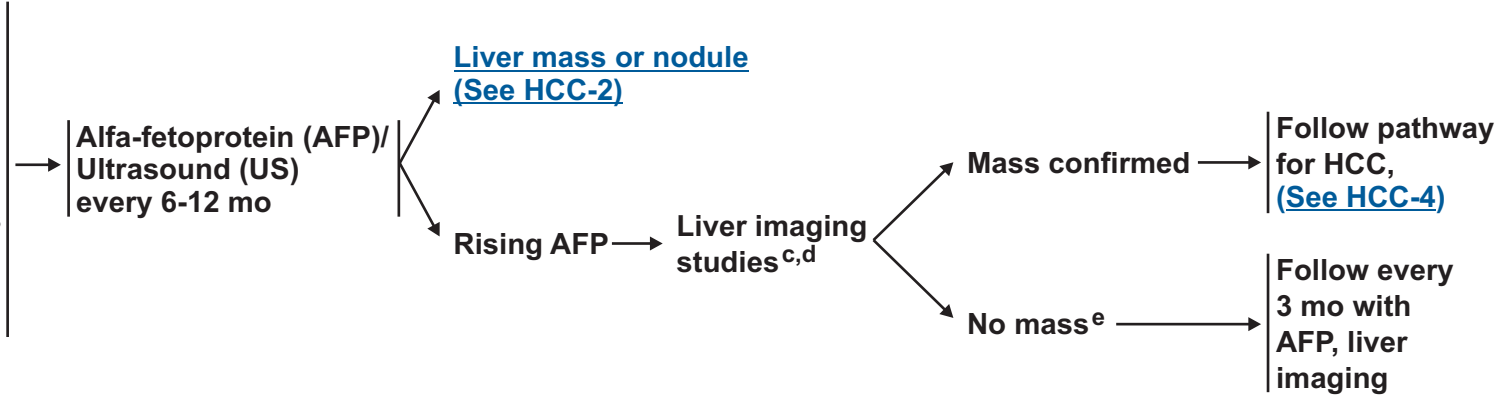
- Primary treatment for Unresectable or Metastatic disease: “Gemcitabine/cisplatin combination therapy” was added as a category 1 recommendation.”



**HEPATOCELLULAR CARCINOMA (HCC)
SCREENING**

Patients at risk for HCC:^a

- **Cirrhosis**
 - ▶ Hepatitis B, C
 - ▶ Alcohol
 - ▶ Genetic hemochromatosis
 - ▶ Non-alcoholic steatohepatitis
 - ▶ Stage 4 primary biliary cirrhosis
 - ▶ Alpha1-antitrypsin deficiency
- **Without cirrhosis**
 - ▶ Hepatitis B carriers^b



^aAdapted with permission from Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010; <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>.

^bAdditional risk factors include patients with, family history of HCC, Asian males ≥ 40 y, Asian females ≥ 50 y, African/North American Blacks with hepatitis B.

^cIf ultrasound negative, CT/MRI should be performed.

^d4-phase liver protocol CT or MRI including late arterial phase and portal venous phase to determine perfusion characteristics, extent and number of lesions, vascular anatomy, and extrahepatic disease. PET/CT is not adequate. (Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010; <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>)

^eRule out germ cell tumor if clinically indicated.

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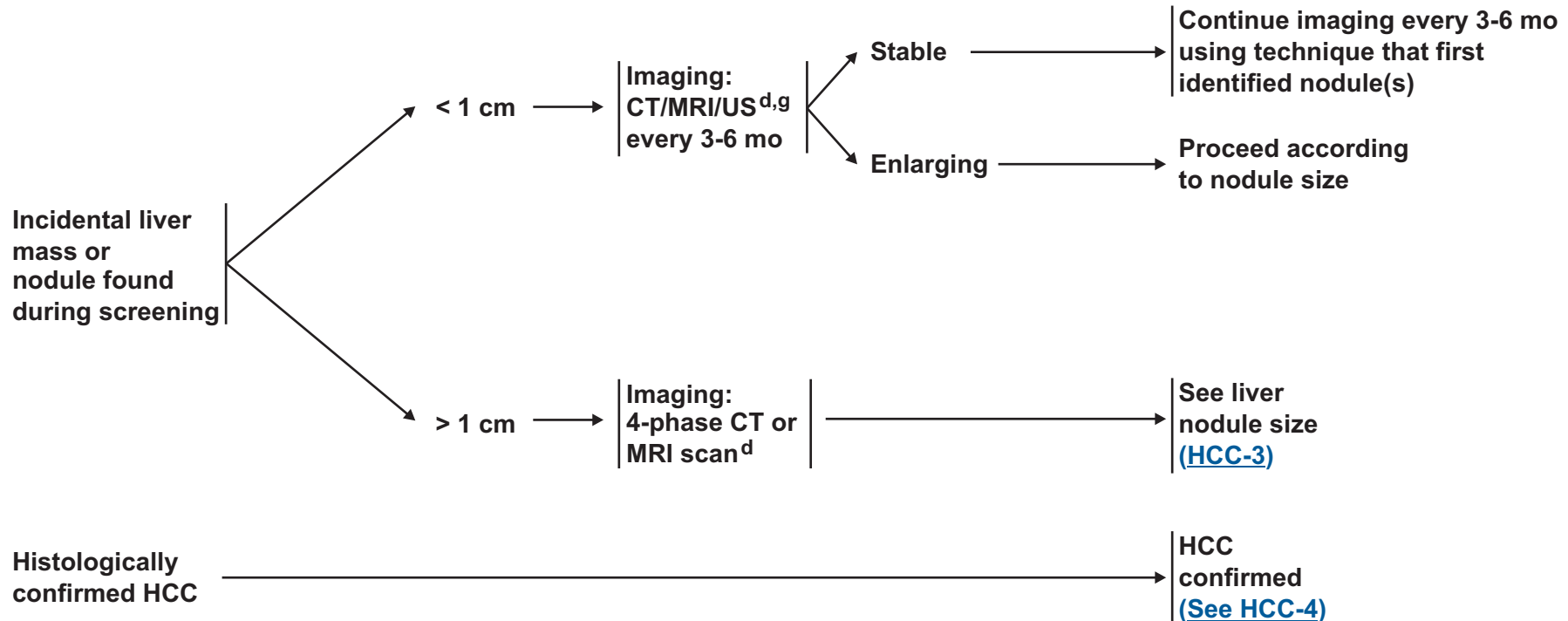
DIAGNOSIS OF HCC^a

**CLINICAL
PRESENTATION^f**

**LIVER
NODULE
SIZE**

**ADDITIONAL
IMAGING**

FINDINGS



^aAdapted with permission from Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010; <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>.

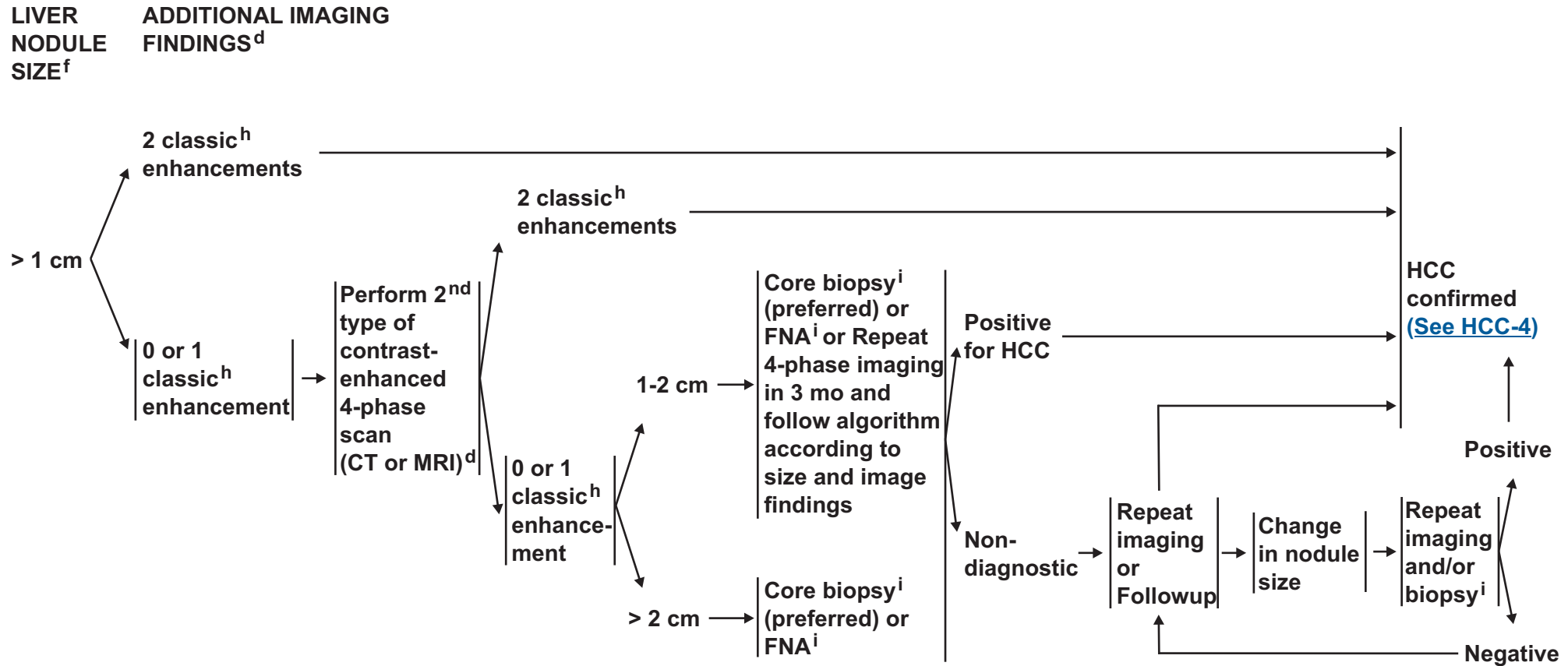
^d4-phase liver protocol CT or MRI including late arterial phase and portal venous phase to determine perfusion characteristics, extent and number of lesions, vascular anatomy, and extrahepatic disease. PET/CT is not adequate. (Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010; <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>)

^fThese guidelines apply to nodules identified in cirrhotic patients. In patients without cirrhosis or known liver disease, biopsy should be strongly considered.

^gContrast enhanced ultrasound where available.

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DIAGNOSIS OF HCC^a



^aAdapted with permission from Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010;1-35 (<http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>).

^d4-phase liver protocol CT or MRI including late arterial phase and portal venous phase to determine perfusion characteristics, extent and number of lesions, vascular anatomy, and extrahepatic disease. PET/CT is not adequate. (Bruix J and Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology July 2010; <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>)

^fThese guidelines apply to nodules identified in cirrhotic patients. In patients without cirrhosis or known liver disease, biopsy should be strongly considered.

^hClassic 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.

ⁱIf transplant is a consideration, consider referral to a transplant center before biopsy.

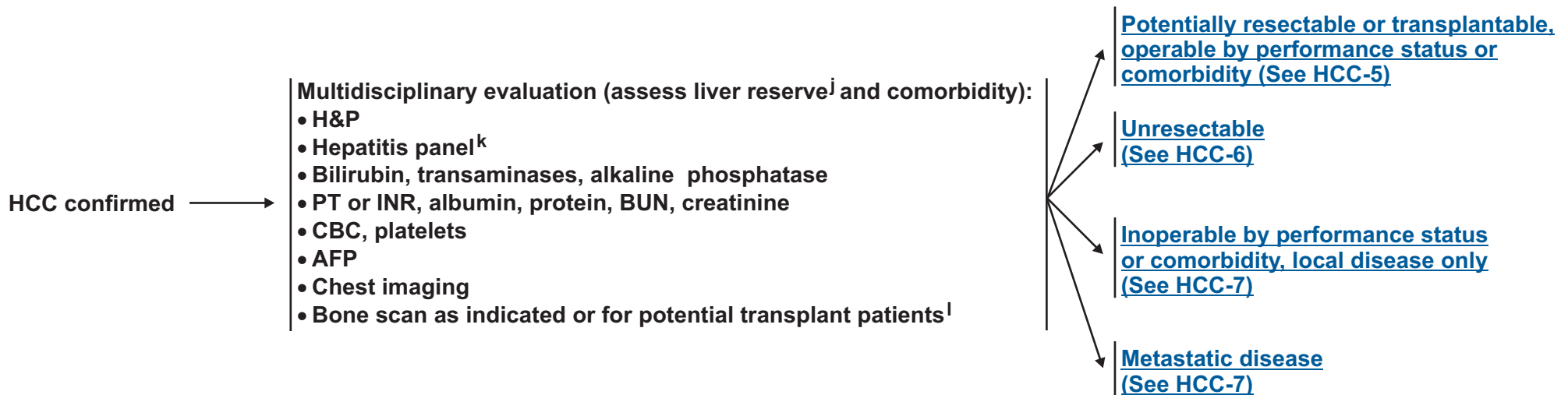
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**CLINICAL
PRESENTATION**

WORKUP



^jSee [Child-Pugh Score \(HCC-A\)](#) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

^kAn appropriate hepatitis panel should preferably include:

- Hepatitis B surface antigen (HBsAg). HBe and anti-HBc (IgM) are included if HBsAg is positive by PCR. If sAg, eAg, and/or viral load are positive, patients should be evaluated by hepatology for appropriate antiviral therapy.
- Hepatitis B surface antibody (for HBIG or vaccine evaluation only)
- Hepatitis C virus antibodies. If low positive, HCV viral load confirmation test is performed

^lSee www.unos.org.

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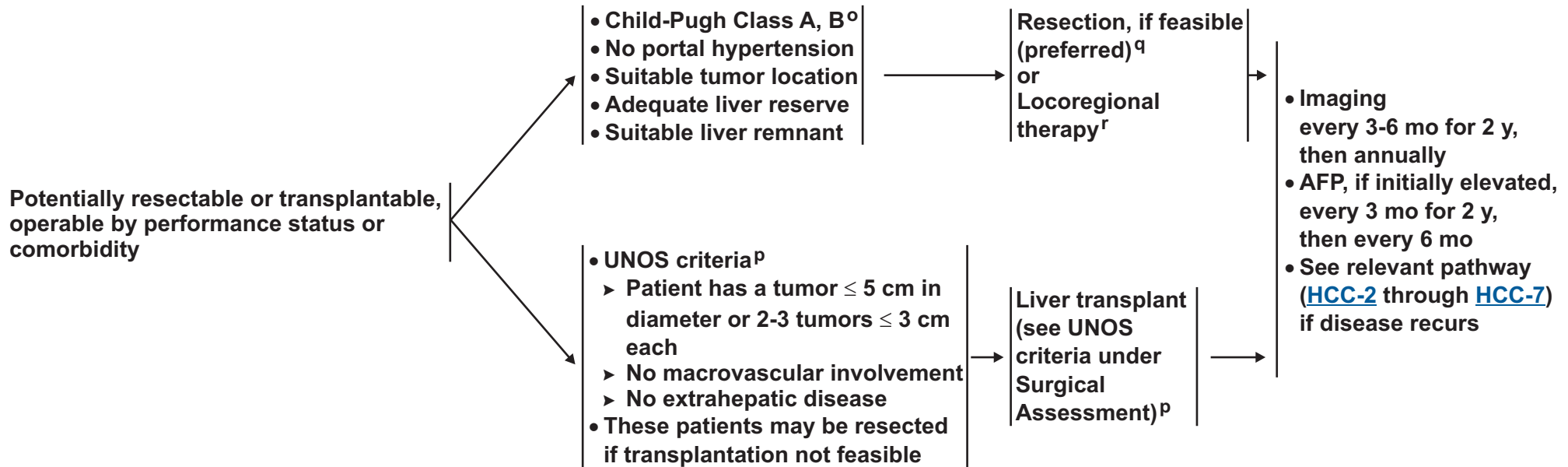


CLINICAL PRESENTATION

SURGICAL ASSESSMENT^{m,n}

TREATMENT

SURVEILLANCE



^mDiscussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

ⁿPatients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) 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.

^oIn highly selected Child-Pugh Class B patients with limited resection.

^pMazzaferro 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.

^qSee [Principles of Surgery \(HCC-B\)](#).

