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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# Hepatobiliary Cancers

Version 2.2013

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**Principles of Surgery: (Gallbladder Cancer, Intrahepatic and Extrahepatic Cholangiocarcinoma)**

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§ Radiotherapy/Radiation Oncology/Interventional Radiology  
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**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](#)



# NCCN Guidelines Version 2.2013 Updates Hepatobiliary Cancers

Updates in version 2.2013 of the NCCN Guidelines for Hepatobiliary Cancer from version 1.2013 include:

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

- The section on “Arterially directed therapies” was revised.

[MS-1](#): The Discussion text was updated to reflect the changes in the algorithm.

Updates in version 1.2013 of the NCCN Guidelines for Hepatobiliary Cancer from version 2.2012 include:

## [Global Changes:](#)

- A new “Principles of Surgery” page was added for the following sites: Gallbladder Cancer ([GALL-A](#)), Intrahepatic cholangiocarcinoma ([INTRA-A](#)), Extrahepatic Cholangiocarcinoma ([EXTRA-A](#)).

## [Hepatocellular Carcinoma:](#)

### [HCC-1](#)

- Footnote “b” was revised: There is evidence suggesting improved outcomes for patients with HCC in the setting of HBV or HCV cirrhosis when the HBV/HCV is successfully treated. Referral of ~~management of these patients~~ to a hepatologist should be considered for the management of these patients.

### [HCC-2](#)

- Additional Imaging: For liver nodules < 1 cm, the recommendation was clarified as “At least a 3-phase CT or MRI or CEUS every 3-6 mo”. Previously it stated “MRI;US”.

### [HCC-3](#)

- Footnote “k” was revised: “~~Consider for surgical assessment and if transplant is a consideration, consider referral to a transplant center before biopsy.~~ Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.”

### [HCC-4](#)

- Workup:
  - Seventh bullet: “Chest imaging” changed to “Chest CT”.
  - Eighth bullet: Changed to “Bone scan as if clinically indicated”.

### [HCC-5](#)

- Footnote “u” is new to the algorithm: “MRI or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.”

### [HCC-6](#)

- After “Unresectable,” the pathway “Extensive liver burden” moved to page HCC-7.
- For patients who are not transplant candidates, the options for treatment were rearranged for clarity.
- Footnote “w” was revised: “Order does not indicate preference ~~with the exception of category 1 options which are listed first.~~”

### [HCC-7](#)

- Clinical presentation: Changed to “Metastatic disease or Extensive liver tumor burden.”

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

- This page was extensively revised.

## [Gallbladder Cancer:](#)

### [GALL-1](#)

- The following footnote was removed: “Include porta hepatis, gastrohepatic ligament, retroduodenal. Patients with nodal disease outside this area are unresectable,” and include in the new “Principles of Surgery” section ([GALL-A](#)).
- Footnote “c” was added: “Order does not indicate preference”.

### [GALL-2](#)

- Postoperative Workup:
  - First bullet: Changed to “CT/MRI, chest imaging CT”.
  - Second bullet: Changed to “~~Strongly~~ Consider staging laparoscopy”.

### [GALL-3](#)

- Workup; Fourth bullet: Changed to “Chest imaging CT”.

**Gallbladder Cancer--continued****GALL-4**

- **Workup for jaundice:** The third bullet changed to “**Chest imaging CT**”.
- The following footnote was removed and included in the new “Principles of Surgery” section: “In patients with jaundice, if gallbladder cancer is suspected, then surgery should only be performed with curative intent. These patients need careful surgical evaluation and referral to an experienced center should be considered”.

**GALL-5**

- **Post resection:**
  - ▶ **Adjuvant treatment**
    - ◊ “Observe” was added as an option.
    - ◊ “Consider fluoropyrimidine chemoradiation (except T1b, N0)” clarified as “...except T1a or T1b, N0”.
  - ▶ **Surveillance:** Changed to “Consider imaging every 6 mo for 2 y if clinically indicated”.

**Intrahepatic Cholangiocarcinoma:****INTRA-1**

- **Workup**
  - ▶ **Third bullet:** Changed to “**Chest imaging CT**”.
  - ▶ “Consider viral hepatitis serologies” was added.
- **Resectable; Primary Treatment:** The recommendation changed to “**Resection ± ablation**”. “Consider lymphadenectomy for accurate staging” was added as an option.

**INTRA-2**

- **Post resection status**
  - ▶ **No residual local disease (R0 resection); Additional Therapy:** Fluoropyrimidine chemoradiation or Fluoropyrimidine-based or gemcitabine-based chemotherapy regimen” were added as treatment options.
  - ▶ **Microscopic margins (R1) or Residual local disease (R2 resection); Additional Therapy:** The following were removed as treatment options “Consider re-resection” and “Ablation”.
  - ▶ **Surveillance:** The recommendation changed to “Consider imaging every 6 mo for 2 y if clinically indicated”.

**INTRA-2--continued**

- The following footnote was removed: “R1 or R2 resections should be evaluated by an experienced hepatobiliary surgeon for the uncommon scenario where re-resection may be considered”.

**Extrahepatic Cholangiocarcinoma:****EXTRA-1**

- **Workup:** “Chest CT” was added.
- **Unresectable pathway:** First bullet changed to “Biliary drainage, if indicated (~~surgical bypass versus stent~~)”.
- **Resectable pathway:** For clarity, after “Resectable” the statement “Resection” was added.
- **Metastatic disease pathway:** First bullet changed to “Biliary drainage, if indicated (~~stent preferred~~)”.
- **Footnote “e” is new to the algorithm:** “Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.”.
- The “Surgical Procedures for Resectable Disease” table was removed from this page and the recommendations were incorporated into the new “Principles of Surgery” page (EXTRA-A).

**EXTRA-2**

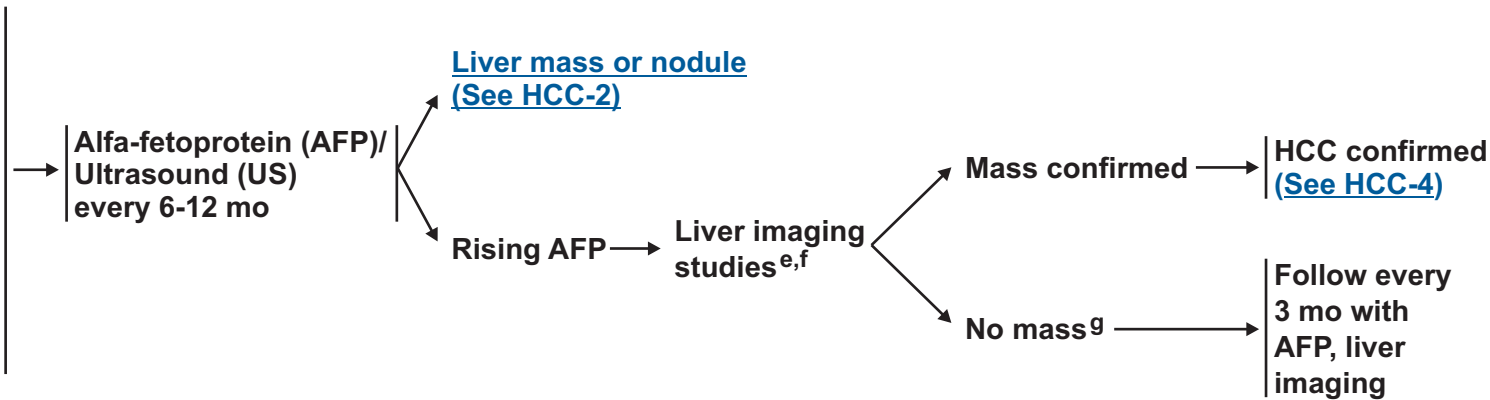
- **Resected, positive margin (R1) or Resected gross residual disease (R2):**
  - ▶ “Carcinoma in situ at margin” was removed from this pathway and is now grouped with and has the same treatment options as the “Resected, negative margin (R0), Negative regional nodes” pathway.
  - ▶ **Secondary or Adjuvant treatment:** Revised as follows: “Consider fluoropyrimidine chemoradiation (~~brachytherapy or external beam~~)”.
- **Surveillance:** The recommendation changed to “Consider imaging every 6 mo for 2 y if clinically indicated”.
- **Footnote “g” was revised:** “~~Multidisciplinary team review.~~ R1 or R2 resections should be evaluated by a multidisciplinary team”.



### HEPATOCELLULAR CARCINOMA (HCC) SCREENING

#### Patients at risk for HCC:<sup>a</sup>

- **Cirrhosis**
  - ▶ Hepatitis B, C<sup>b</sup>
  - ▶ Alcohol
  - ▶ Genetic hemochromatosis
  - ▶ Non-alcoholic steatohepatitis
  - ▶ Stage 4 primary biliary cirrhosis
  - ▶ Alpha1-antitrypsin deficiency
  - ▶ Other causes of cirrhosis<sup>c</sup>
- **Without cirrhosis**
  - ▶ Hepatitis B carriers<sup>d</sup>



<sup>a</sup>Adapted with permission from Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Alexandria, VA: American Association for the Study of Liver Diseases, 2010. This updates a previous version: Bruix J, Sherman M. Management of Hepatocellular Carcinoma. Hepatology 2005;42:1208-1236. (<http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf>).

<sup>b</sup>There is evidence suggesting improved outcomes for patients with HCC in the setting of HBV or HCV cirrhosis when the HBV/HCV is successfully treated. Referral to a hepatologist should be considered for the management of these patients.

<sup>c</sup>Schiff ER, Sorrell MF, and Maddrey WC. Schiff's Diseases of the Liver. Philadelphia: Lippincott Williams & Wilkins (LWW); 2007.

<sup>d</sup>Additional risk factors include patients with, family history of HCC, Asian males ≥ 40 y, Asian females ≥ 50 y, African/North American Blacks with hepatitis B.

<sup>e</sup>If ultrasound is negative, CT/MRI should be performed.

<sup>f</sup>At least a 3-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, Sherman M. Management of Hepatocellular Carcinoma: An Update. Alexandria, VA: American Association for the Study of Liver Diseases, 2010. This updates a previous version: Bruix J, Sherman M. Management of Hepatocellular Carcinoma. Hepatology 2005;42:1208-1236 (<http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf>)).

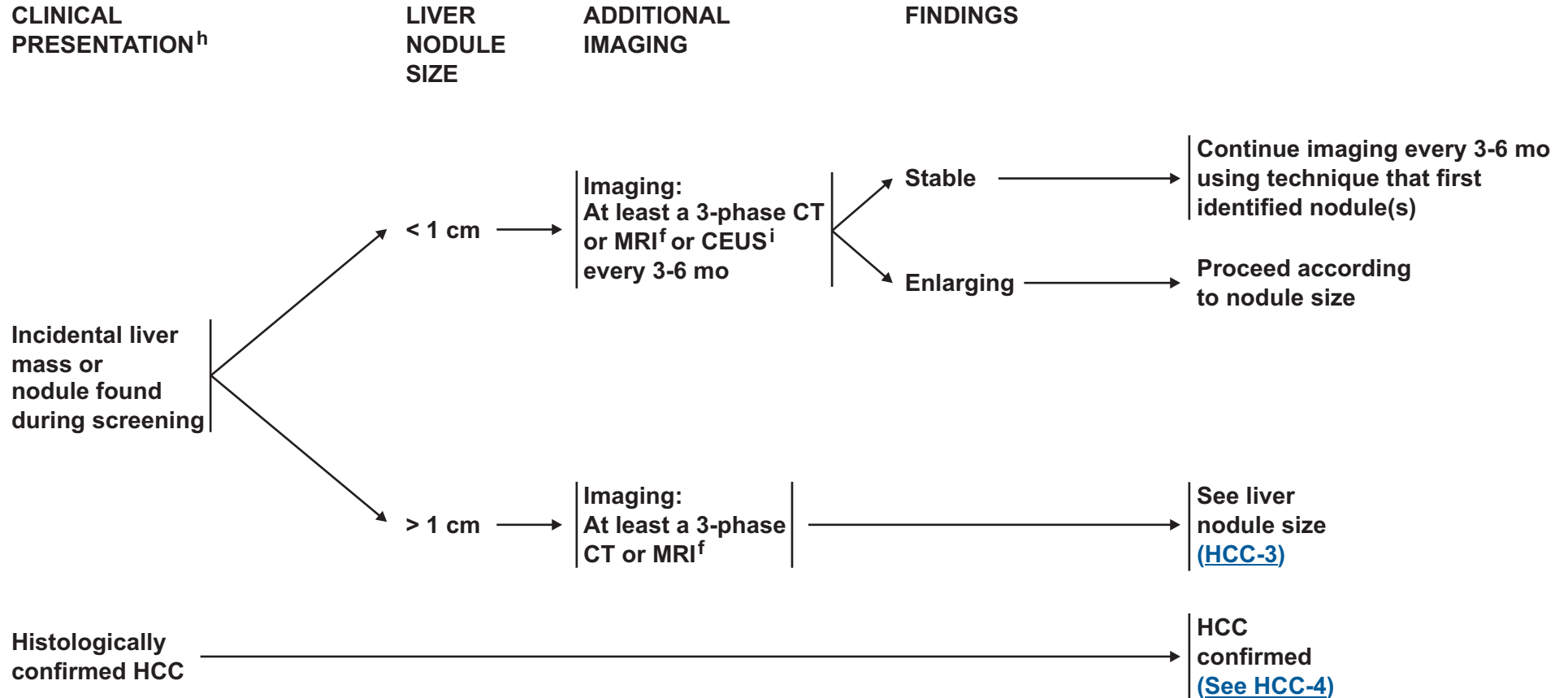
<sup>g</sup>Rule out germ cell tumor if clinically indicated.

**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.



### DIAGNOSIS OF HCC<sup>a</sup>



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<sup>h</sup>These guidelines apply to nodules identified in cirrhotic patients. In patients without cirrhosis or known liver disease, biopsy should be strongly considered.

<sup>i</sup>Contrast enhanced ultrasound (CEUS) where available.

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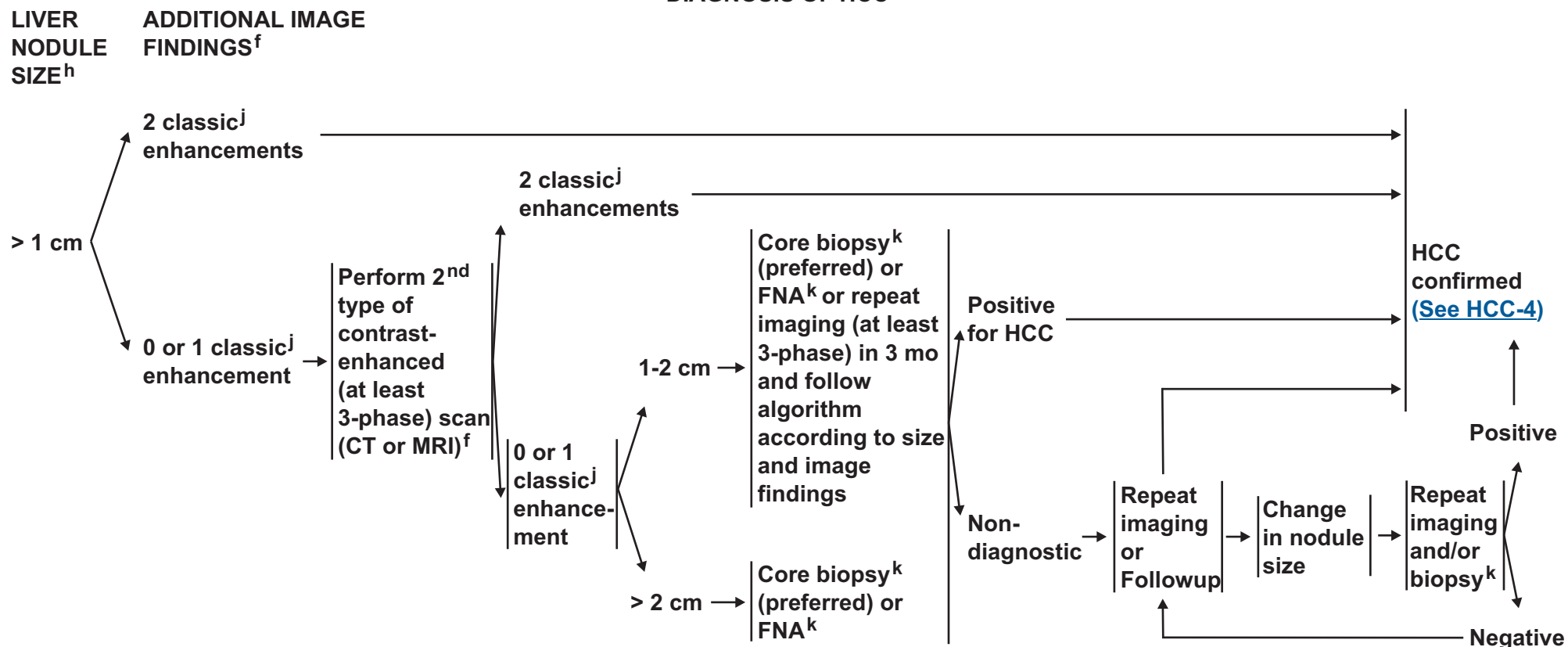




# NCCN Guidelines Version 2.2013

## Hepatocellular Carcinoma

### DIAGNOSIS OF HCC<sup>a</sup>



<sup>a</sup>Adapted with permission from Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Alexandria, VA: American Association for the Study of Liver Diseases, 2010. This updates a previous version: Bruix J, Sherman M. Management of Hepatocellular Carcinoma. Hepatology 2005 Nov; 42(5):1208-1236. (<http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/HCCUpdate2010.pdf>).

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<sup>h</sup>These guidelines apply to nodules identified in cirrhotic patients. In patients without cirrhosis or known liver disease, biopsy should be strongly considered.

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

<sup>k</sup>Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.

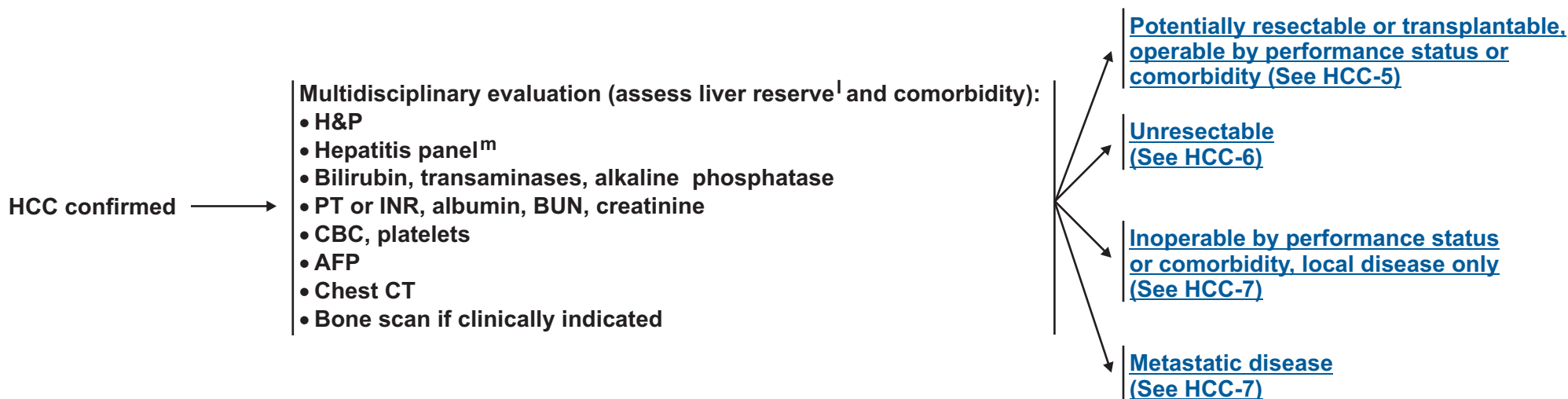
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### CLINICAL PRESENTATION

### WORKUP



<sup>l</sup>See [Child-Pugh Score \(HCC-A\)](#) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

<sup>m</sup>An appropriate hepatitis panel should preferably include:

- Hepatitis B surface antigen (HBsAg). If the HBsAg is positive, check HBeAg, HBeAb and quantitative HBV DNA and refer to hepatologist.
- Hepatitis B surface antibody (for vaccine evaluation only).
- Hepatitis B core antibody (HBcAb) IgG. The HBcAb IgM should only be checked in cases of acute viral hepatitis. An isolated HBcAb IgG may still be chronic HBV and should prompt testing for a quantitative HBV DNA.
- Hepatitis C antibody. If positive, check quantitative HCV RNA and HCV genotype and refer to hepatologist.

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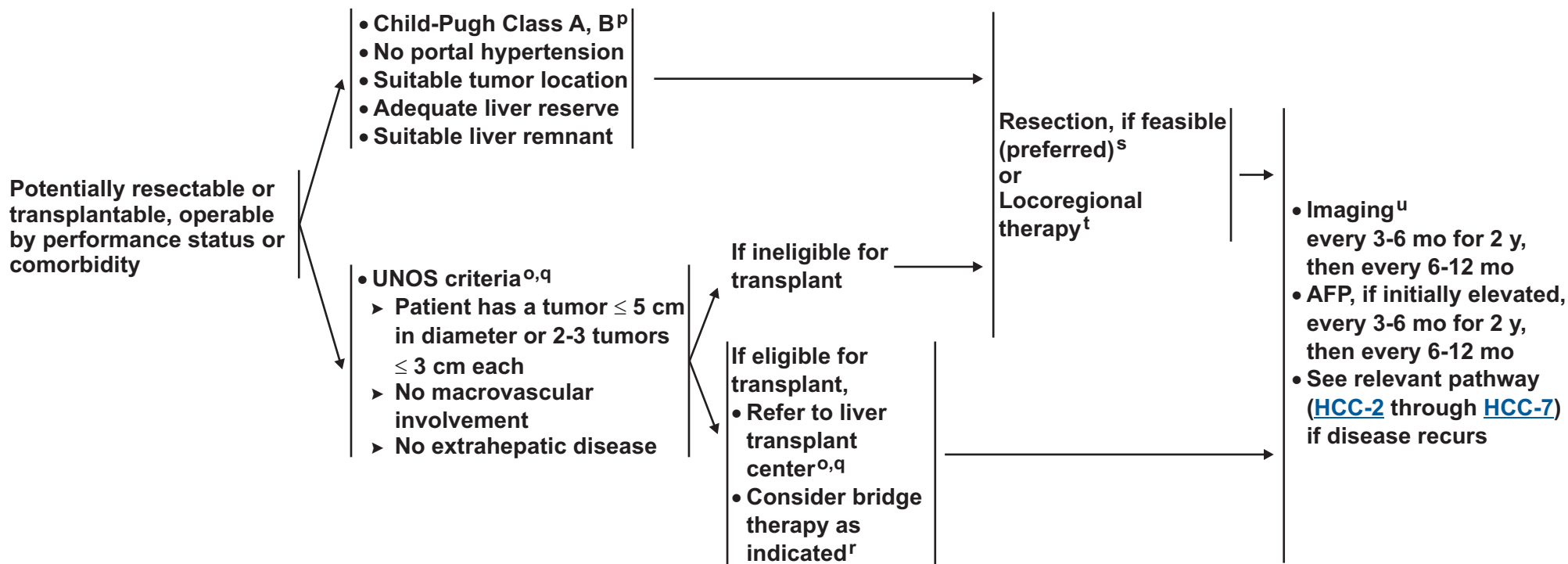
## Hepatocellular Carcinoma

### CLINICAL PRESENTATION

### SURGICAL ASSESSMENT<sup>n,o</sup>

### TREATMENT

### SURVEILLANCE



<sup>n</sup>Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

<sup>o</sup>Patients with Child-Pugh Class A liver function, who fit UNOS criteria ([www.unos.org](http://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.

<sup>p</sup>In highly selected Child-Pugh Class B patients with limited resection.

<sup>q</sup>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;334:693-700.

<sup>r</sup>Many transplant centers consider bridge therapy for transplant candidates. (See [Discussion](#))

<sup>s</sup>See [Principles of Surgery \(HCC-B\)](#).

<sup>t</sup>See [Principles of Locoregional Therapy \(HCC-C\)](#).

<sup>u</sup>MRI or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.

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



### CLINICAL PRESENTATION

Unresectable →

- Inadequate hepatic reserve<sup>u</sup>
- Tumor location

Evaluate whether patient a candidate for transplant (See UNOS criteria under Surgical Assessment [HCC-5](#))<sup>q</sup>

Transplant candidate →

Not a transplant candidate →

### TREATMENT

- Refer to liver transplant center
- Consider bridge therapy as indicated<sup>r</sup>

Options:<sup>w</sup>

- Sorafenib (Child-Pugh Class A [category 1] or B)<sup>v,x,y</sup>
- Chemotherapy ± RT only in the context of a clinical trial
  - ▶ Systemic chemotherapy
  - ▶ Intra-arterial chemotherapy
- Clinical trial
- Locoregional therapy<sup>t,z</sup>
- RT (conformal or stereotactic)<sup>aa</sup> (category 2B)
- Supportive care

### SURVEILLANCE

- Imaging<sup>u</sup> every 3-6 mo for 2 y, then every 6-12 mo
- AFP, if initially elevated, every 3-6 mo for 2 y, then every 6-12 mo
- See relevant pathway ([HCC-2](#) through [HCC-7](#)) if disease recurs

<sup>q</sup>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;334:693-700.

<sup>r</sup>Many transplant centers consider bridge therapy for transplant candidates. ([See Discussion](#))

<sup>t</sup>See Principles of Locoregional Therapy ([HCC-C](#)).

<sup>u</sup>MRI or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.

<sup>v</sup>See Child-Pugh Score ([HCC-A](#)).

<sup>w</sup>Order does not indicate preference.

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

<sup>y</sup>Caution: There are limited safety data available for Child-Pugh Class B or C 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). The impact of sorafenib on patients potentially eligible for transplant is unknown.