^rSee [Principles of Locoregional Therapy \(HCC-C\)](#).

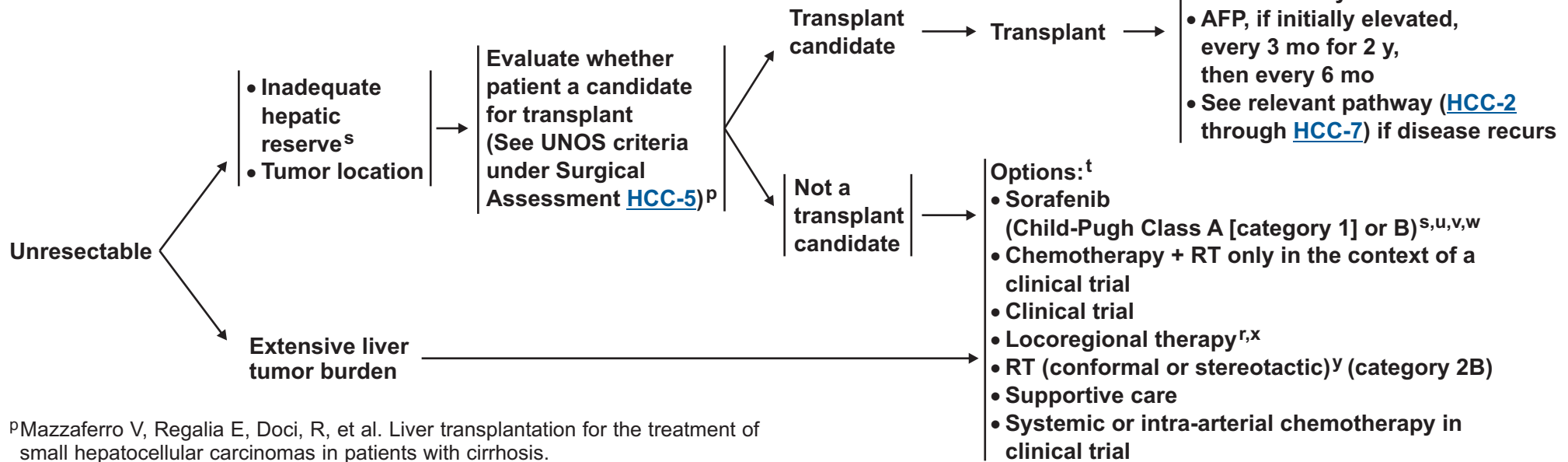
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For relapse, see initial [Workup \(HCC-4\)](#)



CLINICAL PRESENTATION



^PMazzaferro 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.

^rSee [Principles of Locoregional Therapy \(HCC-C\)](#).

^tOrder does not indicate preference with the exception of category 1 options which^w are listed first.

^sSee [Child-Pugh Score \(HCC-A\)](#).

^uThe 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).

^vFor 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).

^wCaution: 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. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Onc* 2009;27:1800-1805).

^xUse of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care. (Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35:1164-1171 and Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-1739.)

^yThere 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 or local disease with minimal extrahepatic disease only



- Options:^t**
- Sorafenib (Child-Pugh Class A [category 1] or B)^{s,u,v,w}
 - Clinical trial
 - Locoregional therapy^r
 - RT (conformal or stereotactic)^y (category 2B)
 - Supportive care

Metastatic disease



- Options:^t**
- Sorafenib (Child-Pugh Class A [category 1] or B)^{s,u,v,w}
 - Supportive care
 - Clinical trial

^rSee [Principles of Locoregional Therapy \(HCC-C\)](#).

^sSee [Child-Pugh Score \(HCC-A\)](#).

^tOrder does not indicate preference with the exception of category 1 options which are listed first.

^uThe 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).

^vFor 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).

^wCaution: 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. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Onc* 2009;27:1800-1805).

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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)	1-2	2-3	> 3
• For primary biliary cirrhosis	1-4	4-10	> 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

¹Trey 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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²Corresponding 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 Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)
- Hepatic resection is controversial in the following circumstances, but can be considered:
 - ▶ Limited and resectable 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 or deceased donor.
- Patients with Child-Pugh Class 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.

¹Farges 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, diaphragm, and other intra-abdominal organs.
- Sorafenib is appropriate for post transcatheter arterial chemoembolization (TACE)/ablation therapy in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with TACE/ablative procedures is being investigated in ongoing clinical trials.

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 a relative contraindication in cases of main portal vein thrombosis and an absolute contraindication for 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.

Stereotactic body radiotherapy (SBRT) and external-beam radiotherapy

- There is growing evidence for the usefulness of radiotherapy in the management of HCC.^{7,8} All tumors irrespective of location may be amenable to SBRT or external-beam conformal radiation. SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions, if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. There should be no extra-hepatic disease or it should be minimal and addressed in a comprehensive management plan. Most patients treated today were in the Child-Pugh A category. Radiotherapy can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed.

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[References on next page](#)

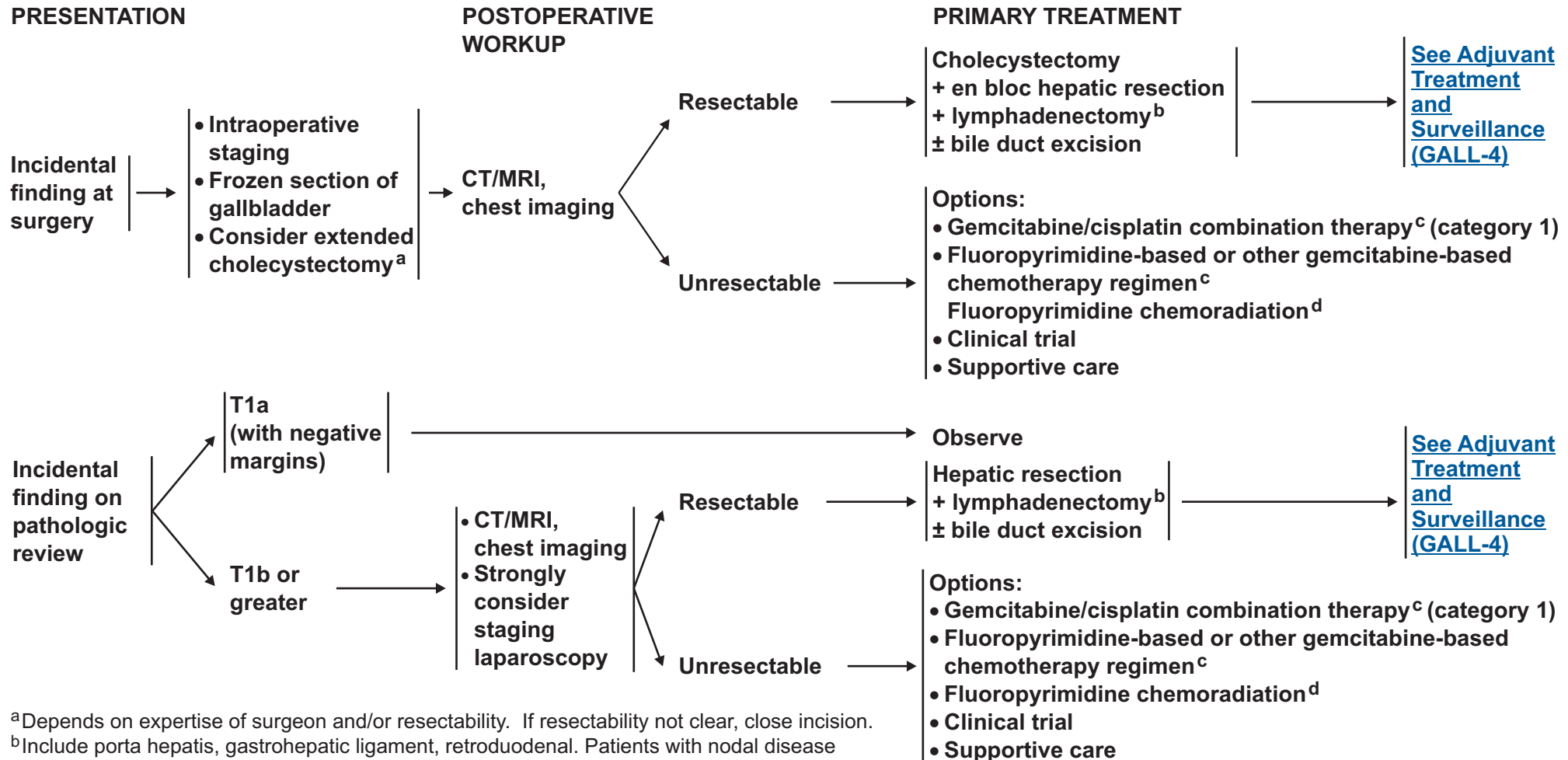


PRINCIPLES OF LOCOREGIONAL THERAPY

- ¹Yamakado, K., et al., Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. *Radiology* 2008; 247(1):260-266.
- ²Maluccio, 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.
- ³Maluccio, 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.
- ⁴Kulik, 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.
- ⁵Llovet, 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.
- ⁶Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 Pt 2):S211-21.
- ⁷Cardenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. *Clin Transl Oncol* 2010;12: 218-225.
- ⁸Tse RV, Hawkins M, Lockwood G, K, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol* 2008;26:657-664.

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^aDepends on expertise of surgeon and/or resectability. If resectability not clear, close incision.

^bInclude porta hepatis, gastrohepatic ligament, retroduodenal. Patients with nodal disease outside this area are unresectable.

^cA 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. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281. 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)

^dThere 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).

Note: All recommendations are category 2A unless otherwise indicated.

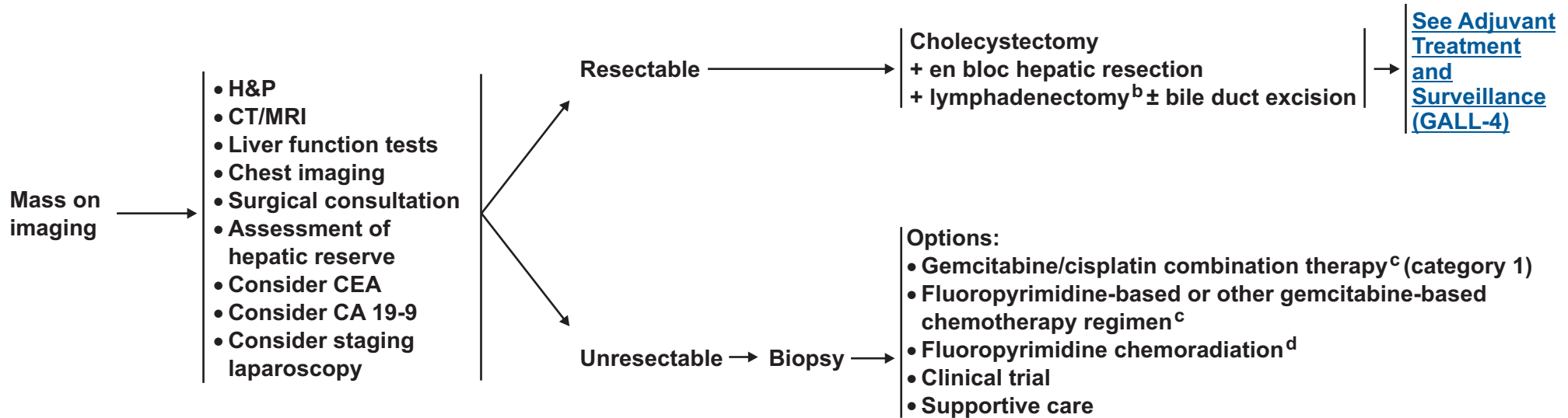
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

[Other Clinical Presentations](#)
[\(See GALL-2\)](#)
[and \(GALL-3\)](#)



PRESENTATION WORKUP

PRIMARY TREATMENT



^bInclude porta hepatis, gastrohepatic ligament, retroduodenal.

^cA 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. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281) 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)

^dThere 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)

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 and GALL-3)



PRESENTATION WORKUP

- Jaundice** →
- H&P
 - Liver function tests
 - Chest imaging
 - CT/MRI
 - Cholangiography^e
 - Surgical consultation^f
 - Consider CEA
 - Consider CA 19-9
 - Consider staging laparoscopy

Resectable

Unresectable → Biopsy

PRIMARY TREATMENT

- Cholecystectomy
- + en bloc hepatic resection
- + lymphadenectomy^b + bile duct excision

[See Adjuvant Treatment and Surveillance \(GALL-4\)](#)

Options:

- Biliary drainage^g
- Gemcitabine/cisplatin combination therapy^c (category 1)
- Other gemcitabine-based or fluoropyrimidine-based chemotherapy regimen^c
- Fluoropyrimidine chemoradiation^d
- Clinical trial
- Supportive care

Options:

- Biliary drainage^g
- Gemcitabine/cisplatin combination therapy^c (category 1)
- Other gemcitabine-based or fluoropyrimidine-based chemotherapy regimen^c
- Clinical trial
- Supportive care

Metastases →

^bInclude porta hepatis, gastrohepatic ligament, retroduodenal.

^cA 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. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281. 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)

^dThere 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)

^eMagnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic MR cholangiography (ERCP/PTC) are used more for therapeutic intervention.

^fConsult with a multidisciplinary team.

^gIt is expected that patients will have biliary drainage for jaundice prior to instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.

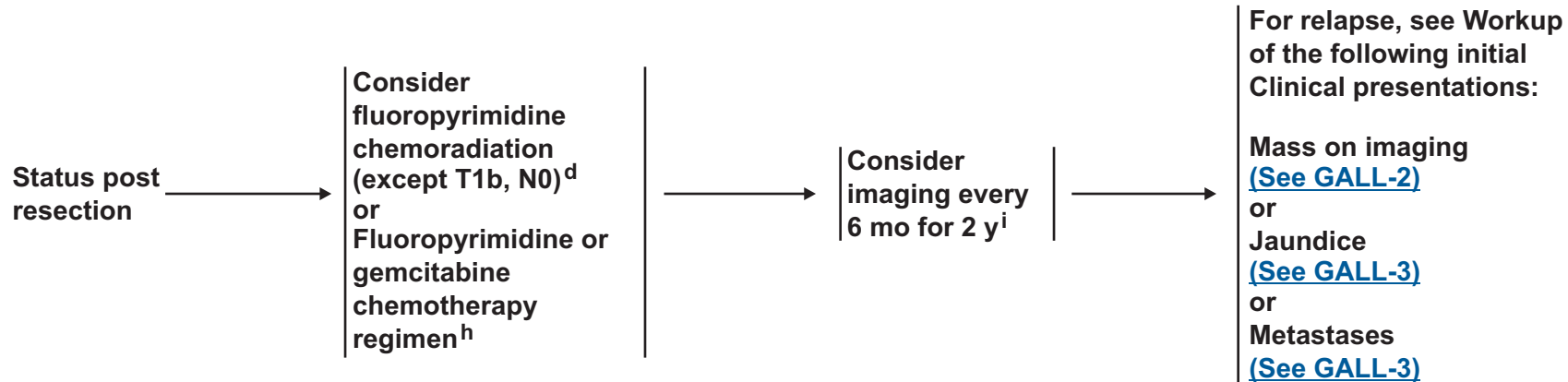
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

[Other Clinical Presentations](#)
[\(See GALL-1\) and GALL-2\)](#)



ADJUVANT TREATMENT

SURVEILLANCE



^dThere 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)

^hThere 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.

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

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.



NCCN Guidelines™ Version 2.011

Intrahepatic Cholangiocarcinoma

PRESENTATION

WORKUP

PRIMARY TREATMENT

Isolated intrahepatic mass
Biopsy Adenocarcinoma
(See [NCCN Occult Primary Guidelines](#))

- H&P
- CT/MRI^a
- Chest imaging
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Surgical consultation^b
- Consider laparoscopy^c
- Consider Esophagogastroduodenoscopy (EGD) and colonoscopy^d

Resectable

Unresectable

Metastatic

Resection
± ablation

[See Additional
Therapy and
Surveillance
\(INTRA-2\)](#)

Options:

- Gemcitabine/cisplatin combination therapy^e (category 1)
- Clinical trial^f
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen^e
- Fluoropyrimidine chemoradiation^g
- Supportive care

Options:

- Gemcitabine/cisplatin combination therapy^e (category 1)
- Clinical trial^f
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen^e
- Supportive care

^aRecommend delayed contrast-enhanced imaging.