<sup>z</sup>Use 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.)

<sup>aa</sup>There are limited data to support the use of RT in this setting.

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### CLINICAL PRESENTATION

### TREATMENT

Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only



- Options:<sup>w</sup>
- Sorafenib (Child-Pugh Class A [category 1] or B)<sup>v,x,y</sup>
  - Clinical trial
  - Locoregional therapy<sup>t</sup>
  - RT (conformal or stereotactic)<sup>aa</sup> (category 2B)
  - Supportive care

Metastatic disease or Extensive liver tumor burden



- Options:<sup>w</sup>
- Sorafenib (Child-Pugh Class A [category 1] or B)<sup>v,x,y</sup>
  - Supportive care
  - Clinical trial

<sup>t</sup>See [Principles of Locoregional Therapy \(HCC-C\)](#).

<sup>v</sup>See [Child-Pugh Score \(HCC-A\)](#).

<sup>w</sup>Order does not indicate preference.

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

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<sup>aa</sup>There are limited data to support the use of RT in this setting.

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**CHILD-PUGH SCORE****Chemical and Biochemical Parameters****Scores (Points) for Increasing Abnormality**

	<b>1</b>	<b>2</b>	<b>3</b>
<b>Encephalopathy (grade)<sup>1</sup></b>	<b>None</b>	<b>1-2</b>	<b>3-4</b>
<b>Ascites</b>	<b>None</b>	<b>Slight</b>	<b>Moderate</b>
<b>Albumin (g/dL)</b>	<b>&gt; 3.5</b>	<b>2.8-3.5</b>	<b>&lt; 2.8</b>
<b>Prothrombin time prolonged (sec)<sup>2</sup></b>	<b>1-4</b>	<b>4-6</b>	<b>&gt; 6</b>
<b>Bilirubin (mg/dL)</b>	<b>&lt; 2</b>	<b>2-3</b>	<b>&gt; 3</b>
<b>• For primary biliary cirrhosis</b>	<b>&lt; 4</b>	<b>4-10</b>	<b>&gt; 10</b>

**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**

<sup>1</sup> Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med 1966;274(9):473-481.

Source: Pugh R, Murray-Lyon I, Dawson J, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J of Surg 1973;60(8):646-649.

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<sup>2</sup>Corresponding International Normalized Ratio (INR) measurements are Score points 1: < 1.7; Score points 2: 1.8 - 2.3; Score points 3: > 2.3

(van Rijn JL, Schmidt NA, Rutten WP. Correction of instrument- and reagent-based differences in determination of the International Normalized Ratio (INR) for monitoring anticoagulant therapy. Clin Chem 1989;35(5):840-843).

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



### PRINCIPLES OF SURGERY

- 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.<sup>1</sup>
- Patients meeting the UNOS criteria ([single lesion  $\leq$  5 cm, or 2 or 3 lesions  $\leq$  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.

<sup>1</sup>Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg 2003;237:208-217.

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### PRINCIPLES OF LOCOREGIONAL THERAPY

All patients with HCC should be evaluated for potential curative therapies (resection, transplantation). Locoregional therapy should be considered in those patients not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation and arterially directed therapies.

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

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors  $\leq 3$  cm. Lesions 3-5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.<sup>1</sup> Unresectable/inoperable lesions  $> 5$  cm should be considered for treatment using arterially directed or systemic therapy.<sup>2-4</sup>
- Sorafenib may be appropriate following ablative 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 adjuvant sorafenib following ablation is being investigated in an ongoing clinical trial.<sup>5</sup>

#### Arterially directed therapies:

- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- Arterially directed therapies include transarterial bland embolization (TAE),<sup>3,4,6</sup> chemoembolization (transarterial chemoembolization [TACE]<sup>7</sup> and TACE with drug-eluting beads [DEB-TACE]<sup>4,8</sup>) and radioembolization with Yttrium-90 microspheres.<sup>9,10</sup>
- All arterially directed therapies are relatively contraindicated in patients with bilirubin  $> 3$  mg/dL unless segmental injections can be performed.<sup>11</sup> Radioembolization with Yttrium-90 microspheres has an increased risk of radiation induced liver disease in patients with bilirubin over 2 mg/dL.<sup>10</sup>
- Arterially directed therapies are relatively contraindicated in patients with main portal vein thrombosis and Child-Pugh Class C.
- The angiographic endpoint of embolization may be chosen by the treating physician.
- Sorafenib may be appropriate following arterially directed therapies 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 arterially directed therapies and/or ablation is being investigated in ongoing clinical trials.<sup>12</sup>

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.

[Continue](#)





### PRINCIPLES OF LOCOREGIONAL THERAPY

#### External-beam radiation therapy (EBRT)

- All tumors irrespective of the location may be amenable to EBRT (Stereotactic body radiation therapy [SBRT] or 3D-conformal radiation therapy).
- SBRT is an advanced technique of EBRT that delivers large ablative doses of radiation in 1 week or less
- There is growing evidence for the usefulness of SBRT in the management of patients with HCC.<sup>13</sup> SBRT can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed or are contraindicated.
- SBRT is often used for 1-3 tumors with a cumulative diameter under 6 cm. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient 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. Patients with Child-Pugh A category are preferred. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.<sup>14</sup> Child-Pugh C cirrhosis is a relative contraindication, and these patients should be considered for a clinical trial.<sup>15,16</sup>

**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.

[References on next page](#)



### PRINCIPLES OF LOCOREGIONAL THERAPY

- <sup>1</sup>Peng ZW, Zhang YJ, Liang HH, et al. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology* 2012;262:689-700.
- <sup>2</sup>Yamakado, K., et al., Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. *Radiology* 2008; 247:260-266.
- <sup>3</sup>Maluccio, M., et al., Comparison of survival rates after bland arterial embolization and ablation versus surgical resection for treating solitary hepatocellular carcinoma up to 7 cm. *J Vasc Interv Radiol* 2005;16: 955-961.
- <sup>4</sup>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.
- <sup>5</sup>Printz C. Clinical trials of note. Sorafenib as adjuvant treatment in the prevention of disease recurrence in patients with hepatocellular carcinoma (HCC) (STORM). *Cancer* 2009;115:46. (<http://clinicaltrials.gov/show/NCT00692770>)
- <sup>6</sup>Maluccio, M.A., et al., Transcatheter arterial embolization with only particles for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2008; 19:862-869.
- <sup>7</sup>Llovet, J.M., et al., Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359(9319):1734-1739.
- <sup>8</sup>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.
- <sup>9</sup>Kulik, L.M., et al., Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008;47:71-81.
- <sup>10</sup>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.
- <sup>11</sup>Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13(9 Pt 2):S211-21.
- <sup>12</sup>Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. *J Clin Oncol* 2011;29:3960-3967.
- <sup>13</sup>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.
- <sup>14</sup>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.
- <sup>15</sup>Tse 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.
- <sup>16</sup>Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e447-453.

**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.



### PRESENTATION

Incidental finding at surgery

- Intraoperative staging
- Frozen section of gallbladder
- Consider extended cholecystectomy<sup>a</sup>

Incidental finding on pathologic review → [See \(GALL-2\)](#)

### POSTOPERATIVE WORKUP

CT/MRI, chest CT

Resectable<sup>b</sup>

Unresectable

### PRIMARY TREATMENT

**Cholecystectomy<sup>b</sup>**  
**+ en bloc hepatic resection**  
**+ lymphadenectomy**  
**± bile duct excision**

**Options:<sup>c</sup>**

- Gemcitabine/cisplatin combination therapy<sup>d</sup> (category 1)
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>d</sup>
- Fluoropyrimidine chemoradiation<sup>e</sup>
- Clinical trial
- Supportive care

[See Adjuvant Treatment and Surveillance \(GALL-5\)](#)

<sup>a</sup>Depends on expertise of surgeon and/or resectability. If resectability not clear, close incision.

<sup>b</sup>See [Principles of Surgery \(GALL-A\)](#).

<sup>c</sup>Order does not indicate preference.

<sup>d</sup>A 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)

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

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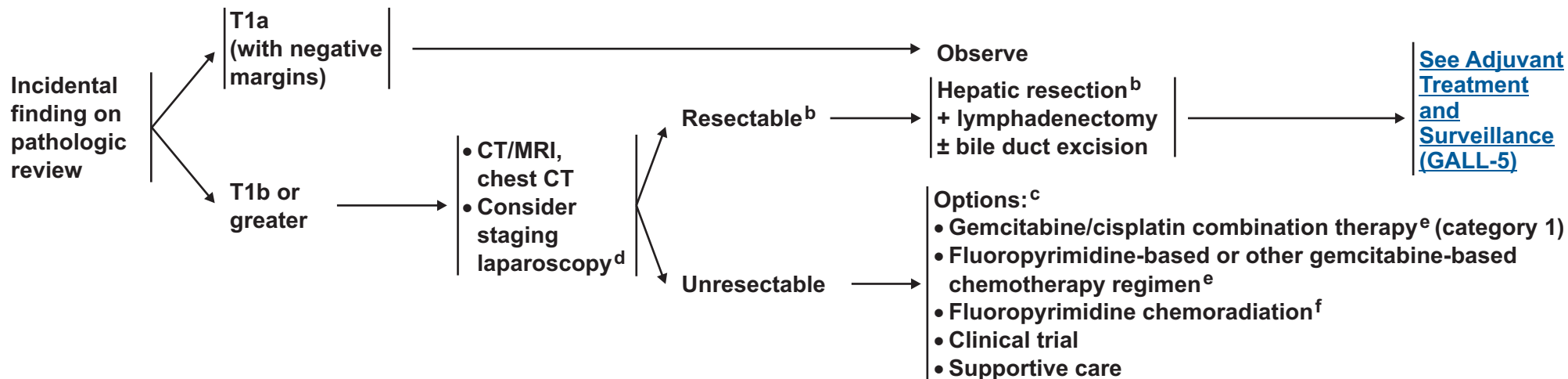
[Other Clinical Presentations \(See GALL-3 and \(GALL-4\)](#)



### PRESENTATION

### POSTOPERATIVE WORKUP

### PRIMARY TREATMENT



<sup>a</sup>Depends on expertise of surgeon and/or resectability. If resectability not clear, close incision.

<sup>b</sup>See [Principles of Surgery \(GALL-A\)](#).

<sup>c</sup>Order does not indicate preference.

<sup>d</sup>Butte JM, Gonen M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB (Oxford)* 2011;13:463-472.

<sup>e</sup>A 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)

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

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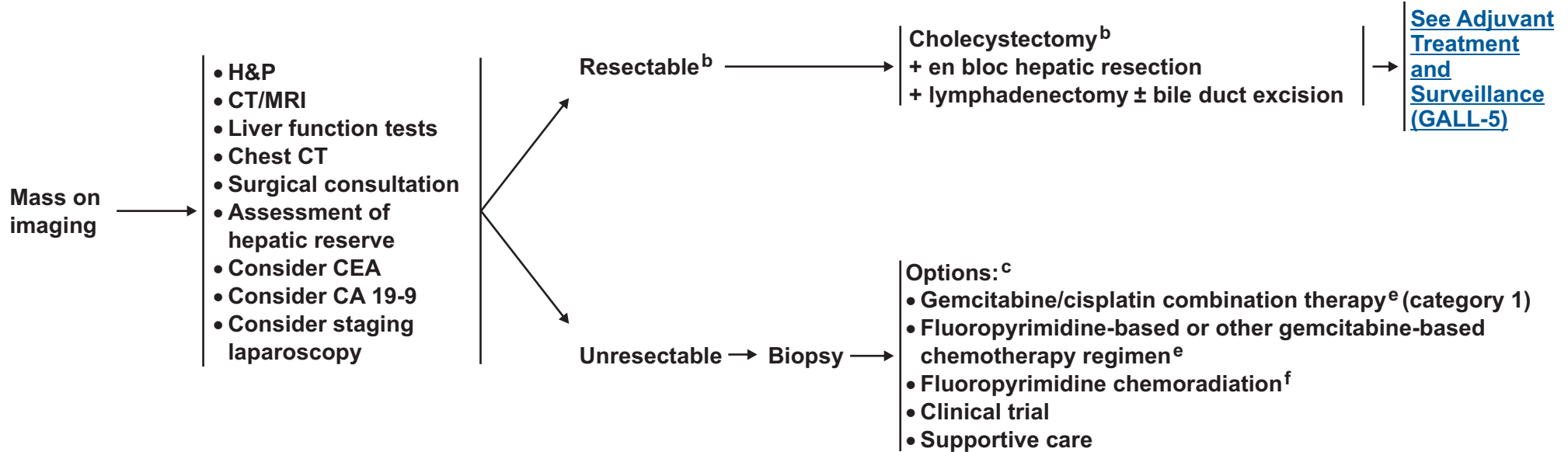
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

[Other Clinical Presentations](#)  
(See [GALL-3](#))  
and ([GALL-4](#))



**PRESENTATION WORKUP**

**PRIMARY TREATMENT**



<sup>b</sup>See Principles of Surgery (GALL-A).

<sup>c</sup>Order does not indicate preference.