^bConsult with multidisciplinary team.

^cLaparoscopy may be done in conjunction with surgery if no distant metastases are found.

^dUpper/Lower endoscopy may not be needed if immunohistochemistry/pathology is conclusive.

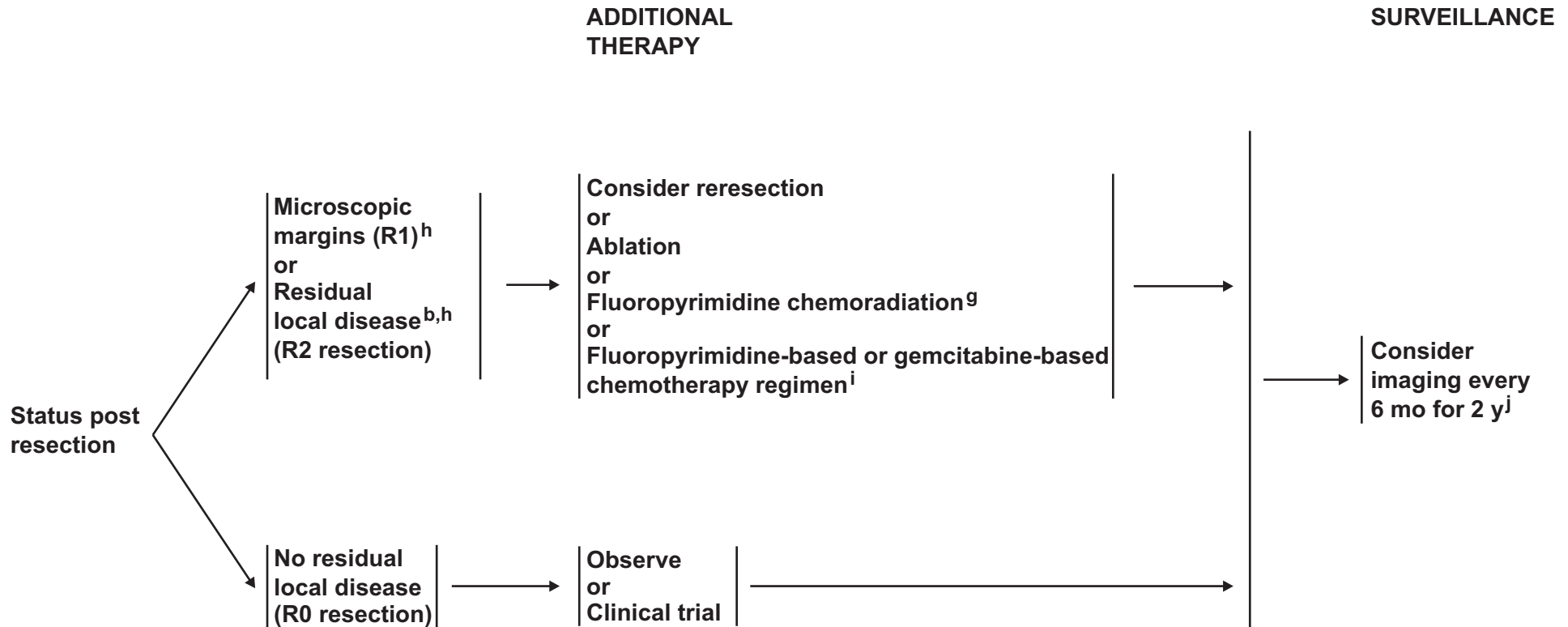
^eA recent Phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Eng J Med* 2010;362:1273-1281.) Clinical trial 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).

^fSystemic or intra-arterial chemotherapy may be used in a clinical trial.

^gThere 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)

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.



^bConsult with multidisciplinary team.

^gThere 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)

^hR1 or R2 resections should be evaluated by an experienced hepatobiliary surgeon for the uncommon scenario where re-resection may be considered.

ⁱThere 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)

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

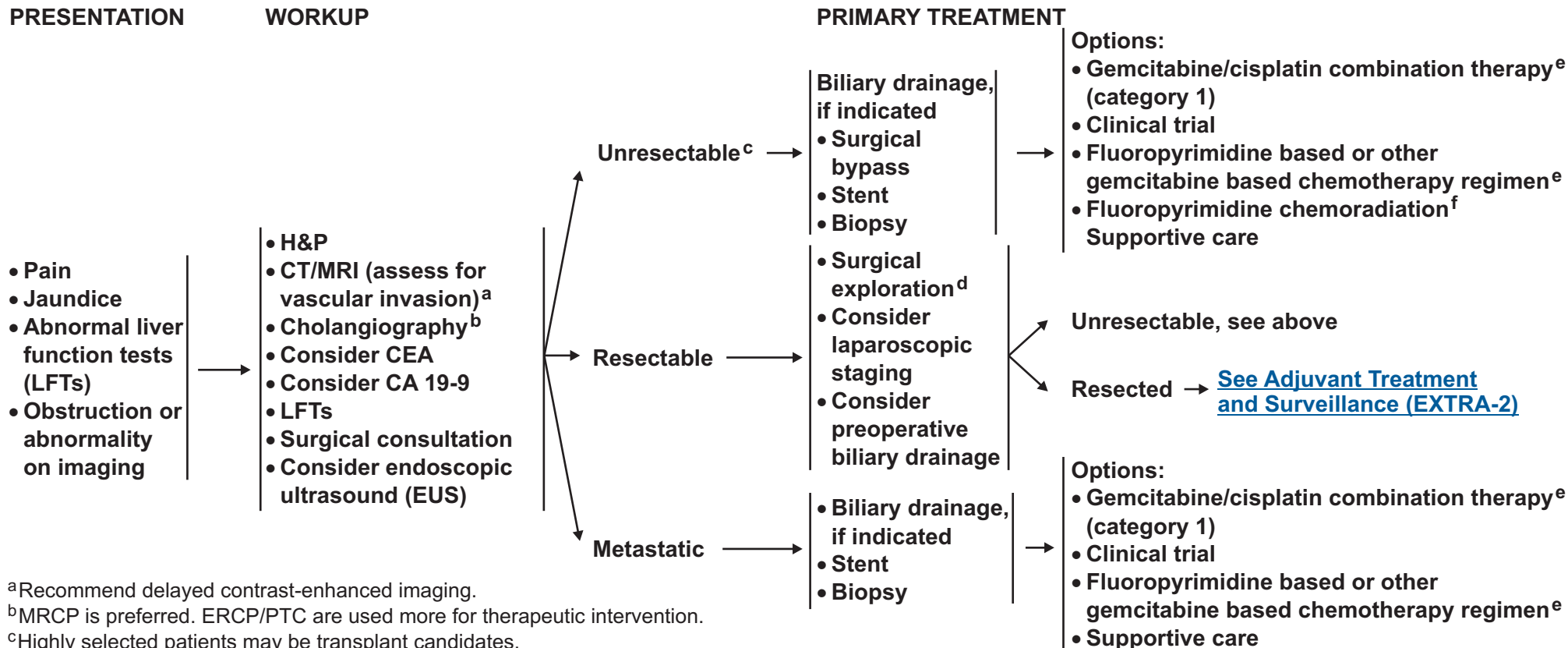
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines™ Version 2.011

Extrahepatic Cholangiocarcinoma



^aRecommend delayed contrast-enhanced imaging.

^bMRCP is preferred. ERCP/PTC are used more for therapeutic intervention.

^cHighly selected patients may be transplant candidates.

^dSurgery may be performed when index of suspicion is high, biopsy not required.

^eA 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. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Eng J Med 2010;362:1273-1281) 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)

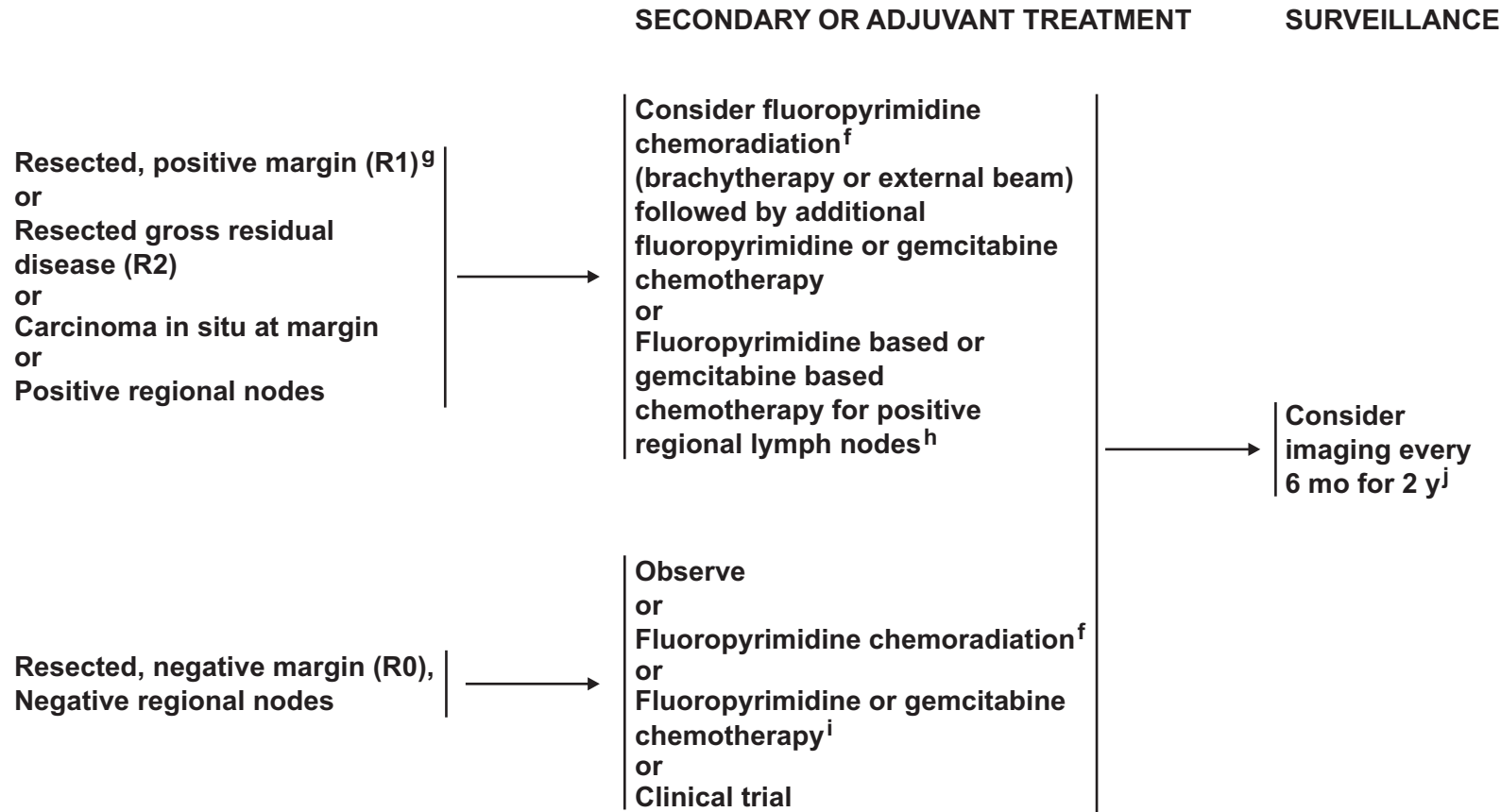
^fThere are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002; 11:941-954)

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.



^fThere 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)

^gMultidisciplinary team review.

^hThere 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)

ⁱThere are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

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

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.



Table 1

**American Joint Committee on Cancer (AJCC)
TNM Staging for Liver Tumors (7th ed., 2010)***

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- T1** Solitary tumor without vascular invasion
- T2** Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- T3a** Multiple tumors more than 5 cm
- T3b** Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein
- T4** Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Anatomic Stage/Prognostic Groups

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

Histologic Grade (G)

- 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, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) 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 SBM, on behalf of the AJCC.



Table 2

**American Joint Committee on Cancer (AJCC)
TNM Staging for Gallbladder Cancer (7th ed., 2010)***

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ*
- T1** Tumor invades lamina propria or muscular layer
- T1a** Tumor invades lamina propria
- T1b** Tumor invades 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 two or more extrahepatic organs or structures

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	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 Intrahepatic Bile Ducts (7th ed., 2010)***

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ* (intraductal tumor)
- T1** Solitary tumor without vascular invasion
- T2a** Solitary tumor with vascular invasion
- T2b** Multiple tumors, with or without vascular invasion
- T3** Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
- T4** Tumor with periductal invasion

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** Regional lymph node metastasis present

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis present

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Histologic Grade (G)

- G1** Well differentiated
- G2** Moderately differentiated
- G3** Poorly differentiated
- G4** Undifferentiated

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Table 4

**American Joint Committee on Cancer (AJCC)
TNM Staging for Perihilar Bile Duct Tumors (7th ed., 2010)***

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ*
- T1** Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
- T2a** Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
- T2b** Tumor invades adjacent hepatic parenchyma
- T3** Tumor invades unilateral branches of the portal vein or hepatic artery
- T4** Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
Stage IVB	Any T	N2	M0
	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 5

**American Joint Committee on Cancer (AJCC)
TNM Staging for Distal Bile Ducts Tumors (7th ed., 2010)***

Primary Tumor (T)

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ*
- T1** Tumor confined to the bile duct histologically
- T2** Tumor invades beyond the wall of the bile duct
- T3** Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery
- T4** Tumor involves the celiac axis, or the superior mesenteric artery

Regional Lymph Nodes (N)

- N0** No regional lymph node metastasis
- N1** Regional lymph node metastasis

Distant Metastasis (M)

- M0** No distant metastasis
- M1** Distant metastasis

Anatomic Stage/Prognostic Groups

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 NCCN Guidelines for Hepatobiliary Cancers 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 viral infections caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV), 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

Seropositivity for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) are associated with an increased risk of HCC in patients with chronic hepatitis B viral infection.^{6,7} Data from large population-based studies have also identified high serum HBV DNA and HCV RNA viral load as independent risk factors for developing HCC in patients with chronic infection.⁸⁻¹¹

Non-viral causes associated with an increased risk of HCC include relatively rare, inherited errors of metabolism such as hereditary

hemochromatosis, porphyria cutanea tarda, alpha1-antitrypsin deficiency, Wilson's disease and stage IV primary biliary cirrhosis.^{2, 12} Recent data suggest that the annual incidence of HCC in patients with autoimmune hepatitis and cirrhosis is about 1.1%, which is not high enough to warrant surveillance for this group of patients.^{4, 13}

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 and the development of HCC.^{14, 15} 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, 16, 17}

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, possibly approaching 90% in the U.S.^{16, 18} Although most studies evaluating the risk of development of HCC in HCV-infected individuals have focused on populations with cirrhosis, there are limited data showing that HCC can occur in some HCV-infected patients with bridging fibrosis in the absence of overt cirrhosis.¹⁹ Importantly, certain populations chronically infected with the HBV (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 30-50% of patients with chronic hepatitis B viral infection who develop HCC do not have underlying cirrhosis.¹⁷ Some risk factors for development of HCC in HBV carriers without evidence of liver cirrhosis include active viral replication, high HBV DNA levels, a family history of HCC, Asian males ≥40 years, Asian females ≥ 50 years, and African/North American

blacks with hepatitis.^{4, 17} 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.^{13, 20} Although the mechanism of HCC development differs according to the underlying disease,¹⁶ 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 HCV,²¹ and the annual incidence rate of HCC among patients with HCV-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 HCV-related HCC is associated with the often prolonged period between viral infection and the manifestation of HCC.^{22, 23}

Approximately 1.5 million people in the United States are chronically infected with HBV.^{24, 25} 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,²⁶ 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.²⁷ 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%.²⁸

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.^{29, 30}

Among the other non-viral risk factors for HCC, genetic hemochromatosis (GH) is a condition characterized by excess iron absorption due to the presence of mutations in the HFE gene. A study from the US National Center for Health Statistics found that patients with a known diagnosis of hemochromatosis at death were 23-fold more likely to have liver cancer compared to those without hemochromatosis. The annual incidence rates of HCC associated with cirrhosis due to GH has been sufficiently high (about 3-4%) and the AASLD guidelines recommend surveillance for this group of patients when cirrhosis is present.⁴ Alcoholic cirrhosis is clearly a risk factor for HCC,⁴ although 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.^{31, 32}

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 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.³³ 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.³⁴ 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.³⁵ 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.³⁶ 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).³⁷⁻³⁹

In these guidelines, the populations considered to be “at risk” for HCC and likely to benefit from participation in an HCC screening program include patients with liver cirrhosis induced by viral as well as non-viral causes (as described in the section on “Risk factors and Epidemiology”)

and hepatitis B carriers without cirrhosis. The panel recommends periodic screening with ultrasonography and AFP testing every 6-12 months for patients at risk for HCC. Additional imaging [4-phase computed tomography (CT) or magnetic resonance imaging (MRI) with contrast] is recommended (as described in the following section on Diagnosis and Initial Workup) in the setting of a rising serum AFP or following identification of a liver mass nodule on ultrasound. It is reasonable to study patients with cross-sectional imaging (CT or MRI) and this is probably the most commonly employed method in the United States, although not well studied.

Diagnosis

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.¹⁵ Paraneoplastic syndromes also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.¹⁶

Imaging

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.⁴⁰ Diagnostic HCC imaging involves the use of one or more of the following modalities 4-phase helical CT; 4-phase dynamic contrast enhanced MRI or contrast-enhanced ultrasonography (CEUS), although the latter modality is not commonly available in the U.S.^{4, 41, 42} Positron emission tomography (PET)/CT is not considered to be adequate. The term 4-phase refers to the phases of scanning: unenhanced phase, an arterial phase, a portal venous phase, and the venous phase after a delay.¹⁸ 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.⁴²⁻⁴⁴

The results of a prospective study evaluating the accuracy of CEUS and dynamic contrast-enhanced MRI for the diagnosis of liver nodules 2 cm or smaller observed on screening ultrasonography, demonstrated that the diagnosis of HCC can be established without biopsy confirmation if both imaging studies are conclusive.⁴⁴ However, as noted earlier, CEUS is not commonly utilized in the US. Other investigators have suggested that a finding of classical arterial enhancement using a single imaging technique is sufficient to diagnose HCC in patients with cirrhosis and 1-2 cm liver nodules detected during surveillance, thereby reducing the need for a biopsy.⁴⁵ In the updated AASLD guidelines, the algorithms for the liver nodules 1-2 cm in size have been changed to reflect these considerations.

Recommendations for imaging included in the NCCN guidelines 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 updated guidelines developed by the AASLD.⁴ The recommendations included in the NCCN guidelines apply only to nodules identified in patients with liver cirrhosis. In patients without liver cirrhosis or known liver disease, biopsy should be strongly considered to confirm the diagnosis of HCC.

Patients with an incidental liver mass or nodule found on ultrasound should be evaluated using one or more of the imaging modalities to determine the perfusion characteristics, extent and the number of lesions, vascular anatomy and extrahepatic disease. The number and type of imaging is dependent on the size of the liver mass or nodule.

Liver lesions less than 1 cm should be evaluated by 4-phase CT or MRI or CEUS every 3-6 months, with enlarging lesions evaluated according to size. Patients with lesions stable in size should be followed with imaging every 3-6 months using the same imaging modality that was first used to identify the nodules.

Liver nodules greater than 1 cm in size should be first evaluated with 4-phase CT or MRI. Additional imaging is dependent on the pattern of classic enhancement observed. A finding of 2 classic enhancements is considered to be diagnostic of HCC, whereas a second imaging (the other of CT or MRI) is recommended if there is only one or no classic enhancement pattern. If there are 2 classic enhancements following additional imaging, the diagnosis of HCC is confirmed. Additional confirmation through tissue sampling (core biopsy is preferred) is recommended if there is only one or no classic enhancement pattern for patients with liver nodules 1-2 cm in size or greater 2 cm. For patients with liver nodules 1-2 cm in size, the NCCN guidelines have included repeat 4-phase imaging in 3 months as an alternative to core biopsy, if there is only one or no classic enhancement pattern following additional imaging.

Biopsy

A diagnosis of HCC can be noninvasive in that biopsy confirmation may not be required. For example, in the evaluation of liver nodules greater than 1 cm in size, the finding of 2 classic enhancements on either one of the recommended imaging modalities (4-phase contrast enhanced CT or MRI) is sufficient to confirm the diagnosis of HCC. However, a core needle biopsy (preferred) or a fine needle aspiration biopsy (FNAB) is recommended when 0 or 1 classic arterial enhancements is observed by the recommended imaging method.⁴⁵ If transplant is a consideration, patients should be referred to a transplant center before biopsy.

Both core biopsy 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.⁴⁶ However, FNAB is highly dependent on the skill of the cytopathologist,⁴⁷ and there are reports of high false-negative rates^{44, 48} as well as the possibility of false-positive findings with this procedure.⁴⁹ Although a core biopsy 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 can be performed on the paraffin wax embedded sample.^{37,46, 48} However, recent evidence indicates that a core biopsy does not provide an accurate determination of tumor grade.⁵⁰

Nevertheless, use of biopsy to diagnose HCC is limited by a number of factors including sampling error, particularly when lesions are greater than 1 cm.^{4,18} 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

Although serum AFP has long been used as a marker for HCC, it is not a sensitive or specific diagnostic test for HCC. Serum AFP levels of more than 400 ng/ml are considered diagnostic of HCC, however, such high values are observed only in a small percentage of patients with HCC. In a series of 1,158 patients with HCC, only 18% of patients had values greater than 400 ng/ mL and 46% of patients had normal serum AFP levels of less than 20 ng/ mL.⁵¹ In patients with chronic liver disease, an elevated AFP could be more indicative of HCC in

non-infected patients.⁵² Furthermore, AFP can also be elevated in intrahepatic cholangiocarcinoma and some metastases from colon cancer.⁴ AFP testing can be useful in conjunction with other test results to guide the management of patients for whom a diagnosis of HCC is suspected. 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,^{53, 54} although the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institutions.

The updated AASLD guidelines no longer recommend AFP testing as part of diagnostic evaluation.⁴ 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,⁵⁵ which is in agreement with the updated AASLD guidelines recommendation.⁴ Additional imaging studies (CT or MRI) are recommended for patients with a rising serum AFP level in the absence of a liver mass. If no liver mass is detected following measurement of an elevated AFP level, the patient should be followed with AFP testing and liver imaging every 3 months.

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.^{18, 56, 57} 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.⁵⁸ 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.³⁸

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 (HBsAg, hepatitis B surface antibody and HCV antibodies) 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. The guidelines recommend confirmation of viral load in patients who test positive for HBsAg and HCV antibodies; if viral load is positive, patients should be evaluated by hepatologist for appropriate antiviral therapy.^{17, 59}

Common sites of HCC metastasis include the lung, abdominal lymph nodes, peritoneum and the bone.^{60, 61} 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. Four phase CT or MRI 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.⁴² Enlarged lymph nodes are seen commonly in patients with viral hepatitis, primary biliary cirrhosis, and other underlying liver disorders that predispose patients to HCC⁶² and the detection of nodal disease by cross-sectional imaging can be challenging in patients with hepatitis.

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AFP), measurement of prothrombin time (PT)/international normalized ratio (INR), albumin, and platelet count (surrogate for portal hypertension). 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,⁶³ and a complete blood count (CBC).

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.^{64, 65} 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. 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, and thrombocytopenia). Evidence of portal hypertension may also be evident on CT/MRI.⁴² Measurement of hepatic venous pressure gradient (HVPG) is an evolving tool for the assessment of portal hypertension.⁶⁶⁻⁶⁹

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.⁷⁰ 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.⁷¹ 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.⁶⁵

Pathology and Staging

Pathology

Three gross morphologic types of HCC have been identified: nodular, massive and diffuse.⁷² 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 interventions, and by providing risk stratification information following treatment. The key factors affecting prognosis in patients with HCC are the clinical stage, aggressiveness and growth rate of the tumor, the general health of the patient, the liver function of the patient and the treatments administered.⁴¹ A number of staging systems for patients with HCC have been devised.^{74, 75} Each of the staging systems includes variables which evaluate one or more of the factors listed above. For example, the Child-Pugh⁶⁴ and MELD scores⁷⁶ can be considered to be staging systems which evaluate aspects of liver function only.

The American Joint Committee on Cancer (AJCC) TNM staging system (Table 1) provides information on pathologic characteristics of resected specimens only,⁷⁷ whereas the Okuda system incorporates aspects of liver function and tumor characteristics.⁷⁸ The French classification (GRETCH) system incorporates the Karnofsky performance score as well as measurements of liver function and serum AFP.⁷⁹ Several staging systems include all parameters from other staging systems as well as additional parameters. For example, the Chinese University Prognostic Index (CUPI) system⁸⁰ and the Japanese Integrated Staging (JIS)⁸¹ scores incorporate the TNM staging system and the Cancer of the Liver Italian Program (CLIP),⁸² Barcelona Clinic Liver Cancer (BCLC),⁸³ SLiDe,⁸⁴ and JIS systems include the Child-Pugh score (with modified versions of CLIP and JIS substituting the MELD score for the Child-Pugh score.⁸⁵⁻⁸⁷ In addition, the BCLC system also incorporates the Okuda system, as well other tumor characteristics, measurements of liver function, and patient performance status.⁸⁸

Although some of these systems have been found to have use in all stages of HCC (eg, BCLC),^{18, 88, 89} 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 likely related to differing etiologies. 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.⁹⁰ The CLIP, CUPI and GRETCH staging systems have been shown to perform well in predicting survival in patients with advanced disease.⁹¹

The CLIP system has been specifically identified as being useful for staging patients who underwent transarterial chemoembolization and those treated in a palliative setting.^{92, 93} 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.⁹⁴ 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.⁷⁵ Furthermore, the BCLC staging system was recently shown to be very useful for predicting outcome in patients following radiofrequency ablation therapy.⁹⁵ 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.⁹⁶ 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,⁹⁷ and this staging system has been retrospectively validated in a population of patients with early HCC.⁹⁸

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 patients are stratified into one of 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 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.⁹⁹ 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.¹⁸

Surgery

Partial hepatectomy (ie, liver resection) is a potentially curative therapy for patients with early-stage HCC who are eligible to undergo the procedure.^{100,101} Partial hepatectomy for selected patients with HCC

can now be performed with low operative morbidity and mortality (in the range of 5% or less).^{102, 103} Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC,¹⁰³⁻¹⁰⁵ 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%.^{105,106, 107} However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.^{88, 104}

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.¹⁰⁸ 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.

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).¹⁰⁹ An evaluation of the presence of significant portal hypertension is also an important part of the surgical assessment. 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. 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.⁴² CT/ MRI 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 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.^{102,110} 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.¹⁰² Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence.^{102,111, 112} The role of liver resection for patients with limited and resectable multifocal disease and/or signs of major vascular invasion is controversial,^{101, 111,113} although results of a recent retrospective analysis showed a 5-year overall survival rate of 81% for selected patients with single tumor of 5 cm or less or 3 or fewer tumors of 3 cm or less undergoing liver resection.¹¹⁴ Liver resection in patients with major vascular invasion should only be performed in highly selected situations by experienced teams.

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.¹¹⁵ The panel recommends that this ratio be at least 20% in patients without cirrhosis and least 30-40% in patients with a Child-Pugh A score.¹¹⁶ 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.¹¹⁷

The consensus of the panel is that hepatic resection is indicated as a potentially curative option for patients with the following disease characteristics: adequate liver function (Child-Pugh class A without portal hypertension), solitary mass without major vascular invasion and adequate liver remnant. The presence of extrahepatic metastasis is considered to be a contraindication for resection.

Liver Transplantation

Liver transplantation is an attractive, potentially curative therapeutic option for patients with early HCC.¹⁰⁰ 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. proposed the Milan criteria (single tumors 5 cm or less in diameter or no more than three tumor nodules 3 cm or less in diameter in patients with multiple tumors) for patients with unresectable HCC and cirrhosis.¹¹⁸ The 4-year overall and recurrence-free survival rates were 85% and 92%, respectively, when liver transplantation was restricted to a subgroup of patients meeting the Milan selection criteria. These results have been supported by more recent studies in which patient selection for liver transplantation was based on these criteria.¹¹⁹ 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) 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 (www.unos.org).

The UNOS criteria also specify that patients eligible for liver transplantation should not be candidates for liver resection. 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 controversial.¹²⁰⁻¹²³ 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.¹²⁴

The MELD score as a measure of liver function 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 (www.unos.org), 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”).⁷¹ 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”.¹²⁵ 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,¹²⁵ 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.^{88,119,126, 127} 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).¹²⁸ 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%).¹²⁶⁻¹³⁰ 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. 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.^{119, 126, 129} 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.¹²⁵

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.¹²⁴

Treatment before Liver Transplantation

Bridge therapy

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list. It is considered for patients who meet the transplant criteria. A number of studies have investigated the role of locoregional treatment as a bridge to liver transplantation in patients on a waiting list.^{131, 132}

These studies include use of radiofrequency ablation (RFA),¹³³⁻¹³⁶ conformal radiation therapy,¹³⁷ chemoembolization,^{135,138} transarterial chemoembolization (TACE)^{135,139,140} and sorafenib¹⁴¹ 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.^{142,143} Nevertheless, use of bridge therapy in this setting is increasing, and it is administered at some NCCN centers.

Downstaging Therapy

Downstaging therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria.¹⁴⁴ Recent prospective studies have demonstrated that downstaging with RFA,^{145,146} TACE,¹⁴⁵⁻¹⁴⁸ percutaneous ethanol injection¹⁴⁵ and transarterial radioembolization (TARE) with yttrium 90 microspheres¹⁴⁸ prior to transplant improves

disease-free survival following transplant. However, such studies have used different selection criteria for the downstaging therapy and different transplant criteria after successful downstaging. In some studies response to locoregional therapy has been associated with good outcomes after transplantation.¹⁴⁹⁻¹⁵¹ Further validation is needed to define the end-points for successful downstaging prior to transplant.

Locoregional Therapy

Locoregional therapies for the treatment of patients with HCC are directed toward inducing selective tumor necrosis, and fall into one of 2 categories: ablation or embolization. The extent of tumor necrosis induced by locoregional therapy is typically approximated by dynamic CT/MRI at a specified time following treatment (as opposed to a histologic assessment). 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. A number of factors are involved in measuring the effectiveness of locoregional therapies, and the criteria for evaluating tumor response are evolving.^{41, 152-155} AFP response to locoregional therapy has also been reported to be a reliable predictor of tumor response, TTP, PFS, and OS.¹⁵⁶

The effectiveness of local regional approaches in the treatment of HCC has not been established to be comparable to that of liver resection or transplantation.^{109, 157} The consensus of the panel is that liver resection, if feasible is preferred for patients who meet surgical selection criteria. Locoregional therapy can be considered if patients are not amenable to surgery.