<sup>e</sup>A 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)

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

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[Other Clinical Presentations](#)  
[\(See GALL-1\), GALL-2, and GALL-4\)](#)



**PRESENTATION WORKUP**

- Jaundice** →
- H&P
  - Liver function tests
  - Chest CT
  - CT/MRI
  - Cholangiography<sup>g</sup>
  - Surgical consultation<sup>h</sup>
  - Consider CEA
  - Consider CA 19-9
  - Consider staging laparoscopy

Resectable<sup>b</sup>

Unresectable → Biopsy →

**PRIMARY TREATMENT**

- Cholecystectomy<sup>b</sup>**  
+ en bloc hepatic resection  
+ lymphadenectomy + bile duct excision

[See Adjuvant Treatment and Surveillance \(GALL-5\)](#)

Options:<sup>c</sup>

- Biliary drainage<sup>i</sup>
- Gemcitabine/cisplatin combination therapy<sup>c</sup> (category 1)
- Other gemcitabine-based or fluoropyrimidine-based chemotherapy regimen<sup>e</sup>
- Fluoropyrimidine chemoradiation<sup>f</sup>
- Clinical trial
- Supportive care

Options:<sup>c</sup>

- Biliary drainage<sup>i</sup>
- Gemcitabine/cisplatin combination therapy<sup>e</sup> (category 1)
- Other gemcitabine-based or fluoropyrimidine-based chemotherapy regimen<sup>e</sup>
- Clinical trial
- Supportive care

**Metastatic disease** →

<sup>b</sup>See [Principles of Surgery \(GALL-A\)](#).

<sup>c</sup>Order does not indicate preference.

<sup>e</sup>A 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)

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

<sup>g</sup>Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic MR cholangiography (ERCP/PTC) are used more for therapeutic intervention.

<sup>h</sup>Consult with a multidisciplinary team.

<sup>i</sup>It is expected that patients will have biliary drainage for jaundice prior to instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.

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

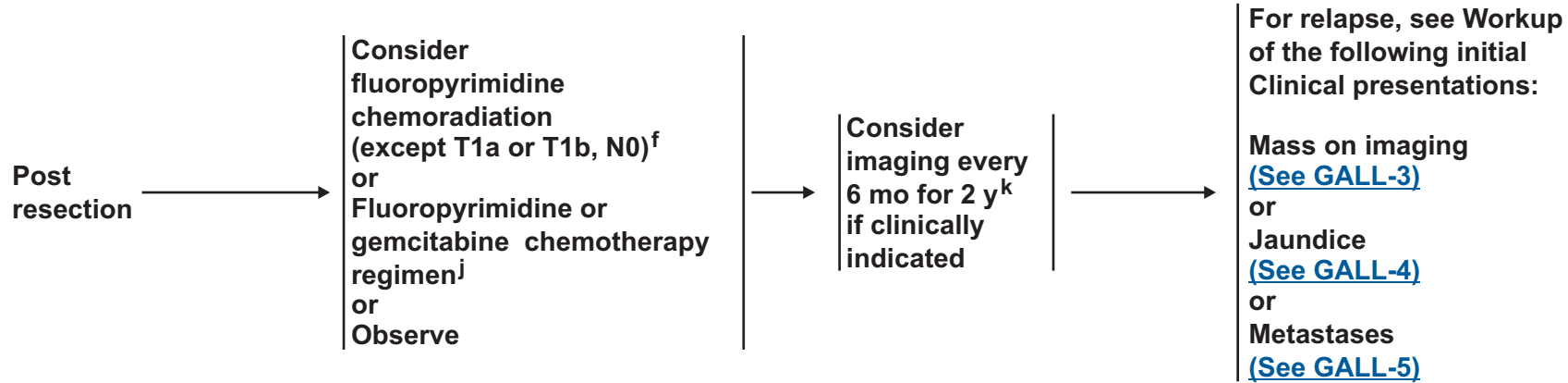


# NCCN Guidelines Version 2.2013

## Gallbladder Cancer

### ADJUVANT TREATMENT

### SURVEILLANCE



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

<sup>j</sup>There are no randomized phase III clinical trial data to support a standard adjuvant regimen. Clinical trial participation is encouraged. Single agent fluoropyrimidine or gemcitabine is generally recommended in the adjuvant setting.

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

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### PRINCIPLES OF SURGERY

#### Incidental Finding at Surgery:

- If expertise is unavailable, document all relevant findings and refer the patient to a center with available expertise. If there is a suspicious mass, a biopsy is not necessary as this can result in peritoneal dissemination.
- If expertise is available and there is convincing clinical evidence of cancer, a definitive resection should be performed as written below. If the diagnosis is not clear, frozen section biopsies can be considered in selected cases before proceeding with definitive resection
- The principles of resection are the same as below consisting of radical cholecystectomy including segments IV B and V and lymphadenectomy and extended hepatic or biliary resection as necessary to obtain a negative margin

#### Incidental Finding on Pathologic Review:

- Review the operative note and/or speak to surgeon to check for completeness of cholecystectomy, signs of disseminated disease, location of tumor and any other pertinent information
- Review the pathology report for T stage, cystic duct margin status and other margins
- Diagnostic laparoscopy can be performed but is of relatively low yield. Higher yields may be seen in patients with T3 or higher tumors, poorly differentiated tumors or with a margin positive cholecystectomy. Diagnostic laparoscopy should also be considered in patients with any suspicion of metastatic disease on imaging that is not amenable to percutaneous biopsy.<sup>1</sup>
- Repeat cross-sectional imaging of the chest, abdomen and pelvis should be performed prior to definitive resection
- Initial exploration should rule out distant lymph node metastases in the celiac axis or aorto-caval groove as these contraindicate further resection
- Hepatic resection should be performed to obtain clear margins which usually consists of segments IV B and V. Extended resections beyond segments IV B and V may be needed in some patients to obtain negative margins
- Lymphadenectomy should be performed to clear all lymph nodes in the porta hepatis.
- Resection of the bile duct may be needed to obtain negative margins. Routine resection of the bile duct for lymphadenectomy has been shown to increase morbidity without convincing evidence for improved survival<sup>2,3</sup>
- Port site resection has not been shown to be effective as the presence of a port site implant is a surrogate marker of underlying disseminated disease and has not been shown to improve outcomes.<sup>4</sup>

<sup>1</sup>Butte JM, Gonen M, Allen PJ et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB* 2011;13:463-472.

<sup>2</sup>Fuks D, Regimbeau JM, Le Treut YP et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. *W J of Surg* 2011;35:1887-1897.

<sup>3</sup>D'Angelica M, Dalal KM, Dematteo RP et al. Analysis of extent of resection for adenocarcinoma of gallbladder. *Ann Surg Onc* 2009;16: 806-816

<sup>4</sup>Maker AV, Butte JM, Oxenberg J et al. Is Port site resection necessary in the surgical management of gallbladder cancer. *Ann Surg Onc* 2012;19: 409-417.

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### PRINCIPLES OF SURGERY

#### **Mass on Imaging: Patients presenting with gallbladder mass/disease suspicious for gallbladder cancer**

- Staging should be carried out with cross-sectional imaging of the chest, abdomen and pelvis
- If there is a suspicious mass, a biopsy is not necessary and a definitive resection should be carried out.
- Diagnostic laparoscopy is recommended prior to definitive resection
- In selected cases where the diagnosis is not clear it may be reasonable to perform a cholecystectomy (including intra-operative frozen section) followed by the definitive resection during the same setting if pathology confirms cancer.
- The resection is carried out as per the principles described above

#### **Gallbladder cancer and jaundice**

- The presence of jaundice in gallbladder cancer usually portends a poor prognosis.<sup>1,2</sup> These patients need careful surgical evaluation.
- Although a relative contraindication, in select patients curative intent resection can be attempted for resectable disease in centers with available expertise.

<sup>1</sup>Hawkins WG, DeMatteo RP, Jarnagin WR, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann Surg Oncol* 2004;11:310-315.

<sup>2</sup>Regimbeau JM, Fuks D, Bachellier P, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC -GBC-2009 study group. *Eur J Surg Oncol* 2011;37: 505-512.

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# NCCN Guidelines Version 2.2013 Intrahepatic Cholangiocarcinoma

## PRESENTATION

## WORKUP

## PRIMARY TREATMENT

Isolated intrahepatic mass  
(biopsy proven adenocarcinoma)  
[\(See NCCN Guidelines for Occult Primary Cancers\)](#)

- H&P
- CT/MRI<sup>a</sup>
- Chest CT
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Surgical consultation<sup>b</sup>
- Consider laparoscopy<sup>c</sup>
- Consider Esophagogastroduodenoscopy (EGD) and colonoscopy<sup>d</sup>
- Consider viral hepatitis serologies

Resectable<sup>e</sup>

Unresectable

Metastatic disease

Resection<sup>e</sup>  
Consider  
lymphadenectomy for  
accurate staging

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

Options:<sup>f</sup>

- Gemcitabine/cisplatin combination therapy<sup>g</sup> (category 1)
- Clinical trial<sup>h</sup>
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>g</sup>
- Fluoropyrimidine chemoradiation<sup>i</sup>
- Supportive care

Options:<sup>f</sup>

- Gemcitabine/cisplatin combination therapy<sup>g</sup> (category 1)
- Clinical trial<sup>h</sup>
- Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen<sup>g</sup>
- Supportive care

<sup>a</sup>Recommend delayed contrast-enhanced imaging.

<sup>b</sup>Consult with multidisciplinary team.

<sup>c</sup>Laparoscopy may be done in conjunction with surgery if no distant metastases are found.

<sup>d</sup>Upper/Lower endoscopy may not be needed if immunohistochemistry/pathology is conclusive.

<sup>e</sup>[See Principles of Surgery \(INTRA-A\)](#).

<sup>f</sup>Order does not indicate preference.

<sup>g</sup>A recent phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. 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).

<sup>h</sup>Systemic or intra-arterial chemotherapy may be used in a clinical trial.

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

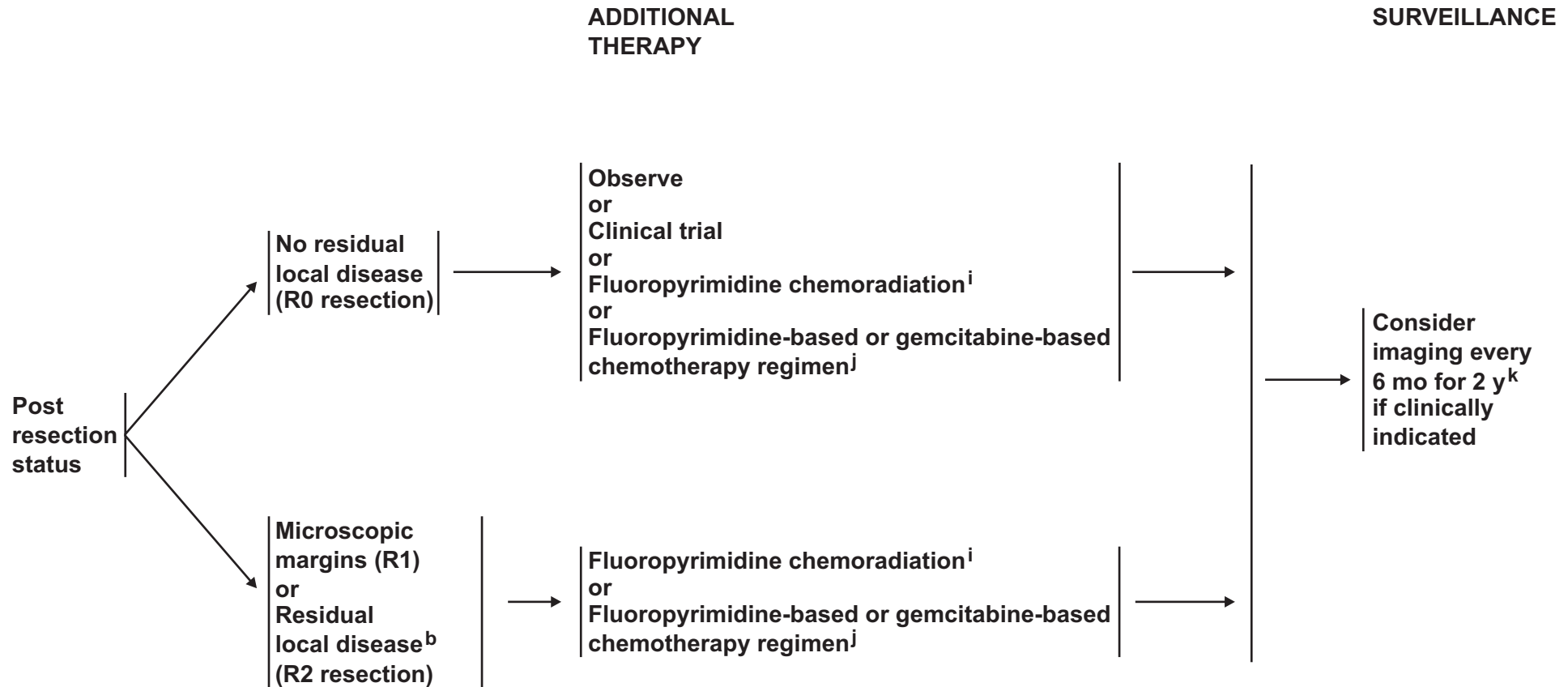
**Note:** All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 2.2013

## Intrahepatic Cholangiocarcinoma



<sup>b</sup>Consult with multidisciplinary team.