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).^{35, 100} 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 PEI, the major complication and mortality rates were 4.8% and 0%, respectively.¹⁵⁸

Studies have shown that ablative therapy is most effective on smaller HCC tumors.^{133, 134, 159-161} 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. 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, PEI, or a combination of both methods while awaiting liver transplantation. The results of this study showed complete and partial necrosis rates of 47% and 53%, respectively, when RFA was used, and 23% and 46%, respectively, following PEI therapy with 31% of tumors showing no evidence of necrosis with PEI therapy. The overall rate of complete necrosis was 53% for HCC tumors < 3 cm and 14% for tumors ≥ 3 cm ($P=0.033$). However, this rate increased to 62% when the subset of tumors less than 3 cm treated by RFA was evaluated.¹³³ 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.¹³⁴ 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.¹⁶²⁻¹⁶⁴ RFA was shown to be superior to PEI with respect to complete response rate (65.7% vs. 36.2% respectively [$P=0.0005$]),¹⁶³ and rate of local recurrence.^{162, 164} In addition, in one study patients in the RFA arm were shown to require fewer treatment sessions.¹⁶⁴ However, the benefit of RFA compared with PEI on overall survival was demonstrated in 2 of these studies,^{162, 164} but not in a third which showed no significant overall survival differences between the 2 treatment arms.¹⁶³ RFA has also been compared with liver resection in a prospective randomized controlled study.¹⁶¹ 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. The results of a recent randomized trial showed survival benefit with surgical resection over RFA in 235 patients with small HCC conforming to the Milan criteria.¹⁶⁵ The 5-year overall survival rates were 54.8% and 75.6% respectively for the RFA group and surgical resection. The corresponding recurrence-free survival rates for the 2 groups were 28.7% and 51.3% respectively. 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 (\leq

3 cm).¹⁶⁴ However, another study found less than 3% of patients with single HCC tumors \leq 2 cm who underwent repeated applications of RFA to have a recurrence of disease at 31 months.¹⁶⁰

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.^{166,167} Nevertheless reported rates of overall survival vary widely across studies of patients treated with ablation.^{161-164,166-168}

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.^{167,168}

It should be emphasized that ablative techniques are limited by anatomic location. Lesions in certain portions of the liver (eg, dome) may not be accessible to a percutaneous approach. Similarly, ablative treatment of tumors located on the liver capsule may cause tumor rupture with track seeding. Major vessels in close proximity to the tumor can absorb large amounts of heat (known as the ‘heat sink effect’) when methods such as radiofrequency ablation is performed which decrease the effectiveness and significantly increase local recurrence rates.¹⁸ The panel emphasizes that caution should be exercised when ablating lesions near major bile ducts, and other intra-abdominal organs such as the colon, stomach, diaphragm, heart and gallbladder and these organs can be damaged.

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.¹⁶⁹ 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.⁴⁰ 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.¹⁷⁰⁻¹⁷³ 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.

General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large volume extrahepatic disease. Minimal extrahepatic disease is considered a ‘relative’ contraindication for embolization procedures. 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 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.

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.^{171, 174, 175} 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.¹⁷⁴ Results of two randomized clinical trials have shown a survival benefit for use of TACE therapy vs. supportive care in patients with unresectable HCC.^{173, 176} In one study patients were randomly assigned to TAE, TACE, and supportive care treatment arms.¹⁷³ 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, 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. In the other study which randomized patients with unresectable HCC to TACE or best supportive care, the actuarial survival was significantly better in the TACE group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; $P = .002$).¹⁷⁶ Although death from liver failure was more frequent in patients who

received TACE, the liver functions of the survivors were not significantly different between the two groups.

Many of the clinical studies evaluating the effectiveness of TAE and/or TACE 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.^{171, 175} In a recent retrospective analysis of patients undergoing TAE 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.¹⁷¹

In the study of Maluccio et al., predictors of poor prognosis on multivariate analysis following TAE 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.¹⁷¹ However, there is evidence showing portal vein obstruction,^{177, 178} liver function categorized as Child-Pugh class C and total serum bilirubin level of > 3 mg/mL^{178, 179} to be significant predictors of poor prognosis in patients treated with TACE.

Complications of TAE and TACE can include acute portal vein thrombosis, cholecystitis, and bone marrow suppression, in addition to other toxicities, although the reported frequencies of serious adverse events vary across studies.^{35, 180} A post-embolization syndrome involving fever, abdominal pain, and intestinal ileus has been reported to be relatively common in patients undergoing these procedures.^{35, 180}

Reported rates of TAE and TACE treatment-associated mortality for are usually less than 5%.^{35, 171, 173,180}

Hence, the panel considers main portal vein thrombosis to be a relative contraindication for TACE, and recommends against its use in those with liver function characterized as Child-Pugh class C (absolute contraindication). Because TAE can increase the risk of hepatic necrosis and liver abscess formation in patients with biliary obstruction,¹⁷⁴ the panel recommends that a total bilirubin level > 3 mg/mL should be considered as a relative contraindication for TACE or TAE unless segmental injections can be performed. Furthermore, patients with previous biliary-enteric bypass have an increased risk of intrahepatic abscess following TACE.¹⁷⁴

Recent studies have evaluated TACE with drug-eluting-beads in patients with unresectable HCC.¹⁸¹⁻¹⁸⁵ A randomized study comparing TACE with 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 two methods although toxicity was significantly decreased with the former approach.¹⁸³ However, in other prospective randomized studies, TACE with doxorubicin-eluting beads was associated with survival advantage, better local response, fewer recurrences and a longer time-to-progression.^{184, 185} These results need to be confirmed in large prospective studies.

Radioembolization

Radioembolization is a newer embolization method that provides for the internal delivery of high-dose radiation to the tumor-associated capillary bed.^{169,186} Transarterial radioembolization (TARE) 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.¹⁷²

A partial response rate of 42.2% was observed in a phase II study of 108 patients with unresectable HCC with and without portal vein thrombosis treated with radioembolization and followed for up to 6 months.¹⁷² 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).¹⁸⁷ Median survival for patients with disease characterized by Child-Pugh class B liver function and portal vein thrombosis was 5.6 months. In a recent comparative effective analysis, patients with HCC treated with chemoembolization or radioembolization with yttrium-90 microspheres had similar survival times.¹⁸⁸ However, radioembolization resulted in a longer time-to-progression and less toxicity than chemoembolization. Reported complications of radioembolization therapy include cholecystitis/bilirubin toxicity and abscess formation.^{172,187,189} Randomized controlled studies of the use of radioembolization 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 TAE is that the focused heat delivery of RFA may be enhanced by vessel occlusion through TAE 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.¹⁷⁰ 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.¹¹⁴

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.

External beam radiation therapy

External-beam radiation therapy (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 or inoperable liver disease.^{190,191}

There is growing evidence supporting the usefulness of conformal or stereotactic body radiation therapy (SBRT) for patients with

unresectable disease.^{192, 193} The panel encourages prospective clinical trials evaluating the role of SBRT in patients with unresectable HCC. All tumors irrespective of their location may be amenable to conformal or SBRT. SBRT is often used for patients in the Child-Pugh A category with 1-3 tumors with a cumulative diameter of less than 6 cm and with minimal or no extrahepatic disease. It could be considered for larger lesions if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. The panel recommends that radiation therapy can be considered (category 2B) as an alternative to ablation/embolization techniques or when these therapies have failed in 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. It is not included in the guidelines as an option for patients with metastatic disease.

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 patients with very advanced disease who are referred for systemic therapy.

Clinical studies evaluating the use of cytotoxic chemotherapy 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.¹⁹⁴⁻¹⁹⁶ The panel recommends that systemic cytotoxic chemotherapy (single agent or combination), intra-arterial chemotherapy, as well as the combination of cytotoxic chemotherapy and radiation therapy be given to patients with unresectable HCC only in the context of a clinical trial.

Sorafenib, an oral multikinase inhibitor which suppresses tumor cell proliferation and angiogenesis, has been evaluated in one phase II trials and two randomized placebo controlled phase III trials for the treatment of patients with advanced or metastatic HCC.¹⁹⁶⁻¹⁹⁸

In the phase III trial [Sorafenib in Advanced Hepatocellular Carcinoma (SHARP) study], 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.¹⁹⁶ 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, $\geq 95\%$ 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 III 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).¹⁹⁷ Although inclusion/exclusion criteria and the percentage of patients with Child-Pugh A liver function (97%) were similar in the Asia-Pacific and SHARP studies, there were significant differences in patient and disease characteristics between the two studies. Only Asian patients were enrolled in the Asia-Pacific study and these patients were more likely to be younger, to have HBV-related disease (ie, over 70%), symptomatic disease, and a higher number of

tumor sites than 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 study, a number of analyses have been performed to investigate the efficacy of sorafenib in particular patient subgroups. Results of these analyses suggest that sorafenib is an effective treatment in patients with advanced HCC irrespective of baseline ECOG performance status (0-2) and presence or absence of macroscopic vascular invasion and/or extrahepatic spread¹⁹⁹ and those with alcohol-related,²⁰⁰ and hepatitis C viral-related HCC,²⁰¹ and it is an effective treatment irrespective of ALT/AST/AFP levels, and that hepatic function is not appreciably affected.²⁰² 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.¹⁹⁶

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).²⁰³ 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.¹⁹⁸ A subgroup analysis of data from this study showed lower median overall survival for patients in the Child-Pugh class B group compared with those in the Child-Pugh class A group (3.2 months vs. 9.5 months).²⁰⁴ In another large retrospective study by Pinter et al., the median overall survival for Child-Pugh class B patients was 4.3 months compared to 8.3 months for Child-Pugh class A patients and it was only 1.5 months for Child-Pugh class C patients.²⁰⁵ 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.²⁰⁴ 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.²⁰⁶ In a phase II study by Yao et al., which included 36 patients with Child-Pugh A cirrhosis, 13 patients had Child-Pugh B cirrhosis and 2 had Child-Pugh C cirrhosis, there were no significant differences between Child-Pugh A and Child-Pugh B/C patients in overall survival (5.5 months vs. 5 months), grade 3 or 4 hematologic (17% vs. 33%; $P = 0.18$) and nonhematologic toxicities (47% vs. 47%; $P = 0.97$). However, the grade 3 or 4 liver toxicity, (although not statistically different) was 73% for Child-Pugh B/C patients compared to 56% for the Child-Pugh A patients.²⁰⁷ Therefore, more mature results from ongoing studies are needed to recommend sorafenib for Child-Pugh B or C patients. Finally, it is important to mention that validated criteria to evaluate tumor response to sorafenib are needed since true objective volumetric responses are rare.²⁰³

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 disease. 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.

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.

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 recurrence.

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.^{208, 209}

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.²⁰⁸ 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.

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.²⁰⁸ 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.⁴² 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.^{209, 210}

For patients presenting with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor.⁴² 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 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.^{211, 212}

Pathology and Staging

Approximately 80% of gallbladder cancers are adenocarcinomas.^{208, 213} Gallbladder cancer is often characterized by early spread to lymph tissue and the bloodstream.^{208, 214}

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.²¹⁵ 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.²¹³ Median survival was 12.0 months and 5.8 months for those with stage IA-III and stage IV disease, respectively.²¹³

Management

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.²¹³ Factors determining gallbladder tumor resectability include the stage of the tumor according to AJCC TNM staging criteria as well as tumor location.²⁰⁸ Nodal disease outside of this area (most commonly, celiac, retropancreatic or in the interaortocaval groove) should be considered unresectable.

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.²¹⁶ Another study which retrospectively evaluated data from 115 patients who underwent re-resection for incidental gallbladder cancer showed that achievement of R0 resection margins strongly correlated with long-term survival.²¹⁷ 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.²¹³ With these data in mind the optimal resection (extended cholecystectomy) is a limited hepatic resection and portal lymphadenectomy to encompass the tumor with negative margins. Major hepatic resections and bile duct resections should be performed when necessary to achieve an R0 resection.

Resectable disease

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.

All patients should undergo CT/MRI 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.

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. For patients with an incidental finding of gallbladder cancer at the time of surgery or for those with a suspicious mass detected on imaging or those with gallbladder cancer and jaundice, the panel recommends that those patients deemed as having resectable gallbladder cancer should undergo cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision.^{208, 218} Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct if possible.

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 and long term survival approaches 100% with simple cholecystectomy.²⁰⁹ For patients with T1b or greater lesions, extended cholecystectomy 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 significant percentage of these patients and an association between increasing risk of metastasis to locoregional lymph nodes and increasing T stage.²¹⁷ Therefore, if resectable, patients should undergo hepatic resection and lymphadenectomy with or without bile duct excision.²¹⁹ 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 procedure. 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, although these comparisons are difficult to interpret due to selection bias.^{220, 221} 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 role of adjuvant treatment strategy for patients with resected gallbladder cancer has not been determined, options include consideration of fluoropyrimidine chemoradiation (except T1b, N0) and fluoropyrimidine or gemcitabine chemotherapy (see section on “Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”).

Unresectable disease

For patients with unresectable disease (includes distant metastases, nodal metastases beyond the porta hepatis and extensive involvement of the porta hepatis causing jaundice or vascular encasement) after preoperative evaluation, a biopsy should be performed to confirm the diagnosis. Treatment options for these patients include fluoropyrimidine-based or gemcitabine-based chemotherapy and fluoropyrimidine chemoradiation (in patients with localized disease) (see section on “Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”), participation in a clinical trial or best supportive care. 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. CA 19-9 testing can be considered after biliary decompression. Biliary drainage followed by chemotherapy can result in improved quality of life.²²²

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 relapse or progression.

Cholangiocarcinomas

The term cholangiocarcinoma encompasses all tumors originating in the epithelium of the bile duct.^{223, 224} 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 are located within the hepatic parenchyma and have also been called “peripheral cholangiocarcinomas” (Figure 1). 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 (Figure 1). Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas and perihilar cholangiocarcinoma is most common type of extrahepatic cholangiocarcinoma.²²⁵ In these Guidelines, extrahepatic cholangiocarcinomas include perihilar cholangiocarcinomas (also called Klatskin tumors) which occur at or near the junction of the right and left hepatic ducts and the distal bile duct tumors arising in the extrahepatic bile ducts above the ampulla of Vater. The guidelines do not include tumors of the ampulla of Vater.

Risk Factors

No predisposing factors have been identified in most patients diagnosed with cholangiocarcinoma,²²⁶ 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.^{224, 227} Unlike gallbladder cancer, however, cholelithiasis is not thought to be closely linked with the etiology of cholangiocarcinoma. Recently, however, intrahepatic cholangiocarcinoma has been associated with hepatitis C viral infection,²²⁸ and this may be responsible for the increased incidence of intrahepatic cholangiocarcinoma recently observed at some centers.²²⁹ Nevertheless, future studies are needed to further explore this putative association.²³⁰

Diagnosis and Initial Workup

Early stage cholangiocarcinomas are typically asymptomatic. The patient with intrahepatic cholangiocarcinoma is more likely to present 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.⁴² 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.²⁰⁸

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,²⁰⁸ and are also associated with other malignancies and benign conditions.²³¹ Early surgical consultation

with a multidisciplinary team is recommended as part of the initial workup for assessment of resectability in both types of cholangiocarcinomas.

Delayed contrast CT/MRI is recommended as part of the workup of patients with intrahepatic cholangiocarcinoma. Although there are no pathognomonic CT/MRI features associated with intrahepatic cholangiocarcinoma, CT/MRI 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.⁴² In addition, chest imaging should be performed, and laparoscopy may be done in conjunction with surgery if no distant metastasis is found. Upper and lower endoscopy should be considered to exclude extrahepatic primary gastrointestinal tumors. However, this may not be necessary if immunohistochemistry/pathology is conclusive of intrahepatic cholangiocarcinoma. Immunostaining with cytokeratins 7 and 20 have been found to be helpful in distinguishing intrahepatic cholangiocarcinoma (CK7+, CK20- and CDX2-) from metastasis from colon cancer (CDX2+, CK20+).²³² The panel emphasizes 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/MRI 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.⁴² Since many of these patients present with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor.⁴² Magnetic resonance cholangiography (MRCP) is noninvasive and 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 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.^{211, 212}

Pathology and Staging

More than 90% of cholangiocarcinomas are adenocarcinomas.²³³ Cholangiocarcinomas can be divided into 3 types depending on macroscopic appearance: mass-forming; periductal-infiltrating; and intraductal-growing.^{223, 233}

The AJCC has developed staging systems for cholangiocarcinomas. In the 6th edition of the AJCC staging system, intrahepatic cholangiocarcinoma was staged identical to HCC. However, this staging system did not include predictive clinicopathologic features that are specific to intrahepatic cholangiocarcinoma. Other more practical staging systems for intrahepatic cholangiocarcinoma have been used.^{234, 235} In the revised 7th edition of the AJCC staging classification, intrahepatic cholangiocarcinoma has a new staging system that is independent of the staging system used for HCC.⁷⁷ The 7th AJCC staging classification is based on the data from the SEER program on 598 patients with intrahepatic cholangiocarcinoma who had undergone surgery.²³⁵ In this study by Nathan et al., tumor size had no independent effect on survival.²³⁵ In addition, multiple tumors and vascular invasion had similar effects on prognosis, but the presence of both of these factors did not confer additional risk compared to the

presence of either one.⁹⁸ Based on the results of this study, the new staging system focuses on multiple tumors, vascular invasion and lymph node metastasis. Farges et al from the AFC-IHCC study group validated the new staging classification in 163 patients with resectable intrahepatic cholangiocarcinoma.²³⁶ The revised classification was useful in predicting survival according to the TNM staging. With an average follow-up of 34 months, the median survival was not reached for patients with stage I disease, 53 months for those with stage II disease (P = 0.01) and 16 months for stage III disease (P < 0.0001).