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

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

<sup>k</sup>There 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.**





### PRINCIPLES OF SURGERY<sup>1,2</sup>

- **A preoperative biopsy is not always necessary before proceeding with a definitive potentially curative resection. A suspicious mass on imaging in the proper clinical setting should be treated as malignant.**
- **Diagnostic laparoscopy to rule out unresectable disseminated disease should be considered**
- **Initial exploration should assess for multi-focal hepatic disease, lymph node metastases and distant metastases. Lymph node metastases beyond the porta hepatis and distant metastatic disease contraindicate resection.**
- **Hepatic resection with negative margins is the goal of surgical therapy. While major resections are often necessary, wedge resections and segmental resections are all appropriate given that a negative margin can be achieved**
- **A portal lymphadenectomy is reasonable as this provides relevant staging information**
- **Multi-focal liver disease is generally representative of metastatic disease and is a contraindication to resection. In highly selected cases with limited multi-focal disease resection can be considered.**
- **Gross lymph node metastases to the porta hepatis portend a poor prognosis and resection should only be considered in highly selected cases.**

<sup>1</sup>Endo I, Gonen M, Yopp A. Intrahepatic cholangiocarcinoma: rising frequency, improved survival and determinants of outcome after resection. *Ann Surg* 2008;248:84-96  
<sup>2</sup>de Jong MC, Nathan H, Sotiropoulos GC. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors. *J Clin Oncol* 2011;29:3140-3145.

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# NCCN Guidelines Version 2.2013

## Extrahepatic Cholangiocarcinoma

### PRESENTATION

### WORKUP

### PRIMARY TREATMENT

- Pain
- Jaundice
- Abnormal liver function tests (LFTs)
- Obstruction or abnormality on imaging

- H&P
- CT/MRI (assess for vascular invasion)<sup>a</sup>
- Chest CT
- Cholangiography<sup>b</sup>
- Consider CEA
- Consider CA 19-9
- LFTs
- Surgical consultation
- Consider endoscopic ultrasound (EUS)

Unresectable<sup>c</sup>

- Biliary drainage, if indicated
- Biopsy<sup>e</sup>

Resectable<sup>d</sup>

- Surgical exploration<sup>f</sup>
- Consider laparoscopic staging
- Consider preoperative biliary drainage

Metastatic disease

- Biliary drainage, if indicated
- Biopsy

Options:

- Gemcitabine/cisplatin combination therapy<sup>h</sup> (category 1)
- Clinical trial
- Fluoropyrimidine based or other gemcitabine based chemotherapy regimen<sup>h</sup>
- Fluoropyrimidine chemoradiation<sup>i</sup>
- Supportive care

Unresectable, see above

Resectable<sup>d</sup> → Resection<sup>d</sup> →

[See Adjuvant Treatment and Surveillance \(EXTRA-2\)](#)

Options:

- Gemcitabine/cisplatin combination therapy<sup>h</sup> (category 1)
- Clinical trial
- Fluoropyrimidine based or other gemcitabine based chemotherapy regimen<sup>h</sup>
- Supportive care

<sup>a</sup>Recommend delayed contrast-enhanced imaging.

<sup>b</sup>MRCP is preferred. ERCP/PTC are used more for therapeutic intervention.

<sup>c</sup>Highly selected patients may be transplant candidates.

<sup>d</sup>[See Principles of Surgery \(EXTRA-A\)](#).

<sup>e</sup>Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.

<sup>f</sup>Surgery may be performed when index of suspicion is high; biopsy not required.

<sup>g</sup>Order does not indicate preference.

<sup>h</sup>A recent phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. 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)

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

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

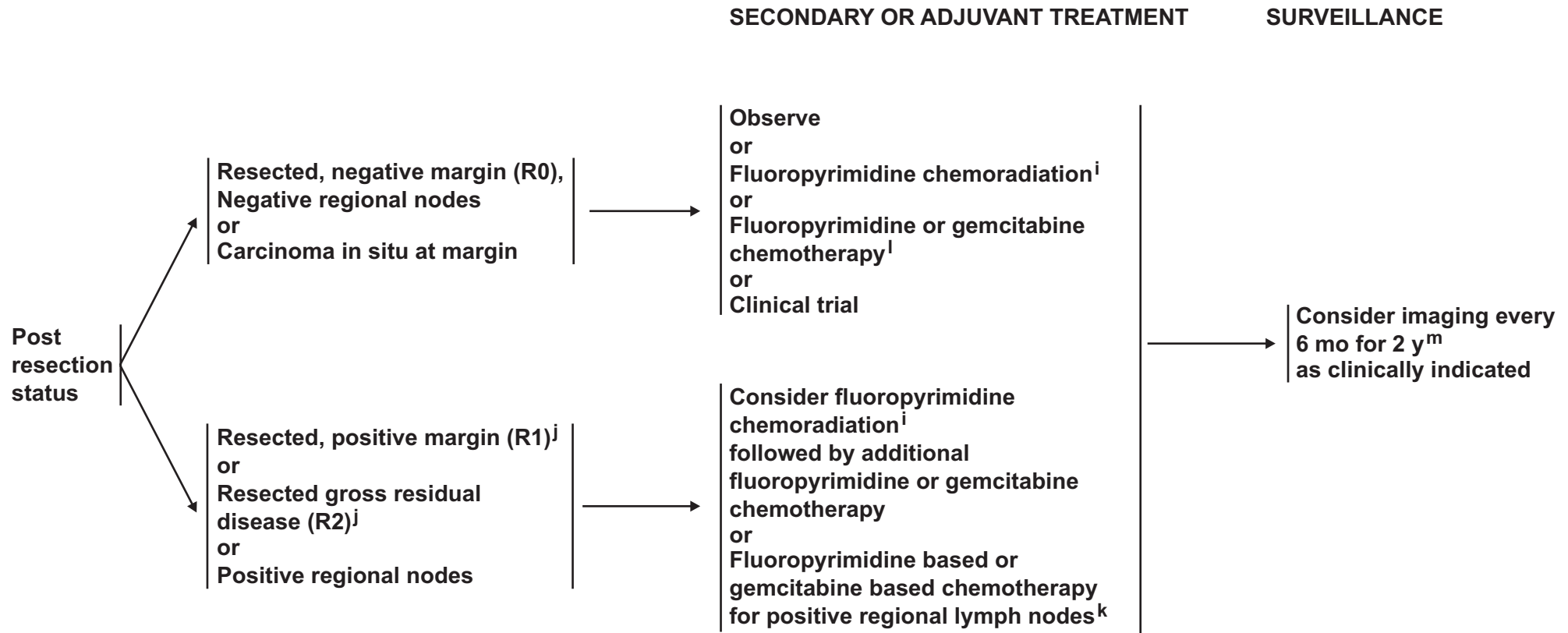
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.





# NCCN Guidelines Version 2.2013

## Extrahepatic Cholangiocarcinoma



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

<sup>j</sup>R1 or R2 resections should be evaluated by a multidisciplinary team.

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

<sup>l</sup>There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

<sup>m</sup>There 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.**



### PRINCIPLES OF SURGERY

- The basic principle is a complete resection with negative margins and regional lymphadenectomy. This generally requires a pancreaticoduodenectomy for distal bile duct tumors and a major hepatic resection for hilar tumors. Rarely, a mid bile duct tumor can be resected with a bile duct resection and regional lymphadenectomy.
- Diagnostic laparoscopy should be considered.
- Occasionally a bile duct tumor will involve the biliary tree over a long distance such that a hepatic resection and pancreaticoduodenectomy will be necessary. These are relatively morbid procedures and should only be carried out in very healthy patients without significant comorbidity. Nonetheless, these can be potentially curative procedures and should be considered in the proper clinical setting. Combined liver and pancreatic resections performed to clear distant nodal disease are not recommended.

#### Hilar cholangiocarcinoma

- Detailed descriptions of imaging assessment of resectability are beyond the scope of this outline. The basic principle is that the tumor will need to be resected along with the involved biliary tree and the involved hemi-liver with a reasonable chance of a margin negative resection. The contra-lateral liver requires intact arterial and portal inflow as well as biliary drainage.<sup>1,2,3</sup>
- Detailed descriptions of pre-operative surgical planning are beyond the scope of this outline but require an assessment of the future liver remnant (FLR). This requires an assessment of biliary drainage and volumetrics of the FLR. While not necessary in all cases, the use of pre-operative biliary drainage of the FLR and contralateral portal vein embolization should be considered in cases of a small future liver remnant.<sup>4,5</sup>
- Initial exploration rules out distant metastatic disease to the liver, peritoneum or distant lymph nodes beyond the porta hepatis as these findings contraindicate resection. Further exploration must confirm local resectability
- Since hilar tumors, by definition, abut or invade the central portion of the liver they require major hepatic resections on the involved side to encompass the biliary confluence and generally require a caudate resection.
- Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection and require expertise in these procedures.
- Biliary reconstruction is generally through a Roux-en-Y hepaticojejunostomy
- A regional lymphadenectomy of the porta hepatis is carried out.
- Frozen section assessment of proximal and distal bile duct margins are recommended if further resection can be carried out

#### Distal cholangiocarcinoma

- Initial assessment to rule out distant metastatic disease and local resectability
- The operation generally requires a pancreaticoduodenectomy with typical reconstruction

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.

[References on next page](#)



### PRINCIPLES OF SURGERY

#### (References)

- <sup>1</sup>Nishio H, Nagino M, Nimura Y. Surgical management of hilar cholangiocarcinoma: the Nagoya experience. *HPB* 2005;7:259-262.
- <sup>2</sup>Matsuo K, Rocha FG, Ito K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg* 2012;215:343-355.
- <sup>3</sup>Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability and outcomes in 225 patients with hilar cholangiocarcinoma. *Ann Surg* 2001;234:507-517.
- <sup>4</sup>Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma. *HPB* 2008;10:130-133
- <sup>5</sup>Kennedy TJ, Yopp A, Qin Y, et al. Role of preoperative biliary drainage of live remnant prior to extended liver resection of hilar cholangiocarcinoma. *HPB* 2009;11:445-451.

**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**

<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2	N0	M0
<b>Stage IIIA</b>	T3a	N0	M0
<b>IIIB</b>	T3b	N0	M0
<b>IIIC</b>	T4	N0	M0
<b>Stage IVA</b>	Any T	N1	M0
<b>Stage IVB</b>	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](http://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.



# NCCN Guidelines Version 2.2013 Staging Hepatobiliary Cancers

**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**

<b>Stage 0</b>	Tis	N0	M0
<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2	N0	M0
<b>Stage IIIA</b>	T3	N0	M0
<b>Stage IIIB</b>	T1-3	N1	M0
<b>Stage IVA</b>	T4	N0-1	M0
<b>Stage IVB</b>	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**

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

**Histologic Grade (G)**

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

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# NCCN Guidelines Version 2.2013 Staging Hepatobiliary Cancers

**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**

<b>Stage 0</b>	Tis	N0	M0
<b>Stage I</b>	T1	N0	M0
<b>Stage II</b>	T2a-b	N0	M0
<b>Stage IIIA</b>	T3	N0	M0
<b>Stage IIIB</b>	T1-3	N1	M0
<b>Stage IVA</b>	T4	N0-1	M0
<b>Stage IVB</b>	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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# NCCN Guidelines Version 2.2013 Staging Hepatobiliary Cancers

**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**

<b>Stage 0</b>	Tis	N0	M0
<b>Stage IA</b>	T1	N0	M0
<b>Stage IB</b>	T2	N0	M0
<b>Stage IIA</b>	T3	N0	M0
<b>Stage IIB</b>	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
<b>Stage III</b>	T4	Any N	M0
<b>Stage IV</b>	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:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

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### Overview

Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma; HCC), gall bladder, and bile ducts (intrahepatic and extrahepatic cholangiocarcinoma). Gallbladder cancer and cholangiocarcinomas are collectively known as biliary tract cancers. In 2013, an estimated 30,640 people in the United States will be diagnosed with liver cancer and an additional 10,310 people will be diagnosed with intrahepatic bile duct cancer, gallbladder cancer, or other biliary tract cancer. There will be approximately 21,670 deaths from liver or intrahepatic bile duct cancer, and 3,230 deaths due to gallbladder cancer or other biliary tract cancer.<sup>1</sup>

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: HCC, gallbladder cancer, and intrahepatic 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.<sup>2</sup> 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.<sup>3,4</sup> A retrospective analysis of patients at liver transplantation centers in the United States 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.<sup>5</sup>

Seropositivity for hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) are associated with an increased risk for HCC in patients with chronic hepatitis B viral infection.<sup>6,7</sup> 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.<sup>8-11</sup>

Non-viral causes associated with an increased risk for HCC include alcoholic cirrhosis, inherited errors of metabolism (relatively rare) such as hereditary hemochromatosis, porphyria cutanea tarda, and alpha1-antitrypsin deficiency, Wilson's disease, and stage IV primary biliary cirrhosis.<sup>2,12</sup> 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.<sup>2,4,13</sup> 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.<sup>4,14</sup>

Alcoholic cirrhosis is clearly a risk factor for HCC,<sup>4</sup> 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 such as viral hepatitis infection, which can interact synergistically in the pathogenesis of HCC.<sup>15,16</sup>

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 National Center for Health Statistics found that patients with a known diagnosis of hemochromatosis at death were 23 times more likely to have liver cancer than those without GH. The annual incidence rates of HCC associated with cirrhosis due to GH has been sufficiently high (about 3% to 4%) and the AASLD guidelines recommend surveillance for this group of patients when cirrhosis is present.<sup>4</sup>

There is also growing evidence for an association between the sequelae of non-alcoholic fatty liver disease, such as non-alcoholic steatohepatitis (NASH, a spectrum of conditions characterized by histologic 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.<sup>17,18</sup> Estimations of the prevalence of NASH in the United States are in the range of 3% to 5%, indicating that this sizable subpopulation is at risk for cirrhosis and development of HCC.<sup>19</sup> 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%.<sup>20</sup> 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.<sup>21,22</sup>

In most cases, the risk factors for HCC are also risk factors for liver cirrhosis. It has been estimated that 60% to 80% of persons with HCC have underlying cirrhosis, possibly approaching 90% in the United States.<sup>23</sup> 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.<sup>24</sup> Importantly, certain populations chronically infected with the HBV (ie, hepatitis B carriers) have been identified as being at increased risk for HCC in the absence of cirrhosis, especially when other risk factors are present,<sup>4</sup> and it has been estimated that 30% to 50% of patients with chronic hepatitis B viral infection who develop HCC do not have underlying cirrhosis.<sup>13</sup> Some risk factors for the 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  $\geq 40$  years, Asian females  $\geq 50$  years, and African/North American blacks with hepatitis.<sup>4,13</sup> 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.<sup>14,25</sup> Although the mechanism of HCC development differs according to the underlying disease, 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.<sup>2</sup>

The incidence of HCC is increasing in the United States, particularly in the population infected with HCV. Approximately 4 million individuals in the United States are chronically infected with the HCV,<sup>26</sup> and the annual incidence rate of HCC among patients with HCV-related cirrhosis has been estimated to be between 2% and 8%.<sup>4</sup> 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.<sup>27,28</sup>

Approximately 1.5 million people in the United States are chronically infected with HBV.<sup>29,30</sup> 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,<sup>31</sup> although studies have shown wide variation in the annual incidence rate of HCC among individuals with chronic hepatitis B infection.<sup>4</sup>

### 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 Diseases (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.”<sup>4</sup>

Support for enrolling individuals at high risk for 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 ultrasound 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.<sup>32</sup> 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.<sup>33</sup> Although survival did not differ in the two 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 ultrasound are the most widely used methods of screening for HCC.<sup>34</sup> In a screening study involving a large population

of patients in China infected with the HBV or those with chronic hepatitis, the detection rate, false-positive rate, and positive predictive value were 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.<sup>35</sup> These results demonstrate that ultrasound imaging alone is a better HCC screening approach than AFP testing alone. Nevertheless, since ultrasound is highly operator dependent, the addition of AFP can increase the likelihood of detecting HCC in a screening setting. However, AFP is frequently not elevated in early stage disease and its utility as a screening biomarker is limited.<sup>36-38</sup>

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 (Hepatitis B, C) as well as non-viral causes (alcoholic cirrhosis, GH, NASH, stage IV primary biliary cirrhosis, alpha-1 antitrypsin deficiency, and cirrhosis related to other causes) and hepatitis B carriers without cirrhosis. Other less common causes of cirrhosis include secondary biliary serosis, Wilson’s disease, sclerosing cholangitis, granulomatous disease, type IV glycogen storage disease, drug-induced liver disease, venous outflow obstruction, chronic right-sided heart failure, and tricuspid regurgitation.<sup>39</sup>

There is evidence suggesting improved outcomes in patients with HCC developing in the setting of HBV or HCV cirrhosis when the viral hepatitis is successfully treated. Referral to a hepatologist should be considered for this group of patients. The panel recommends periodic screening with ultrasound and AFP testing every 6 to 12 months for patients at risk for HCC. Additional imaging (at least a 3-phase CT scan or MRI) is recommended 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, though not well-studied, method in the United States.

### Diagnosis

HCC is asymptomatic for much of its natural history. Nonspecific symptoms associated with HCC can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites.<sup>18</sup> Paraneoplastic syndromes also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.<sup>40</sup>

### Imaging

HCC lesions are characterized by arterial hypervascularity, deriving most of their blood supply from the hepatic artery. This is unlike the surrounding liver, which receives most of its supply of blood from the portal vein.<sup>41</sup> 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 ultrasound (CEUS), although the latter modality is not commonly available in the United States.<sup>4,42,43</sup> PET/CT is not considered to be adequate. The term “4-phase” refers to the phases of scanning: unenhanced phase, arterial phase, portal venous phase, and venous phase after a delay.<sup>23</sup> 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.<sup>43-45</sup>

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 ultrasound demonstrated that the diagnosis of HCC can be established without biopsy confirmation if both imaging studies are conclusive.<sup>45</sup> However, as noted earlier, CEUS is not commonly utilized in the United States. 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 liver nodules between 1 and 2 cm detected during surveillance, thereby reducing the need for a biopsy.<sup>46</sup> In the updated AASLD guidelines, the algorithms for the liver nodules between 1 and 2 cm 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 ultrasound or in the setting of a rising serum AFP level) are adapted from the updated guidelines developed by the AASLD.<sup>4</sup> 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.

For patients with an incidental liver mass or nodule found on ultrasound, the guidelines recommend evaluation using one or more of the imaging modalities (at least a 3-phase contrast-enhanced CT or MRI including the arterial and portal venous phase) to determine the perfusion characteristics, extent and the number of lesions, vascular anatomy, and extrahepatic disease. The number and type of imaging are dependent on the size of the liver mass or nodule.

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

Liver nodules greater than 1 cm in size should first be evaluated with 3-phase contrast-enhanced 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 that are between 1 and 2 cm or greater than 2 cm. For patients with liver nodules between 1 and 2 cm, the NCCN Guidelines have included repeat 3-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 (3-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 enhancement is observed by the recommended imaging method.<sup>46</sup> 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 cytologic samples can provide for immediate determinations of whether a sufficient sample has been obtained, as well as the possibility of an upfront tentative diagnosis.<sup>47</sup> However, FNAB is highly dependent on the skill of the cytopathologist,<sup>48</sup> and there are reports of high false-negative rates<sup>45,49</sup> as well as the possibility of false-positive findings with this procedure.<sup>50</sup> 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 histologic and immunohistochemical tests can be performed on the paraffin wax embedded sample.<sup>36,47,49</sup> However, recent evidence indicates that a core biopsy does not provide an accurate determination of tumor grade.<sup>51</sup>

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.<sup>4,23</sup> 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 less than 20 ng/mL.<sup>52</sup> In patients with chronic liver disease, an elevated AFP could be more indicative of HCC in non-infected patients.<sup>53</sup> Furthermore, AFP can also be elevated in intrahepatic cholangiocarcinoma and some metastases from colon cancer.<sup>4</sup> 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.<sup>54,55</sup> However, the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institution.

The updated AASLD guidelines no longer recommend AFP testing as part of diagnostic evaluation.<sup>4</sup> 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,<sup>56</sup> which is in agreement with the updated AASLD guidelines recommendation.<sup>4</sup> 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.<sup>23,57,58</sup> 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 was considered optimal in this setting.<sup>59</sup> 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.<sup>37</sup>

### Initial Workup

The foundation of the initial workup of the patient diagnosed with HCC is a multidisciplinary evaluation involving investigations into the etiologic origin of liver disease, including a hepatitis panel for detection of hepatitis B and/or C viral infection (HBsAg, hepatitis B surface antibody, hepatitis B core antibody [HBcAb], IgG, and HCV antibody) 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 a hepatologist for appropriate antiviral therapy.<sup>13,60</sup>

Common sites of HCC metastasis include the lung, abdominal lymph nodes, peritoneum, and bone.<sup>61,62</sup> Hence, chest imaging and a bone scan (if suspicious bone pain is present) are recommended as part of the initial workup. At least a 3-phase CT or MRI is 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 (FLR) in relation to the total liver volume.<sup>43</sup> Enlarged lymph nodes are seen commonly in patients with viral hepatitis, primary biliary cirrhosis, and other underlying liver disorders that predispose patients to HCC,<sup>63</sup> 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 (ALP), measurement of prothrombin time (PT)/international normalized ratio (INR), albumin, and platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count and tests of kidney function (blood urea nitrogen and creatinine), which are established prognostic markers in patients with liver disease.<sup>64</sup>

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.<sup>65,66</sup> The Child-Pugh classification provides a rough estimate of liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis. The Child-Pugh score is an empirical score that incorporates laboratory measurements (ie, serum albumin, bilirubin, PT) as well as more subjective clinical assessments of encephalopathy and ascites. More recently, a version of the Child-Pugh score that 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.<sup>43</sup> Measurement of hepatic venous pressure gradient (HVPG) is an evolving tool for the assessment of portal hypertension.<sup>67-70</sup>

Another system for evaluation of hepatic reserve is the Model for End-Stage Liver Disease (MELD), which is a numerical scale ranging from 6 (less ill) to 40 (gravely ill) for individuals 12 years or older. It is

derived using three laboratory values (serum bilirubin, creatinine, and INR) and was originally devised to provide an assessment of mortality for patients undergoing transjugular intrahepatic portosystemic shunts.<sup>71</sup> The MELD score has since been adopted by the United Network for Organ Sharing (UNOS; [www.unos.org](http://www.unos.org)) to stratify patients on the liver transplantation waiting list according to their risk of death within 3 months.<sup>72</sup> 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.<sup>66</sup>

### Pathology and Staging

#### Pathology

Three gross morphologic types of HCC have been identified: nodular, massive, and diffuse. 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 they 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.<sup>42</sup> A number of staging systems for patients with HCC have been devised.<sup>73,74</sup> Each of the staging systems includes variables that evaluate one or more of the factors listed above. For example, the Child-Pugh<sup>65</sup> and MELD scores<sup>75</sup> can be considered to be staging systems that evaluate aspects of liver function only.

The AJCC staging system provides information on the pathologic characteristics of resected specimens only,<sup>76</sup> whereas the Okuda system incorporates aspects of liver function and tumor characteristics.<sup>77</sup> The French classification (GRETCH) system incorporates the Karnofsky performance score as well as measurements of liver function and serum AFP.<sup>78</sup> Several staging systems include all parameters from other staging systems as well as additional parameters. For example, the Chinese University Prognostic Index (CUPI) system<sup>79</sup> and the Japanese Integrated Staging (JIS)<sup>80</sup> scores incorporate the TNM staging system and the Cancer of the Liver Italian Program (CLIP),<sup>81</sup> Barcelona Clinic Liver Cancer (BCLC),<sup>82</sup> and SLiDe,<sup>83</sup> and JIS systems include the Child-Pugh score (with modified versions of CLIP and JIS substituting the MELD score for the Child-Pugh score).<sup>84-86</sup> In addition, the BCLC system also incorporates the Okuda system, as well other tumor characteristics, measurements of liver function, and patient performance status.<sup>87</sup>

Although some of these systems have been found to be applicable for all stages of HCC (eg, BCLC),<sup>23,87,88</sup> limitations of all of these systems have been identified. For example, the AJCC staging 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 staging system has been shown to accurately predict survival for patients who underwent orthotopic liver transplantation.<sup>89</sup> The CLIP, CUPI, and GRETCH staging systems have been shown to perform well in predicting survival in patients with advanced disease.<sup>90</sup>

The CLIP system has been specifically identified as being useful for staging patients who underwent transarterial chemoembolization (TACE) and those treated in a palliative setting.<sup>91,92</sup> 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.<sup>93</sup> 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.<sup>74</sup> Furthermore, the BCLC staging system was recently shown to be very useful for predicting outcome in patients following liver transplantation or radiofrequency ablation (RFA).<sup>94,95</sup> In a multicenter cohort study of 1328 patients with HCC eligible for liver transplantation, survival benefit for liver transplantation was seen in patients with advanced liver cirrhosis and in those with intermediate tumors (BCLC stage D and stages B–C, respectively), regardless of the number and size of the lesions, provided there was no macroscopic vascular invasion and extrahepatic disease.