The 7th Edition of AJCC staging system for extrahepatic cholangiocarcinomas includes separate staging for perihilar and distal bile duct tumors.⁷⁷ It is based on pathologic criteria but it is not useful for determining resectability or predicting outcome. Jarnagin and colleagues have developed a useful preoperative staging system for hilar cholangiocarcinoma that predicts resectability, likelihood of metastatic disease, and survival.²³⁷

Management

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. Endo et al reported that multiple hepatic tumors, regional nodal involvement and large tumor size independently predicted poor recurrence-free survival following resection.²²⁹ More recently, Nathan et al. reported that multiple lesions and vascular invasion predicted adverse prognosis following resection; lymph node status was of prognostic significance among patients without distant metastases.²³⁵ The 3- and 5-year survival rates were 40% and 25% respectively for patients with N0M0 disease compared to 21% and 4% respectively for those with N1M0 disease.²³⁵ Multifocal tumors and lymph node

metastases are considered contraindications to surgery due to the poor survival after resection but surgical approaches can be considered in highly selected cases.

Surgery involves hepatic resection whose extent is dictated by what is necessary to achieve clear margins (eg. removal of hepatic lobe or segment along the bile duct in which the tumor is located).²³⁸ 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.²³⁹ Five-year survival rates in the range of 20% to 43% have been reported.²³⁹⁻²⁴² 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. These patients should also be evaluated by an experienced hepatobiliary surgeon to determine if re-resection (although uncommon) may be considered. 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 section on “Chemoradiation and 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. 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.^{237,243} 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.²⁰⁸ 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^{237, 244, 245} and 37% for bile duct cancers in the distal third of the extrahepatic biliary tree.²²³

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 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.^{246, 247} Pre-operative biliary drainage is accomplished by ERCP or PTC.

Among patients with resectable disease, those 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), gross 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: fluoropyrimidine chemoradiation (brachytherapy or external beam) followed by additional fluoropyrimidine or gemcitabine chemotherapy or fluoropyrimidine-based or gemcitabine-based chemotherapy for patients with positive regional nodes. Data to support particular chemoradiation and chemotherapy regimens are limited. (See section on “Chemoradiation/Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”).

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 be considered for biliary drainage using either surgical bypass (although rarely used) or an endoscopic (ERCP) or percutaneous approach (PTC), most often involving biliary stent placement.^{208, 248-250} Biopsy is also recommended to confirm diagnosis before initiation of further treatment. Additional treatment options include participation in a clinical trial, fluoropyrimidine chemoradiation, fluoropyrimidine-based or gemcitabine-based chemotherapy or best supportive care. 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. Data to support particular chemoradiation and chemotherapy regimens are limited. (See section on “Chemoradiation and Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”).

Radioembolization with Yttrium-90 microspheres has been shown to be a safe and effective therapeutic option in 2 small series of patients with intrahepatic cholangiocarcinoma.^{251, 252} Photodynamic therapy (PDT) 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 in patients with cholangiocarcinoma.^{253, 254} The combination of PDT with biliary stenting was reported to improve the overall survival of patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.^{255, 256}

Liver transplantation is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma.^{257, 258} 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.²⁵⁹ Nevertheless, there were substantial differences in the characteristics of patients in the two treatment groups in this study. The panel encourages continuation of clinical research in this area.

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.

Chemoradiation and Chemotherapy for Treatment of Gallbladder Cancer and Cholangiocarcinoma

Due to the low incidence of biliary tract cancers (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 II 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.²⁶⁰ Nevertheless, due to the limited data and the heterogeneous patient populations in many of the published studies, in most cases, recommendations in these guidelines on the 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.²¹³ 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.²⁶¹

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,^{213, 262} although the number of patients who received such therapy was very limited in one study,²¹³ and chemotherapy did not include newer agents in the latter study which covered the period from 1988-1997.²⁶² A phase III trial evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer.²⁶³ 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.²¹⁴ 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.

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.²⁶⁴⁻²⁶⁶ 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.²⁶¹ 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.^{267, 268} 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 (> 5 years) follow-up.²⁶⁹

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.²⁷⁰ Results of these studies provide support for omitting adjuvant chemoradiation in the post-surgical treatment of patients with gallbladder cancer characterized as T1b, N0.

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.²⁷¹ 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 were 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.²⁷² In another retrospective analysis of patients with curatively extrahepatic cholangiocarcinoma, adjuvant concurrent chemoradiation (CCRT) followed by adjuvant chemotherapy was found to have a survival benefit especially in patients with R1 resection or negative lymph node compared to adjuvant CCRT alone.²⁷³ The 3-year disease-free survival rates for CCRT alone and CCRT followed by adjuvant chemotherapy were 27% and 45.2% ($p = 0.04$), respectively. The corresponding overall survival rates were 31% and 63% ($p < 0.01$), respectively. 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.

Most of the collective experience of chemoradiation in biliary tract cancer involves concurrent chemoradiation and 5-FU.^{264, 265} More recently, concurrent chemoradiation with capecitabine has also been used.^{272, 274} Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.²⁷⁵

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.²⁷⁶ 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.²⁷⁷ A subsequent phase III 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 months vs. 9 months, respectively), although the trial was underpowered to detect such a difference.²⁷⁸ 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 as reviewed by Hezel and Zhu.²⁶⁰ Examples of chemotherapy combinations demonstrated in phase II trials to have activity in the treatment of advanced biliary tract cancers include: gemcitabine and cisplatin,²⁷⁹⁻²⁸¹ gemcitabine and capecitabine,^{282, 283} gemcitabine and oxaliplatin,^{284, 285} capecitabine and oxaliplatin,²⁸⁶ capecitabine/cisplatin²⁸⁷ and 5-FU and cisplatin.²⁸⁸ 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.²⁸⁹ 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.²⁹⁰ 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 III 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.²⁹¹ 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 and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the 2 arms. Based on the results of this study, the combination of gemcitabine and cisplatin is considered to be the standard of care as first-line chemotherapy for patients with advanced or metastatic biliary tract cancers.²⁹¹

The panel has included combination therapy with gemcitabine and cisplatin with a category 1 recommendation for patients with unresectable or advanced biliary tract cancers. Based on the experiences from phase II studies the following gemcitabine-based and fluoropyrimidine-based combination chemotherapy regimens are included with a category 2A recommendation for the treatment of patients with advanced biliary tract cancer: gemcitabine with oxaliplatin or capecitabine; capecitabine with cisplatin or oxaliplatin; 5-FU with cisplatin or oxaliplatin; as well as single agent 5-FU, capecitabine, and gemcitabine. The combination of gemcitabine and 5-FU is not included due to the increased toxicity and decreased efficacy observed with this regimen²⁹² when compared with results of studies of the gemcitabine and capecitabine regimen in the setting of advanced biliary tract cancer.²⁶⁰

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.^{264, 265} 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 71% at 1- and 2-years, respectively).²⁹³ The most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers has been 5-FU,^{264, 265} although capecitabine has been substituted for 5-FU in some studies.²⁷⁴ The panel recommends that concurrent chemoradiation 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 not recommended due to the limited experience and toxicity associated with this treatment.

Summary

Hepatobiliary cancers are associated with a poor prognosis. Many patients with HCC are diagnosed at an advanced stage and patients with biliary tract cancers commonly present with advanced disease. In the past few years, several advances have been made in therapeutic approaches for patients with hepatobiliary cancers.

The safety and efficacy of sorafenib as front-line therapy for patients with advanced HCC and Child-Pugh A liver function was demonstrated in two randomized placebo-controlled studies. Sorafenib is recommended as a category 1 option for this group of patients and is included as a category 2A option for selected patients with Child-Pugh

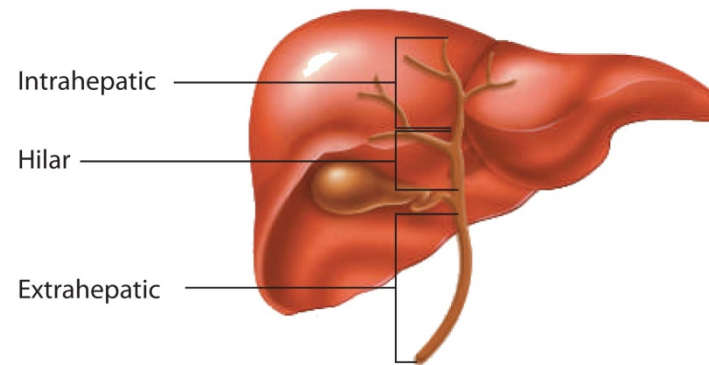


class B liver function. The results of the randomized phase III ABC-02 study demonstrated a survival advantage for the combination of gemcitabine and cisplatin over gemcitabine alone in patients with advanced or metastatic biliary tract cancers. Gemcitabine and cisplatin is included as a category 1 recommendation for this group of patients.

Locoregional therapies such as TACE and radioembolization with yttrium-90 microspheres play a key role in the management of HCC, especially in patients with early stage disease who are not candidates for surgery. Liver transplant is the best available curative option for patients with early stage HCC who meet the Milan criteria and for patients with cholangiocarcinoma.

It is essential that all patients should be evaluated for treatment; 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.

Figure 1: Classification of Cholangiocarcinoma.



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References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20610543>.
2. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127:S35-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15508101>.
3. Bosch FX, Ribes J, Borràs J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999;19:271-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10518307>.
4. Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. *AASLD Practice Guidelines*; 2010. Available at: <http://www.aasld.org/practiceguidelines/Documents/HCCUpdate2010.pdf>.
5. Di Bisceglie AM, Lyra AC, Schwartz M, et al. Hepatitis C-related hepatocellular carcinoma in the United States: influence of ethnic status. *Am J Gastroenterol* 2003;98:2060-2063. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14499788>.
6. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1997;12:S294-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9407350>.
7. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168-174. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12124405>.
8. Chen G, Lin W, Shen F, et al. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006;101:1797-1803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16817842>.
9. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16391218>.
10. Lee MH, Yang HI, Lu SN, et al. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma: long-term predictors from a community-based cohort study. *J Clin Oncol* 2010;28:4587-4593. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20855826>.
11. Ishiguro S, Inoue M, Tanaka Y, et al. Impact of viral load of hepatitis C on the incidence of hepatocellular carcinoma: A population-based cohort study (JPHC Study). *Cancer Lett* 2011;300:173-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21035947>.
12. Blonski W, Kotlyar DS, Forde KA. Non-viral causes of hepatocellular carcinoma. *World J Gastroenterol* 2010;16:3603-3615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20677332>.
13. Yeoman AD, Al-Chalabi T, Karani JB, et al. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. *Hepatology* 2008;48:863-870. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18752332>.
14. Marchesini G, Bugianesi E, Forlani G, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003;37:917-923. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12668987>.
15. Takamatsu S, Noguchi N, Kudoh A, et al. Influence of risk factors for metabolic syndrome and non-alcoholic fatty liver disease on the progression and prognosis of hepatocellular carcinoma. *Hepatogastroenterology* 2008;55:609-614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18613418>.
16. Bartlett DL, Di Bisceglie AM, Dawson LA. Cancer of the liver. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and*

Practice of Oncology (ed 8): Wolters Kluwer; Lippincott Williams & Wilkins; 2008:1129-1156.

17. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. AASLD Practice Guidelines (ed 2009/08/29); 2009. Available at: <http://www.aasld.org/practiceguidelines/Pages/SortablePracticeGuidelinesAlpha.aspx>.

18. Volk ML, Marrero JA. Early detection of liver cancer: diagnosis and management. *Curr Gastroenterol Rep* 2008;10:60-66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18417044>.

19. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology* 2009;136:138-148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18848939>.

20. Beaton MD, Adams PC. Prognostic factors and survival in patients with hereditary hemochromatosis and cirrhosis. *Can J Gastroenterol* 2006;20:257-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16609753>.

21. Department of Health and Human Services Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey. . Available at: <http://www.cdc.gov/nchs/data/nhanes/databriefs/viralhep.pdf>.

22. Alter MJ. The epidemiology of acute and chronic hepatitis C. *Clin Liver Dis* 1997;1:559-568. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15560058>.

23. Ryder SD, Irving WL, Jones DA, et al. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. *Gut* 2004;53:451-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14960533>.

24. Lavanchy D. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. *J Clin Virol* 2005;34 Suppl 1:1-3. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16461208>.

25. Goldstein ST, Zhou F, Hadler SC, et al. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol* 2005;34:1329-1339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16249217>.

26. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981;2:1129-1133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6118576>.

27. Younossi ZM. Review article: current management of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2008;28:2-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18410557>.

28. Ascha MS, Hanouneh IA, Lopez R, et al. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010;51:1972-1978. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20209604>.

29. Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006;43:682-689. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16502396>.

30. Yatsuji S, Hashimoto E, Tobari M, et al. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. *J Gastroenterol Hepatol* 2009;24:248-254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19032450>.

31. Asare GA, Bronz M, Naidoo V, Kew MC. Synergistic interaction between excess hepatic iron and alcohol ingestion in hepatic

mutagenesis. *Toxicology* 2008;254:11-18. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18852013>.

32. Singal AK, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *J Clin Gastroenterol* 2007;41:761-772. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17700425>.

33. Zhang B-H, Yang B-H, Tang Z-Y. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004;130:417-422. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15042359>.

34. Chang P-E, Ong W-C, Lui H-F, Tan C-K. Is the prognosis of young patients with hepatocellular carcinoma poorer than the prognosis of older patients? A comparative analysis of clinical characteristics, prognostic features, and survival outcome. *J Gastroenterol* 2008;43:881-888. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19012042>.

35. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008;134:1752-1763. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18471552>.

36. Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. *J Med Screen* 1999;6:108-110. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10444731>.

37. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. *Hepatology* 2009;49:658-664. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19177576>.

38. Lok AS, Sterling RK, Everhart JE, et al. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology* 2010;138:493-502.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19852963>.

39. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 2000;31:302-308. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11129271>.

40. Breedis C, Young G. The blood supply of neoplasms in the liver. *Am J Pathol* 1954;30:969-977. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/13197542>.

41. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001;35:421-430. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11592607>.

42. Miller G, Schwartz LH, D'Angelica M. The use of imaging in the diagnosis and staging of hepatobiliary malignancies. *Surg Oncol Clin N Am* 2007;16:343-368. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17560517>.

43. Marrero JA, Hussain HK, Nghiem HV, et al. Improving the prediction of hepatocellular carcinoma in cirrhotic patients with an arterially-enhancing liver mass. *Liver Transpl* 2005;11:281-289.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15719410>.

44. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology* 2008;47:97-9104. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18069697>.

45. Sangiovanni A, Manini MA, Iavarone M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. *Gut* 2010;59:638-644.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19951909>.

46. Stewart CJR, Coldewey J, Stewart IS. Comparison of fine needle aspiration cytology and needle core biopsy in the diagnosis of radiologically detected abdominal lesions. *J Clin Pathol* 2002;55:93-97. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11865001>.

47. Pupulim LF, Felce-Dachez M, Paradis V, et al. Algorithm for immediate cytologic diagnosis of hepatic tumors. *AJR Am J Roentgenol* 2008;190:208-212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18287414>.

48. Asmis T, Balaa F, Scully L, et al. Diagnosis and management of hepatocellular carcinoma: results of a consensus meeting of The Ottawa Hospital Cancer Centre. *Curr Oncol* 2010;17:6-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20404972>.

49. Renshaw AA, Haja J, Wilbur DC, Miller TR. Fine-needle aspirates of adenocarcinoma/metastatic carcinoma that resemble hepatocellular carcinoma: correlating cytologic features and performance in the College of American Pathologists Nongynecologic Cytology Program. *Arch Pathol Lab Med* 2005;129:1217-1221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16196506>.

50. Pawlik TM, Gleisner AL, Anders RA, et al. Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. *Ann Surg* 2007;245:435-442. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17435551>.