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.<sup>96</sup> In addition, another study showed tumor size greater than 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.<sup>97</sup> This staging system has been retrospectively validated in a population of patients with early HCC.<sup>98</sup>

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 the following 4 categories:

- Potentially resectable or transplantable, operable by performance status or comorbidity
- Unresectable disease
- Inoperable by performance status or comorbidity with local disease only
- Metastatic disease

### Treatment Guidelines

All patients with HCC should be carefully evaluated for 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. 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.<sup>23</sup>

### Surgery

Partial hepatectomy (ie, liver resection) is a potentially curative therapy for patients with early-stage HCC (solitary tumor  $\leq 5$  cm in size, or  $\leq 3$  tumors each  $\leq 3$  cm in size and no evidence of gross vascular invasion) who are eligible to undergo the procedure.<sup>99</sup> Partial hepatectomy for selected patients with HCC can now be performed with low operative morbidity and mortality (in the range of 5% or less).<sup>100,101</sup> Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC,<sup>101-103</sup> 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%.<sup>103,104,105</sup> However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.<sup>87,102</sup>

Since liver resection for patients with HCC includes 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 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.<sup>106</sup> Likewise, estimates of overall liver function and the size and function of the putative FLR, 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).<sup>107</sup> 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 FLR following resection, preoperative imaging is essential for surgical planning.<sup>43</sup> 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.<sup>100,108</sup> However, in one study, no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors 10 cm or greater.<sup>100</sup> Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence.<sup>100,109,110</sup> The role of liver resection for patients with limited and resectable multifocal disease and/or signs of major vascular invasion is controversial,<sup>99,109,111</sup> although results of a recent retrospective analysis showed a 5-year overall survival (OS) rate of 81% for selected patients with a single tumor 5 cm or less, or 3 or fewer tumors 3 cm or less undergoing liver resection.<sup>112</sup>

Another critical preoperative assessment includes evaluation of the postoperative 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.<sup>113</sup> The panel recommends that this ratio be at least 20% in patients without cirrhosis and least 30% to 40% in patients with a Child-Pugh A score.<sup>114</sup> For patients with an estimated FLR/total liver volume ratio below recommended values who are otherwise suitable candidates for liver resection, preoperative portal vein embolization (PVE) should be considered. PVE is a safe and effective procedure for redirecting blood flow toward the portion of the liver that will remain following surgery. Hypertrophy is induced in these segments of the liver while the embolized portion of the liver undergoes atrophy.<sup>115</sup>

### ***Liver Transplantation***

Liver transplantation is an attractive, potentially curative therapeutic option for patients with early HCC. 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  $\leq 5$  cm in diameter or no more than three nodules  $\leq 3$  cm in diameter in patients with multiple tumors) for patients with unresectable HCC and cirrhosis.<sup>116</sup> The 4-year OS and relapse-free survival (RFS) 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.<sup>117</sup> These selection criteria were adopted by UNOS, because they identify a subgroup of patients with HCC whose liver transplantation results are similar to those who underwent liver transplantation for end-stage cirrhosis without HCC.



The UNOS criteria (radiologic evidence of a single tumor 5 cm or less in diameter, or 2 to 3 tumors 3 cm or less in diameter, and no evidence of macrovascular involvement or extrahepatic disease) 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.<sup>118-121</sup>

The MELD score as a measure of liver function is also used as a measure of pre-transplant mortality. It was adopted by UNOS in 2002 to provide an estimate of risk of death within 3 months for patients on the waiting list for cadaveric liver transplant. According to the current UNOS policy, patients with T2 tumors (defined by UNOS as a single nodule between 2 and 5 cm or 2 or 3 nodules all <3 cm) receive an additional 22 priority MELD points (also called a “MELD-exception”).<sup>72</sup> In a retrospective analysis of data provided by UNOS of 15,906 patients undergoing first-time liver transplantation during 1997 to 2002 and 19,404 patients undergoing the procedure during 2002 to 2007, 4.6% of liver transplant recipients had HCC compared with 26% in 2002 to 2007, with most patients in the latter group receiving an “HCC MELD exception.”<sup>122</sup> In 2002 to 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 a MELD score of 20 or more and serum AFP level of 455 ng/mL or more,<sup>122</sup>

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 between 3 and 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.<sup>87,117,123,124</sup> An expanded set of criteria including patients with a single HCC tumor 6.5 cm or smaller, with a maximum of 3 total tumors with no tumor larger than 4.5 cm (and cumulative tumor size <8 cm) as liver transplant candidates has been proposed by Yao et al at the University of California at San Francisco (UCSF).<sup>125</sup> 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%).<sup>123-127</sup> 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.<sup>117,123,126</sup> 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 between 3 and 5 cm compared with those who had smaller tumors.<sup>122</sup>

### *Bridge Therapy*

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list.<sup>128</sup> It is considered for patients who meet the transplant criteria. A number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list.<sup>129,130</sup> These studies included

RFA,<sup>131-134</sup> chemoembolization,<sup>133,135</sup> TACE,<sup>133,136,137</sup> transarterial radioembolization (TARE) with yttrium-90 microspheres,<sup>138</sup> conformal radiation therapy,<sup>139</sup> and sorafenib<sup>140</sup> 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.<sup>141,142</sup> Nevertheless, the use of bridge therapy in this setting is increasing, and it is administered at some NCCN Member Institutions.

### *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.<sup>143,128</sup> Recent prospective studies have demonstrated that downstaging (prior to transplant) with percutaneous ethanol injection (PEI),<sup>144</sup> RFA,<sup>144,145</sup> TACE,<sup>144-147</sup> and TARE with yttrium-90 microspheres<sup>147</sup> improves disease-free survival (DFS) 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.<sup>148-150</sup> Further validation is needed to define the endpoints for successful downstaging prior to transplant.

### **Management of Resectable Disease**

The consensus of the 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.

Hepatic resection, if feasible, is a potentially curative treatment option and is the preferred treatment for patients with the following disease characteristics: adequate liver function (Child-Pugh class A and selected Child-Pugh class B patients without portal hypertension), solitary mass without major vascular invasion, and adequate liver remnant.<sup>151</sup> The presence of extrahepatic metastasis is considered to be a contraindication for resection. Hepatic resection is controversial in patients with limited and multifocal disease as well as those with major vascular invasion. Liver resection in patients with major vascular invasion should only be performed in highly selected situations by experienced teams.

Transplantation (if feasible), should be considered for patients who meet the UNOS criteria (single tumor ≤5 cm in diameter or 2 to 3 tumors, each ≤3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease). The guidelines have included consideration of bridge therapy as clinically indicated for patients eligible for liver transplant. If transplant is not feasible, the panel recommends hepatic resection for this group of patients.

### **Management of Unresectable Disease**

Liver transplantation is indicated for patients who meet the UNOS criteria. Non-transplant candidates and those with extensive liver tumor burden should consider participation in clinical trials. Alternative treatment options for this group of patients include sorafenib, locoregional therapy, stereotactic body radiation therapy (SBRT), best supportive care, or chemotherapy (systemic or intra-arterial) with or without RT in the context of a clinical trial.

### **Locoregional Therapies**

Locoregional therapies are directed toward inducing selective tumor necrosis, and are broadly classified into ablation and arterially directed

therapies. Tumor necrosis induced by locoregional therapy is typically estimated by the extent to which contrast uptake on dynamic CT/MRI is diminished at a specified time following the treatment when compared with pretreatment imaging findings. The absence of contrast uptake within the treated tumor is believed to be an indication of tumor necrosis. A number of factors are involved in measuring the effectiveness of locoregional therapies, and the criteria for evaluating tumor response are evolving.<sup>42,152-155</sup> AFP response after locoregional therapy has also been reported to be a reliable predictor of tumor response, time to progression (TTP), progression-free survival (PFS), and OS.<sup>156</sup>

### **Ablation**

In an ablative procedure, tumor necrosis can be induced either by direct exposure of the tumor to a chemical substance (eg, ethanol or acetic acid) or an alteration in temperature (RFA, cryoablation, or microwave ablation). Any ablative therapy can be performed by laparoscopic, percutaneous, or open approaches. RFA and PEI are the two most commonly used ablation therapies.

The safety and efficacy of RFA and PEI in the treatment of Child-Pugh class A patients with early-stage HCC tumors (either a single tumor  $\leq 5$  cm or multiple tumors [up to 3 tumors] each  $\leq 3$  cm) has been compared in a number of randomized controlled trials.<sup>157-162</sup> Both RFA and PEI were associated with relatively low complication rates. RFA was shown to be superior to PEI with respect to complete response rate (65.7% vs. 36.2%, respectively;  $P = .0005$ ),<sup>161</sup> and rate of local recurrence.<sup>158-160</sup> In addition, in two studies patients in the RFA arm were shown to require fewer treatment sessions.<sup>157,160</sup> However, the OS benefit for RFA over PEI was demonstrated only in 3 randomized studies performed in Asia,<sup>158-160</sup> whereas the 3 European randomized studies failed to show a significant difference in the OS between the two treatment arms.<sup>157,161,162</sup>

In the recent Italian randomized trial of 143 patients with HCC, the 5-year survival rates were 68% and 70%, respectively, for PEI and RFA groups; the corresponding RFS rates were 12.8% and 11.7%, respectively.<sup>162</sup> Nevertheless, independent meta-analyses of randomized trials that have compared RFA and PEI have confirmed that RFA is superior to PEI with respect to OS and tumor response in patients with early-stage HCC, particularly for tumors larger than 2 cm.<sup>163-165</sup>

Reported rates of local recurrences vary widely across the randomized studies, which may reflect the differences in patient selection criteria and treatment protocols. For example, in one study, Lin et al reported a 3-year cumulative new HCC recurrence rate of 45% and 48%, respectively, for RFA and PEI arms.<sup>159</sup> However, in the study of Shiina et al the estimated 4-year recurrence rates were 70% and 85% in the RFA and PEI arms, respectively, for patients with 3 or fewer small tumors each  $\leq 3$  cm.<sup>160</sup> Results of some long-term studies show survival rates of over 50% at 5 years for patients with early HCC treated with RFA.<sup>166-169</sup> Nevertheless, reported OS rates vary widely across the studies of patients treated with RFA, which is most likely due to differences in the size and number of tumors and, perhaps more importantly, tumor biology and the extent of underlying liver function in the patient populations studied. In multivariate analysis, Child-Pugh class, tumor size, and tumor number were independent predictors of survival.<sup>167-169</sup>

RFA and PEI have also been compared with surgical resection in few randomized studies. In the only randomized study that compared PEI with surgical resection in 76 patients without cirrhosis, with one or two tumors 3 cm or smaller, PEI was equally effective as surgical resection.<sup>170</sup> On the other hand, studies that have compared RFA and surgical resection have failed to provide conclusive evidence. RFA and

liver resection in the treatment of patients with HCC tumors have been evaluated in 3 randomized prospective studies.<sup>171-173</sup> The results of one randomized trial showed a significant survival benefit for surgical resection over RFA in 235 patients with small HCC conforming to the Milan criteria (single tumors  $\leq 5$  cm or multiple tumors with no more than 3 tumor nodules  $\leq 3$  cm).<sup>172</sup> The 5-year OS rates were 54.8% and 75.6%, respectively, for the RFA group and surgical resection. The corresponding RFS rates for the 2 groups were 28.7% and 51.3%, respectively. However, more patients in the resection group were lost to follow-up than the RFA group. Conversely, the other 2 randomized studies failed to show statistically significant differences in OS and DFS between the two treatment groups. However, these studies were limited by the small number of patients (180 patients and 168 patients, respectively) and the lack of a non-inferiority design.<sup>171,173</sup> In addition, in one of the studies, tumor location was an independent risk factor associated with survival, suggesting that percutaneous RFA may be incomplete for the treatment of small HCCs located at specific sites of the liver.<sup>173</sup>

The results of a recent meta-analysis that included 2,535 patients (1,233 treated with surgical resection and 1,302 treated with RFA) revealed that surgical resection is associated with a significantly improved survival and higher rate of complications than ablation for patients with early-stage HCC, although there was no significant difference in local recurrence rates between the 2 treatment groups.<sup>174</sup>

Additionally, some investigators consider RFA as the first-line treatment in patients with HCC tumors that are 2 cm or less in diameter.<sup>175,176</sup> In one study, RFA as the initial treatment in 218 patients with a single HCC lesion 2.0 cm or less induced a complete necrosis in 98% of patients (214 of 218 patients).<sup>175</sup> After a median follow-up of 31 months, the sustained complete response rate was 97% (212 of 218 patients).

More recently, in a retrospective comparative study, Peng et al reported that percutaneous RFA was better than surgical resection in terms of OS and RFS, especially for patients with central HCC tumors less than 2 cm.<sup>176</sup> The 5-year OS rates in patients with central HCC tumors were 80% for RFA compared to 62% for surgical resection ( $P = .02$ ). The corresponding RFS rates were 67% and 40%, respectively ( $P = .033$ ).