51. Farinati F, Marino D, De Giorgio M, et al. Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither? *Am J Gastroenterol* 2006;101:524-532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16542289>.

52. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol* 2001;34:570-575. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11394657>.

53. Torzilli G, Minagawa M, Takayama T, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. *Hepatology* 1999;30:889-893. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10498639>.

54. Levy I, Greig PD, Gallinger S, et al. Resection of hepatocellular carcinoma without preoperative tumor biopsy. *Ann Surg* 2001;234:206-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11505066>.

55. Lok AS, Lai CL. alpha-Fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection: role in the early detection of hepatocellular carcinoma. *Hepatology* 1989;9:110-115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2461890>.

56. Debruyne EN, Delanghe JR. Diagnosing and monitoring hepatocellular carcinoma with alpha-fetoprotein: new aspects and applications. *Clin Chim Acta* 2008;395:19-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18538135>.

57. Durazo FA, Blatt LM, Corey WG, et al. Des-gamma-carboxyprothrombin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. *J Gastroenterol Hepatol* 2008;23:1541-1548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18422961>.

58. Marrero JA, Feng Z, Wang Y, et al. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 2009;137:110-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19362088>.

59. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009;49:1335-1374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19330875>.

60. Kataly S, Oliver JH, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. *Radiology* 2000;216:698-703. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10966697>.
61. Natsuizaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. *J Gastroenterol Hepatol* 2005;20:1781-1787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16246200>.
62. Dodd GD, 3rd, Baron RL, Oliver JH, 3rd, et al. Enlarged abdominal lymph nodes in end-stage cirrhosis: CT-histopathologic correlation in 507 patients. *Radiology* 1997;203:127-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9122379>.
63. Cooper GS, Bellamy P, Dawson NV, et al. A prognostic model for patients with end-stage liver disease. *Gastroenterology* 1997;113:1278-1288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9322523>.
64. Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-649. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4541913>.
65. Cholongitas E, Papatheodoridis GV, Vangelis M, et al. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Aliment Pharmacol Ther* 2005;22:1079-1089. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16305721>.
66. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996;111:1018-1022. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8831597>.
67. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. *Hepatology* 2004;39:280-282. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14767976>.
68. Boyer TD. Changing clinical practice with measurements of portal pressure. *Hepatology* 2004;39:283-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14767977>.
69. Thalheimer U, Mela M, Patch D, Burroughs AK. Targeting portal pressure measurements: a critical reappraisal. *Hepatology* 2004;39:286-290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14767978>.
70. Malinchoc M, Kamath PS, Gordon FD, et al. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864-871. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10733541>.
71. Martin AP, Bartels M, Hauss J, Fangmann J. Overview of the MELD score and the UNOS adult liver allocation system. *Transplant Proc* 2007;39:3169-3174. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18089345>.
72. Clavien P-A, Breitenstein S, Belghiti J, et al. *Malignant Liver Tumors: Current and Emerging Therapies* (ed 3): John Wiley and Sons, Inc.; 2010.
73. Yuki K, Hirohashi S, Sakamoto M, et al. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. *Cancer* 1990;66:2174-2179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2171748>.
74. Dohmen K. Many staging systems for hepatocellular carcinoma: evolution from Child-Pugh, Okuda to SLiDe. *J Gastroenterol Hepatol* 2004;19:1227-1232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15482527>.
75. Marrero JA, Fontana RJ, Barrat A, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort.

Hepatology 2005;41:707-716. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15795889>.

76. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11172350>.

77. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual (ed 7). New York, NY: Springer; 2010.

78. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-928. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/2990661>.

79. Chevret S, Trinchet JC, Mathieu D, et al. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. J Hepatol 1999;31:133-141. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10424293>.

80. Leung TWT, Tang AMY, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. Cancer 2002;94:1760-1769. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11920539>.

81. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207-215. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12673442>.

82. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian

Program (CLIP) investigators. Hepatology 1998;28:751-755. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9731568>.

83. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-338. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10518312>.

84. Omagari K, Honda S, Kadokawa Y, et al. Preliminary analysis of a newly proposed prognostic scoring system (SLiDe score) for hepatocellular carcinoma. J Gastroenterol Hepatol 2004;19:805-811. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15209629>.

85. Huo T-I, Lin H-C, Huang Y-H, et al. The model for end-stage liver disease-based Japan Integrated Scoring system may have a better predictive ability for patients with hepatocellular carcinoma undergoing locoregional therapy. Cancer 2006;107:141-148. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16708358>.

86. Limquiaco JL, Wong GLH, Wong VWS, et al. Evaluation of model for end stage liver disease (MELD)-based systems as prognostic index for hepatocellular carcinoma. J Gastroenterol Hepatol 2009;24:63-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19054256>.

87. Nanashima A, Sumida Y, Abo T, et al. Modified Japan Integrated Staging is currently the best available staging system for hepatocellular carcinoma patients who have undergone hepatectomy. J Gastroenterol 2006;41:250-256. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16699859>.

88. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-1236. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16250051>.

89. Wang J-H, Changchien C-S, Hu T-H, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma - Survival analysis of 3892 patients. Eur J Cancer 2008;44:1000-1006. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18337087>.

90. Vauthey J-N, Ribero D, Abdalla EK, et al. Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation of a uniform staging after surgical treatment. *J Am Coll Surg* 2007;204:1016-1027. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17481532>.
91. Huitzil-Melendez FD, Capanu M, O'Reilly EM, et al. Advanced hepatocellular carcinoma: which staging systems best predict prognosis? *J Clin Oncol* 2010;28:2889-2895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20458042>.
92. Cho YK, Chung JW, Kim JK, et al. Comparison of 7 staging systems for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. *Cancer* 2008;112:352-361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18008352>.
93. Collette S, Bonnetain F, Paoletti X, et al. Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials. *Ann Oncol* 2008;19:1117-1126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18303031>.
94. Cabibbo G, Enea M, Attanasio M, et al. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010;51:1274-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20112254>.
95. Guglielmi A, Ruzzenente A, Pachera S, et al. Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. *Am J Gastroenterol* 2008;103:597-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17970836>.
96. Cho CS, Gonen M, Shia J, et al. A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. *J Am Coll Surg* 2008;206:281-291. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18222381>.
97. Nathan H, Schulick RD, Choti MA, Pawlik TM. Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg* 2009;249:799-805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19387322>.
98. Nathan H, Mentha G, Marques HP, et al. Comparative performances of staging systems for early hepatocellular carcinoma. *HPB (Oxford)* 2009;11:382-390. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768142>.
99. Kelley RK, Venook AP. Sorafenib in hepatocellular carcinoma: separating the hype from the hope. *J Clin Oncol* 2008;26:5845-5848. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19029408>.
100. Jarnagin WR. Management of small hepatocellular carcinoma: a review of transplantation, resection, and ablation. *Ann Surg Oncol* 2010;17:1226-1233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20405327>.
101. Truty MJ, Vauthey J-N. Surgical resection of high-risk hepatocellular carcinoma: patient selection, preoperative considerations, and operative technique. *Ann Surg Oncol* 2010;17:1219-1225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20405326>.
102. Pawlik TM, Poon RT, Abdalla EK, et al. Critical appraisal of the clinical and pathologic predictors of survival after resection of large hepatocellular carcinoma. *Arch Surg* 2005;140:450-457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15897440>.
103. Chok KS, Ng KK, Poon RT, et al. Impact of postoperative complications on long-term outcome of curative resection for hepatocellular carcinoma. *Br J Surg* 2009;96:81-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19065644>.
104. Kianmanesh R, Regimbeau JM, Belghiti J. Selective approach to major hepatic resection for hepatocellular carcinoma in chronic liver

disease. *Surg Oncol Clin N Am* 2003;12:51-63. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12735129>.

105. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30:1434-1440. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10573522>.

106. Poon RT-P, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002;235:373-382. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11882759>.

107. Seo DD, Lee HC, Jang MK, et al. Preoperative portal vein embolization and surgical resection in patients with hepatocellular carcinoma and small future liver remnant volume: comparison with transarterial chemoembolization. *Ann Surg Oncol* 2007;14:3501-3509. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17899289>.

108. Wei AC, Tung-Ping Poon R, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg* 2003;90:33-41. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12520572>.

109. Ribero D, Curley SA, Imamura H, et al. Selection for resection of hepatocellular carcinoma and surgical strategy: indications for resection, evaluation of liver function, portal vein embolization, and resection. *Ann Surg Oncol* 2008;15:986-992. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18236112>.

110. Tsai TJ, Chau GY, Lui WY, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. *Surgery* 2000;127:603-608. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10840353>.

111. Abdalla EK, Denys A, Hasegawa K, et al. Treatment of large and advanced hepatocellular carcinoma. *Ann Surg Oncol* 2008;15:979-985. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18236115>.

112. Jonas S, Bechstein WO, Steinmuller T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001;33:1080-1086. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11343235>.

113. Vauthey J-N, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002;20:1527-1536. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11896101>.

114. Yamakado K, Nakatsuka A, Takaki H, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. *Radiology* 2008;247:260-266. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18305190>.

115. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997;26:1176-1181. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/9362359>.

116. Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. *J Gastrointest Surg* 2003;7:325-330. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12654556>.

117. Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. *Ann Surg* 2003;237:208-217. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12560779>.

118. 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;334:693-699. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/8594428>.

119. Mazzaferro V, Chun YS, Poon RTP, et al. Liver transplantation for hepatocellular carcinoma. *Ann Surg Oncol* 2008;15:1001-1007. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18236119>.

120. Llovet JM, Bruix J, Gores GJ. Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. *Hepatology* 2000;31:1019-1021. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10733561>.

121. Facciuto ME, Koneru B, Rocca JP, et al. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. *Ann Surg Oncol* 2008;15:1383-1391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18320284>.

122. Poon RT. Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection? *Ann Surg Oncol* 2007;14:541-547. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17103069>.

123. Poon RT, Fan ST, Lo CM, et al. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. *Ann Surg* 2007;245:51-58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17197965>.

124. Volk ML, Hernandez JC, Lok AS, Marrero JA. Modified Charlson comorbidity index for predicting survival after liver transplantation. *Liver Transpl* 2007;13:1515-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17969207>.

125. Ioannou GN, Perkins JD, Carithers RL. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. *Gastroenterology* 2008;134:1342-1351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18471511>.

126. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. *Am*

J Transplant 2008;8:839-846. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18318783>.

127. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007;246:502-509. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17717454>.

128. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11391528>.

129. Volk M, Marrero JA. Liver transplantation for hepatocellular carcinoma: who benefits and who is harmed? *Gastroenterology* 2008;134:1612-1614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18471530>.

130. Lee S-G, Hwang S, Moon D-B, et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl* 2008;14:935-945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18581465>.

131. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100:698-711. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18477802>.

132. Majno P, Giostra E, Mentha G. Management of hepatocellular carcinoma on the waiting list before liver transplantation: time for controlled trials? *Liver Transpl* 2007;13:S27-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17969086>.

133. Pompili M, Mirante VG, Rondinara G, et al. Percutaneous ablation procedures in cirrhotic patients with hepatocellular carcinoma submitted to liver transplantation: Assessment of efficacy at explant analysis and of safety for tumor recurrence. *Liver Transpl* 2005;11:1117-1126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16123960>.

134. Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004;240:900-909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15492574>.

135. Yao FY, Bass NM, Nikolai B, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. *Liver Transpl* 2003;9:684-692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12827553>.

136. DuBay DA, Sandroussi C, Kachura JR, et al. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *HPB (Oxford)* 2011;13:24-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21159100>.

137. Sandroussi C, Dawson LA, Lee M, et al. Radiotherapy as a bridge to liver transplantation for hepatocellular carcinoma. *Transpl Int* 2010;23:299-306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19843294>.

138. Richard HM, Silberzweig JE, Mitty HA, et al. Hepatic arterial complications in liver transplant recipients treated with pretransplantation chemoembolization for hepatocellular carcinoma. *Radiology* 2000;214:775-779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10715045>.

139. Graziadei IW, Sandmueller H, Waldenberger P, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003;9:557-563. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12783395>.

140. Hayashi PH, Ludkowski M, Forman LM, et al. Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. *Am J Transplant* 2004;4:782-787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15084175>.

141. Vitale A, Volk ML, Pastorelli D, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. *Hepatology* 2010;51:165-173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19877181>.

142. Freeman RB, Steffick DE, Guidinger MK, et al. Liver and intestine transplantation in the United States, 1997-2006. *Am J Transplant* 2008;8:958-976. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18336699>.

143. Campos BD, Botha JF. Transplantation for hepatocellular carcinoma and cholangiocarcinoma. *J Natl Compr Canc Netw* 2009;7:409-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19406041>.

144. Toso C, Mentha G, Kneteman NM, Majno P. The place of downstaging for hepatocellular carcinoma. *J Hepatol* 2010;52:930-936. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20385428>.

145. Ravaioli M, Grazi GL, Piscaglia F, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008;8:2547-2557. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19032223>.

146. Yao FY, Kerlan RK, Jr., Hirose R, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008;48:819-827. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18688876>.

147. Chapman WC, Majella Doyle MB, Stuart JE, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008;248:617-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18936575>.

148. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009;9:1920-1928. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19552767>.

149. Jang JW, You CR, Kim CW, et al. Benefit of downsizing hepatocellular carcinoma in a liver transplant population. *Aliment Pharmacol Ther* 2010;31:415-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19821808>.

150. Millonig G, Graziadei IW, Freund MC, et al. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007;13:272-279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17256758>.

151. Otto G, Herber S, Heise M, et al. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006;12:1260-1267. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16826556>.

152. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19097774>.

153. Duke E, Deng J, Ibrahim SM, et al. Agreement between competing imaging measures of response of hepatocellular carcinoma to yttrium-90 radioembolization. *J Vasc Interv Radiol* 2010;21:515-521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20172741>.

154. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;30:52-60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20175033>.

155. Riaz A, Miller FH, Kulik LM, et al. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. *JAMA* 2010;303:1062-1069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20233824>.

156. Riaz A, Ryu RK, Kulik LM, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol* 2009;27:5734-5742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19805671>.

157. Vivarelli M, Guglielmi A, Ruzzenente A, et al. Surgical resection versus percutaneous radiofrequency ablation in the treatment of hepatocellular carcinoma on cirrhotic liver. *Ann Surg* 2004;240:102-107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15213625>.

158. Lin SM, Lin CJ, Lin CC, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005;54:1151-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16009687>.

159. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology* 2000;214:761-768. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10715043>.

160. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008;47:82-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18008357>.

161. Chen M-S, Li J-Q, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy

for small hepatocellular carcinoma. *Ann Surg* 2006;243:321-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16495695>.

162. Lin S-M, Lin C-J, Lin C-C, et al. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. *Gastroenterology* 2004;127:1714-1723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15578509>.

163. Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: A randomized controlled trial. *Scand J Gastroenterol* 2008;43:727-735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18569991>.

164. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129:122-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16012942>.

165. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010;252:903-912. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21107100>.

166. Yan K, Chen MH, Yang W, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. *Eur J Radiol* 2008;67:336-347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17765421>.

167. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. *Eur Radiol* 2007;17:684-692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17093964>.

168. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004;40:1352-1360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15565564>.

169. Liapi E, Geschwind J-FH. Intra-arterial therapies for hepatocellular carcinoma: where do we stand? *Ann Surg Oncol* 2010;17:1234-1246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20405328>.

170. Maluccio M, Covey AM, Gandhi R, 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;16:955-961. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16002503>.

171. Maluccio MA, Covey AM, Porat LB, et al. Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2008;19:862-869. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18503900>.

172. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008;47:71-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18027884>.

173. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734-1739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12049862>.

174. Ramsey DE, Kernagis LY, Soulen MC, Geschwind J-FH. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13:211-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12354839>.

175. O'Neil BH, Venook AP. Hepatocellular carcinoma: the role of the North American GI Steering Committee Hepatobiliary Task Force and the advent of effective drug therapy. *Oncologist* 2007;12:1425-1432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18165619>.

176. Lo C-M, Ngan H, Tso W-K, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular

carcinoma. *Hepatology* 2002;35:1164-1171. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11981766>.

177. Stuart K, Stokes K, Jenkins R, et al. Treatment of hepatocellular carcinoma using doxorubicin/ethiodized oil/gelatin powder chemoembolization. *Cancer* 1993;72:3202-3209. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/7694787>.

178. Llado L, Virgili J, Figueras J, et al. A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *Cancer* 2000;88:50-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10618605>.

179. Doan PL, O'Neil BH, Moore DT, Bernard SA. Predictors of survival in patients with hepatocellular carcinoma treated with transarterial chemoembolization. *ASCO Meeting Abstracts* 2008;26:15522. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/15522.

180. Molinari M, Kachura JR, Dixon E, et al. Transarterial chemoembolisation for advanced hepatocellular carcinoma: results from a North American cancer centre. *Clin Oncol (R Coll Radiol)* 2006;18:684-692. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17100154>.

181. Poon RT, Tso WK, Pang RW, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. *Clin Gastroenterol Hepatol* 2007;5:1100-1108. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17627902>.

182. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. *Cancer J* 2009;15:526-532. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20010173>.

183. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33:41-52. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19908093>.

184. Dhanasekaran R, Kooby DA, Staley CA, et al. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocellular carcinoma (HCC). *J Surg Oncol* 2010;101:476-480. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20213741>.

185. Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2010;33:541-551. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19937027>.

186. Ibrahim SM, Lewandowski RJ, Sato KT, et al. Radioembolization for the treatment of unresectable hepatocellular carcinoma: a clinical review. *World J Gastroenterol* 2008;14:1664-1669. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18350597>.

187. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;138:52-64. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19766639>.

188. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization Results in Longer Time-to-Progression and Reduced Toxicity Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. *Gastroenterology* 2011;140:497-507.e492. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21044630>.

189. Atassi B, Bangash AK, Bahrani A, et al. Multimodality imaging following 90Y radioembolization: a comprehensive review and pictorial

essay. Radiographics 2008;28:81-99. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18203932>.

190. Hawkins MA, Dawson LA. Radiation therapy for hepatocellular carcinoma: from palliation to cure. Cancer 2006;106:1653-1663. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16541431>.

191. Hoffe SE, Finkelstein SE, Russell MS, Shridhar R. Nonsurgical options for hepatocellular carcinoma: evolving role of external beam radiotherapy. Cancer Control 2010;17:100-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20404793>.

192. Cardenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clin Transl Oncol 2010;12:218-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20231127>.

193. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26:657-664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18172187>.

194. Thomas MB, O'Beirne JP, Furuse J, et al. Systemic therapy for hepatocellular carcinoma: cytotoxic chemotherapy, targeted therapy and immunotherapy. Ann Surg Oncol 2008;15:1008-1014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18236117>.

195. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005;97:1532-1538. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16234567>.

196. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18650514>.

197. Cheng AL, Kang YK, 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19095497>.

198. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24:4293-4300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16908937>.

199. Bruix J, Cheng A, Kang Y, et al. Effect of macroscopic vascular invasion (MVI), extrahepatic spread (EHS), and ECOG performance status (ECOG PS) on outcome in patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib: Analysis of two phase III, randomized, double-blind trials. ASCO Meeting Abstracts 2009;27:4580. Available at: <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4580>.

200. Craxi A, Porta C, Sangiovanni A, et al. Efficacy and safety of sorafenib in patients with alcohol-related hepatocellular carcinoma: A sub-analysis from the SHARP trial. ASCO Meeting Abstracts 2008;26:15591. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/15591.

201. Bolondi L, Caspary W, Bennouna J, et al. Clinical benefit of sorafenib in hepatitis C patients with hepatocellular carcinoma (HCC): Subgroup analysis of the SHARP trial [abstract]. Presented at the 2008 ASCO Gastrointestinal Cancers Symposium Abstract 129.

202. Raoul J, Sherman M, Nadel A, et al. Efficacy and safety of sorafenib (Sor) in patients (Pts) with advanced hepatocellular carcinoma (HCC): Subgroup analyses of the SHARP trial by baseline (BL) transaminase (ALT/AST)/{alpha}-fetoprotein (AFP) and bilirubin (bil) levels. ASCO Meeting Abstracts 2010;28:4051. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/4051.

203. Abou-Alfa GK. Selection of patients with hepatocellular carcinoma for sorafenib. *J Natl Compr Canc Netw* 2009;7:397-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19406040>.

204. Abou-Alfa GK, Amadori D, Santoro A, et al. Safety and Efficacy of Sorafenib in Patients with Hepatocellular Carcinoma (HCC) and Child-Pugh A versus B Cirrhosis. *Gastrointest Cancer Res* 2011;4:40-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21673874>.

205. Pinter M, Sieghart W, Graziadei I, et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. *Oncologist* 2009;14:70-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19144684>.

206. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. *J Clin Oncol* 2009;27:1800-1805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19255312>.

207. Yau T, Chan P, Ng KK, et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. *Cancer* 2009;115:428-436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19107763>.

208. Bartlett DL, Ramanathan RK, E. B-J. Cancers of the biliary tree. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology* (ed 8): Wolters Kluwer; Lippincott Williams & Wilkins; 2008:1156-1186.

209. Hueman MT, Vollmer CM, Pawlik TM. Evolving treatment strategies for gallbladder cancer. *Ann Surg Oncol* 2009;16:2101-2115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19495882>.

210. Agrawal S, Sonawane RN, Behari A, et al. Laparoscopic staging in gallbladder cancer. *Dig Surg* 2005;22:440-445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16479113>.

211. Petrowsky H, Wildbrett P, Husarik DB, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. *J Hepatol* 2006;45:43-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16690156>.

212. Corvera CU, Blumgart LH, Akhurst T, et al. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. *J Am Coll Surg* 2008;206:57-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18155569>.

213. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *J Surg Oncol* 2008;98:485-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18802958>.

214. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. *Cancer* 2003;98:1689-1700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14534886>.

215. Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989-1995. *Cancer* 1998;83:2618-2628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9874470>.

216. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 2009;16:806-816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18985272>.

217. Pawlik TM, Gleisner AL, Vigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007;11:1478-1486. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17846848>.

218. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. *J Gastrointest Surg* 2007;11:671-681. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17468929>.

219. Jensen EH, Abraham A, Habermann EB, et al. A critical analysis of the surgical management of early-stage gallbladder cancer in the United States. *J Gastrointest Surg* 2009;13:722-727. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19083068>.

220. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg* 2000;232:557-569. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10998654>.

221. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. *Ann Surg* 2007;245:893-901.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17522515>.

222. Daines WP, Rajagopalan V, Grossbard ML, Kozuch P. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 2. *Oncology (Williston Park)* 2004;18:1049-1059. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15328897>.

223. Malhi H, Gores GJ. Cholangiocarcinoma: modern advances in understanding a deadly old disease. *J Hepatol* 2006;45:856-867.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17030071>.

224. Patel T. Cholangiocarcinoma. *Nat Clin Pract Gastroenterol Hepatol* 2006;3:33-42. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16397610>.

225. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755-762. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17457168>.

226. Chapman RW. Risk factors for biliary tract carcinogenesis. *Ann Oncol* 1999;10 Suppl 4:308-311. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10436847>.

227. Rajagopalan V, Daines WP, Grossbard ML, Kozuch P. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 1. *Oncology (Williston Park)* 2004;18:889-896. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15255172>.

228. Yamamoto S, Kubo S, Hai S, et al. Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. *Cancer Sci* 2004;95:592-595. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15245596>.

229. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg* 2008;248:84-96.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18580211>.

230. Chang K-Y, Chang J-Y, Yen Y. Increasing incidence of intrahepatic cholangiocarcinoma and its relationship to chronic viral hepatitis. *J Natl Compr Canc Netw* 2009;7:423-427. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19406042>.

231. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. *World J Gastroenterol* 2009;15:4240-4262. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19750567>.

232. Rullier A, Le Bail B, Fawaz R, et al. Cytokeratin 7 and 20 expression in cholangiocarcinomas varies along the biliary tract but still differs from that in colorectal carcinoma metastasis. *Am J Surg Pathol* 2000;24:870-876. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10843291>.

233. Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. *AJR Am J Roentgenol*

2003;181:819-827. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12933488>.

234. Yamasaki S. Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. *J Hepatobiliary Pancreat Surg* 2003;10:288-291. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14598147>.

235. Nathan H, Aloia TA, Vauthey J-N, et al. A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2009;16:14-22. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18987916>.

236. Farges O, Fuks D, Le Treut Y-P, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma. *Cancer* 2011;117:2170-2177.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21523730>.

237. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001;234:507-517; discussion 517-509. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11573044>.

238. Lieser MJ, Barry MK, Rowland C, et al. Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience. *J Hepatobiliary Pancreat Surg* 1998;5:41-47. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9683753>.

239. Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. *J Am Coll Surg* 2009;208:218-228. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19228533>.

240. Yeh C-N, Jan Y-Y, Yeh T-S, et al. Hepatic resection of the intraductal papillary type of peripheral cholangiocarcinoma. *Ann Surg Oncol* 2004;11:606-611. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15172934>.

241. Nakagohri T, Asano T, Kinoshita H, et al. Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma. *World J Surg* 2003;27:289-293. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12607053>.

242. Isaji S, Kawarada Y, Taoka H, et al. Clinicopathological features and outcome of hepatic resection for intrahepatic cholangiocarcinoma in Japan. *J Hepatobiliary Pancreat Surg* 1999;6:108-116. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10398896>.

243. Ito F, Agni R, Rettammel RJ, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. *Ann Surg* 2008;248:273-279. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18650638>.

244. Silva MA, Tekin K, Aytekin F, et al. Surgery for hilar cholangiocarcinoma; a 10 year experience of a tertiary referral centre in the UK. *Eur J Surg Oncol* 2005;31:533-539. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15922889>.

245. Havlik R, Sbisà E, Tullo A, et al. Results of resection for hilar cholangiocarcinoma with analysis of prognostic factors. *Hepatogastroenterology* 2000;47:927-931. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11020850>.

246. Cherqui D, Benoist S, Malassagne B, et al. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. *Arch Surg* 2000;135:302-308. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10722032>.

247. Hochwald SN, Burke EC, Jarnagin WR, et al. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. *Arch Surg* 1999;134:261-266. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10088565>.

248. Davids PH, Groen AK, Rauws EA, et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal



malignant biliary obstruction. *Lancet* 1992;340:1488-1492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1281903>.

249. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. *Gastrointest Endosc* 1998;47:1-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9468416>.

250. Abraham NS, Barkun JS, Barkun AN. Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life. *Gastrointest Endosc* 2002;56:835-841. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12447294>.

251. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer* 2008;113:2119-2128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18759346>.

252. Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Ann Surg Oncol* 2010;17:484-491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19876691>.

253. Petersen BT, Chuttani R, Croffie J, et al. Photodynamic therapy for gastrointestinal disease. *Gastrointest Endosc* 2006;63:927-932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16733105>.

254. Dumoulin FL, Gerhardt T, Fuchs S, et al. Phase II study of photodynamic therapy and metal stent as palliative treatment for nonresectable hilar cholangiocarcinoma. *Gastrointest Endosc* 2003;57:860-867. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12776033>.

255. Ortner MEJ, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003;125:1355-1363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14598251>.

256. Zoepf T, Jakobs R, Arnold JC, et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005;100:2426-2430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16279895>.

257. Heimbach JK, Haddock MG, Alberts SR, et al. Transplantation for hilar cholangiocarcinoma. *Liver Transpl* 2004;10:65-68. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15382214>.

258. Sudan D, DeRoover A, Chinnakotla S, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002;2:774-779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12243499>.

259. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005;242:451-458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16135931>.

260. Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. *Oncologist* 2008;13:415-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18448556>.

261. Mojica P, Smith D, Ellenhorn J. Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. *J Surg Oncol* 2007;96:8-13. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17516546>.

262. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. *Cancer* 2007;110:572-580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17594719>.

263. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002;95:1685-1695. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12365016>.

264. Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. *Surg Oncol Clin N Am* 2002;11:941-954. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12607581>.

265. Czito BG, Anscher MS, Willett CG. Radiation therapy in the treatment of cholangiocarcinoma. *Oncology (Williston Park)* 2006;20:873-884. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16922259>.

266. Anderson C, Kim R. Adjuvant therapy for resected extrahepatic cholangiocarcinoma: a review of the literature and future directions. *Cancer Treat Rev* 2009;35:322-327. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19147294>.

267. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2009;73:148-153. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18805651>.

268. Hughes MA, Frassica DA, Yeo CJ, et al. Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. *Int J Radiat Oncol Biol Phys* 2007;68:178-182. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17276614>.

269. Fuller CD, Wang SJ, Choi M, et al. Multimodality therapy for locoregional extrahepatic cholangiocarcinoma: a population-based analysis. *Cancer* 2009;115:5175-5183. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19637356>.

270. Wang SJ, Fuller CD, Kim J-S, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. *J Clin Oncol* 2008;26:2112-2117. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18378567>.

271. Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. *Int J Radiat Oncol Biol*

Phys 2008;72:1495-1501. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18472359>.

272. Borghero Y, Crane CH, Szklaruk J, et al. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. *Ann Surg Oncol* 2008;15:3147-3156. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18754070>.

273. Lim KH, Oh DY, Chie EK, et al. Adjuvant concurrent chemoradiation therapy (CCRT) alone versus CCRT followed by adjuvant chemotherapy: which is better in patients with radically resected extrahepatic biliary tract cancer?: a non-randomized, single center study. *BMC Cancer* 2009;9:345. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19781103>.

274. Das P, Wolff RA, Abbruzzese JL, et al. Concurrent capecitabine and upper abdominal radiation therapy is well tolerated. *Radiat Oncol* 2006;1:41-41. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17062148>.

275. Lin LL, Picus J, Drebin JA, et al. A phase II study of alternating cycles of split course radiation therapy and gemcitabine chemotherapy for inoperable pancreatic or biliary tract carcinoma. *Am J Clin Oncol* 2005;28:234-241. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15923794>.

276. Park J, Kim MH, Kim KP, et al. Natural History and Prognostic Factors of Advanced Cholangiocarcinoma without Surgery, Chemotherapy, or Radiotherapy: A Large-Scale Observational Study. *Gut Liver* 2009;3:298-305. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20431764>.

277. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996;7:593-600. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8879373>.

278. Rao S, Cunningham D, Hawkins RE, et al. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. *Br J Cancer* 2005;92:1650-1654. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15856037>.

279. Doval DC, Sekhon JS, Gupta SK, et al. A phase II study of gemcitabine and cisplatin in chemotherapy-naïve, unresectable gall bladder cancer. *Br J Cancer* 2004;90:1516-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15083178>.

280. Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK ABC-01 Study. *Br J Cancer* 2009;101:621-627. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19672264>.

281. Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. *Ann Oncol* 2005;16:279-281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15668284>.

282. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. *J Clin Oncol* 2005;23:2332-2338. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15800324>.

283. Koeberle D, Saletti P, Borner M, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol* 2008;26:3702-3708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18669455>.

284. Andre T, Tournigand C, Rosmorduc O, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann Oncol* 2004;15:1339-1343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15319238>.

285. Malka D, Trarbach T, Fartoux L, et al. A multicenter, randomized phase II trial of gemcitabine and oxaliplatin (GEMOX) alone or in combination with biweekly cetuximab in the first-line treatment of advanced biliary cancer: Interim analysis of the BINGO trial. *ASCO Meeting Abstracts* 2009;27:4520. Available at: <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/4520>.

286. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. *Br J Cancer* 2008;98:309-315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18182984>.

287. Kim TW, Chang HM, Kang HJ, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. *Ann Oncol* 2003;14:1115-1120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12853355>.

288. Kobayashi K, Tsuji A, Morita S, et al. A phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma. *BMC Cancer* 2006;6:121-121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16677397>.

289. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer* 2007;96:896-902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17325704>.

290. Yonemoto N, Furuse J, Okusaka T, et al. A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. *Jpn J Clin Oncol* 2007;37:843-851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17942578>.

291. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010;362:1273-1281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20375404>.



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292. Alberts SR, Al-Khatib H, Mahoney MR, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. *Cancer* 2005;103:111-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15558814>.

293. Ghafoori AP, Nelson JW, Willett CG, et al. Radiotherapy in the Treatment of Patients with Unresectable Extrahepatic Cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20864265>.