Subgroup analyses from some of the retrospective studies suggest that tumor size is a critical factor in determining the effectiveness of RFA or surgical resection.<sup>131,132,177-179</sup> In a series of 126 patients with cirrhosis or chronic hepatitis, although RFA was safe and effective for the treatment of both medium (between 3.1 and 5.0 cm) and large (between 5.1 and 9.5 cm) tumors, smaller and medium and/or noninfiltrating tumors were treated successfully significantly more often than large and/or infiltrating tumors.<sup>177</sup> Mazzaferro et al also reported similar findings in a prospective study of 50 consecutive patients with liver cirrhosis undergoing RFA while awaiting liver transplantation (the rate of overall complete tumor necrosis was 55% and 63% for tumors  $\leq 3$  cm).<sup>132</sup> In a retrospective analysis, Vivarelli et al reported that OS and DFS were significantly higher with surgery compared to percutaneous RFA. The advantage of surgery was more evident for Child-Pugh class A patients with single tumors of more than 3 cm in diameter, and the results were similar in 2 groups for Child-Pugh class B patients.<sup>178</sup> In another retrospective analysis of 40 Child-Pugh class A or B patients with HCC treated with percutaneous ablative procedures, the overall rate of complete necrosis was 53%, which increased to 62% when considering only the subset of tumors less than 3 cm treated with RFA.<sup>131</sup> In a recent propensity case-matched study that compared liver resection and percutaneous ablative therapies in 478 patients with Child-Pugh A cirrhosis, survival was not different between surgical resection and ablation for tumors that met the Milan criteria; however, surgical

resection significantly improved long-term survival for patients with single HCC tumors larger than 5 cm or multiple tumors (up to 3 tumors) larger than 3 cm.<sup>179</sup> Median survival for the surgical resection group was 80 months and 83 months, respectively, compared to 21.5 months and 19 months, respectively, for patients treated with ablative procedures.

Although inconclusive, available evidence suggests that the choice of ablative therapy for patients with early stage HCC should be based on the tumor size and the underlying liver function.

### **Arterially Directed Therapies**

Arterially directed therapy involves the 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.<sup>180</sup> Arterially directed 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.<sup>41</sup> Furthermore, HCC tumors are hypervascular resulting from increased blood flow to tumor relative to normal liver tissue.

Arterially directed therapies that are currently in use include transarterial bland embolization (TAE), TACE, TACE with drug-eluting beads (DEB-TACE), and TARE with yttrium-90 microspheres.

The principle of TAE is to reduce or eliminate 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. TAE has been shown to be an effective treatment option for patients with unresectable HCC.<sup>181-184</sup> In a multicenter retrospective study of 476 patients with unresectable HCC, TAE significantly prolonged survival compared to supportive care ( $P = .0002$ ). The 1-, 2-, and 5-year survival rates were 60.2%, 39.3%, and

11.5%, respectively, for patients who underwent TAE. The corresponding survival rates were 37.3%, 17.6%, and 2%, respectively, for patients who underwent supportive care.<sup>182</sup> In a multivariate analysis, tumor size <5 cm and earlier CLIP stage were independent factors associated with a better survival. In another retrospective analysis of 322 patients undergoing TAE for the treatment of unresectable HCC in which a standardized technique (including small particles to cause terminal vessel blockade) was used, 1-, 2-, and 3-year OS rates of 66%, 46%, and 33%, respectively, were observed. The corresponding survival rates were 84%, 66%, and 51%, respectively, when only the subgroup of patients without extrahepatic spread or portal vein involvement was considered.<sup>183</sup> In multivariate, tumor size 5 cm or larger, 5 or more tumors and extrahepatic disease were identified as predictors of poor prognosis following TAE.

TACE is distinguished from TAE by the catheter-based administration of a concentrated dose of chemotherapy (eg, doxorubicin or cisplatin) combined with iodized oil, usually administered prior to the embolic particles.<sup>185</sup> The results of two randomized clinical trials have shown a survival benefit for TACE compared with supportive care in patients with unresectable HCC.<sup>186,187</sup> In the one study that 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%;  $P = .002$ ).<sup>186</sup> 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. In the other randomized study, which compared TAE or TACE with supportive care for patients with unresectable HCC, the 1- and 2-year survival rates were 82%; 63%, 75%, and 50%; and 63% and 27% for patients in the TACE, TAE, and supportive care arms, respectively.<sup>187</sup>

The majority of the patients in the study had liver function classified as Child-Pugh class A, a performance status of 0, and a 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. However, this study was terminated early. Although this study demonstrated that TACE was significantly more effective than supportive care ( $P = .009$ ), there were insufficient patients in the TAE group to make any statement regarding its effectiveness compared to either TACE or supportive care. A recent retrospective analysis of sequential patients with advanced HCC undergoing embolization in the past 10 years revealed that TACE (with doxorubicin plus mitomycin C) significantly prolonged PFS and TTP but not OS.<sup>188</sup> On a multivariable analysis, the type of embolization and CLIP score were significant predictors of PFS and TTP, whereas CLIP score and AFP were independent predictors of OS.

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. The relative effectiveness of TACE over TAE has not been established in randomized trials.

Complications common to TAE and TACE include non-target embolization, liver failure, and cholecystitis. Additional complications following TACE include acute portal vein thrombosis and bone marrow suppression, although the reported frequencies of serious adverse events vary across studies.<sup>34,189</sup> Reported rates of treatment-related mortality for TAE and TACE are usually less than 5%.<sup>34,183,187,189</sup> A postembolization syndrome involving fever, abdominal pain, and

intestinal ileus has been reported to be relatively common in patients undergoing these procedures.<sup>34,189</sup> There is evidence showing portal vein thrombosis and liver function categorized as Child-Pugh class C to be significant predictors of poor prognosis in patients treated with TACE.<sup>190</sup> 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, the panel recommends that a total bilirubin level greater than 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.<sup>191,192</sup>

DEB-TACE has also been evaluated in patients with unresectable HCC.<sup>193-197</sup> In a randomized study (PRECISION V) of 212 patients with Child-Pugh class A or B cirrhosis and localized, unresectable HCC without nodal involvement, DEB-TACE with doxorubicin-eluting embolic beads induced higher rates of complete response, objective response, and disease control compared with conventional TACE with doxorubicin (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively).<sup>195</sup> Although DEB-TACE was not superior to conventional TACE with doxorubicin ( $P = 0.11$ ) in this study, DEB-TACE was associated with a significant increase in objective response ( $P = 0.038$ ) compared to conventional TACE in patients with Child-Pugh class B, ECOG performance status 1, bilobar disease, and recurrent disease. DEB-TACE was also associated with improved tolerability with a significant reduction in serious liver toxicity and a significantly lower rate of doxorubicin-related side effects.<sup>195</sup> In another prospective randomized study ( $n = 83$ ), Malagari et al also showed that DEB-TACE

resulted in higher response rates, lower recurrences, and longer TTP compared to TAE in patients with intermediate-state HCC; however, this study also did not show any OS benefit for DEB-TACE.<sup>197</sup>

Conversely, Dhanasekaran et al reported a survival advantage for DEB-TACE over conventional TACE in a prospective randomized study of 71 patients with unresectable HCC.<sup>196</sup> However, these results need to be confirmed in large prospective studies.

TACE causes increased hypoxia leading to an up-regulation of vascular endothelial growth factor receptor (VEGFR) and insulin-like growth factor receptor 2 (IGFR-2).<sup>198</sup> Increased plasma levels of VEGFR and IGFR-2 have been associated with the development of metastasis after TACE.<sup>199,200</sup> These findings have led to the evaluation of TACE in combination with sorafenib in patients with residual or recurrent tumor not amenable to additional locoregional therapies. In a phase III randomized trial, sorafenib when given following treatment with TACE did not significantly prolong TTP or OS in patients with unresectable HCC who responded to TACE. This may have been due to delays in starting sorafenib after TACE (median time to receiving sorafenib after TACE was 9 weeks) and/or low daily sorafenib doses.<sup>201</sup> On the other hand, preliminary results from non-randomized phase II studies suggest that concurrent administration of sorafenib with TACE or DEB-TACE may be an effective treatment option for patients with unresectable HCC.<sup>202-205</sup> The results of a phase II randomized trial (SPACE trial) that compared the safety and efficacy of DEB-TACE with sorafenib versus DEB-TACE alone in 307 patients with unresectable intermediate stage HCC also showed that the addition of sorafenib to DEB-TACE improved TTP ( $P = .072$ ) compared to DEB-TACE alone.<sup>206</sup> Ongoing phase III randomized studies are evaluating the combination of sorafenib with TACE or DEB-TACE in patients with unresectable HCC. The findings of

these studies will clarify the optimal scheduling of sorafenib when used in combination with these locoregional approaches.

TARE is a new embolization method that provides for the internal delivery of high-dose radiation to the tumor-associated capillary bed, thereby sparing the normal liver tissue.<sup>180,207</sup> TARE is accomplished through the catheter-based administration of microspheres (glass or resin microspheres) embedded with yttrium-90, an emitter of beta radiation. There is a growing body of literature to suggest that radioembolization might be an effective treatment option for patients with intermediate or advanced HCC.<sup>208-212</sup> Although radioembolization with yttrium-90 microspheres, 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.<sup>208</sup>

Reported complications of TARE include cholecystitis/bilirubin toxicity, gastrointestinal ulceration, radiation-induced liver disease, and abscess formation.<sup>208,210,213</sup> 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 TARE and followed for up to 6 months.<sup>208</sup> 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 TARE showed a significant difference in median survival times based on liver function level (17.2 months for Child-Pugh class A patients and 7.7 months for Child-Pugh class B patients;  $P = .002$ ).<sup>210</sup> Median survival

for Child-Pugh class B patients and those with portal vein thrombosis was 5.6 months.

In comparative effective analyses, patients with HCC treated with TACE or TARE with yttrium-90 microspheres had similar survival times.<sup>214-216</sup> However, TARE resulted in a longer TTP and less toxicity than TACE.<sup>215</sup> These findings need to be confirmed in randomized controlled studies.

### **Combinations of Locoregional Therapies**

Results from retrospective analyses suggest that the combination of TACE with RFA is more effective (both in terms of tumor response and OS) than TACE or RFA alone or surgical resection in patients with single or multiple tumors fulfilling the UNOS or Milan criteria<sup>112,217</sup> or in patients with single tumors up to 7 cm.<sup>218,219</sup> The principle behind the combination of RFA and embolization is that the focused heat delivery of RFA may be enhanced by vessel occlusion through embolization since blood circulation inside the tumor may interfere with the transfer of heat to the tumor.

However, randomized trials that have compared the combination of ablation and embolization with ablation or embolization alone have shown conflicting results. Combination therapy with TACE and PEI resulted in superior survival compared to TACE or PEI alone in the treatment of patients with small HCC tumors, especially for patients with HCC tumors measuring less than 2 cm.<sup>220,221</sup> In a more recent randomized study, Peng et al reported that the combination of TACE and RFA was superior to RFA alone in terms of OS and RFS for patients with tumors less than 7 cm, although this study had several limitations (small sample size and the study did not include TACE alone as one of the treatment arms, thus making it difficult to assess the relative effectiveness of TACE alone compared to the combination of

TACE and RFA).<sup>222</sup> In one prospective randomized study, Shibata et al reported that the combination of RFA and TACE was equally effective as RFA alone for the treatment of patients with small ( $\leq 3$  cm) tumors.<sup>223</sup> Conversely, results from other randomized trials indicate that the survival benefit associated with the combination approach is limited only to patients with tumors that are between 3 cm and 5 cm.<sup>224,225</sup> In the randomized prospective trial that evaluated sequential TACE and RFA versus RFA alone in 139 patients with recurrent HCC  $\leq 5$  cm, the sequential TACE and RFA approach was better than the RFA in terms of OS and RFS only for patients with tumors between 3.1 and 5.0 cm ( $P = .002$  and  $P < .001$ ) but not for those with tumors 3 cm or smaller ( $P = .478$  and  $P = .204$ ).<sup>225</sup>

The results of a recent meta-analysis of 10 randomized clinical trials comparing the outcomes of TACE plus percutaneous ablation with those of TACE or ablation alone suggest that while there is a significant OS benefit for the combination of TACE and PEI compared to TACE alone for patients with large HCC tumors, there was no survival benefit for the combination of TACE and RFA in the treatment of small lesions as compared with that of RFA alone.<sup>226</sup>

Available evidence suggests that the combination of TACE with RFA or PEI may be effective, especially for patients with larger lesions that do not respond to either procedure alone.

### **NCCN Recommendations for Locoregional Therapies**

The relative effectiveness of locoregional therapies compared to surgical resection or liver transplantation in the treatment of patients with HCC has not been established. The consensus of the panel is that liver resection or transplantation, if feasible, is preferred for patients who meet surgical or transplant selection criteria. Locoregional



therapies can be considered if patients are not amenable to surgery or liver transplantation.

All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. Tumors should be in a location accessible for laparoscopic, percutaneous, or open approaches. Lesions in certain portions of the liver may not be accessible for ablation. Similarly, ablative treatment of tumors located on the liver capsule may cause tumor rupture with track seeding. Tumor seeding along the needle track has been reported in less than 1% of patients with HCC treated with RFA.<sup>227-229</sup> Lesions with subcapsular location and poor differentiation seem to be at higher risk for this complication.<sup>227</sup> During an ablation procedure, major vessels in close proximity to the tumor can absorb large amounts of heat (known as the ‘heat sink effect’), which can decrease the effectiveness and significantly increase local recurrence rates. 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 as these organs can be damaged.

The consensus of the panel is that ablation alone may be a curative treatment for tumors 3 cm or smaller, and tumors between 3 and 5 cm may be treated with a combination of ablation and arterially directed therapies to prolong survival, as long as the tumor location is favorable to ablation.<sup>224,225,230</sup> The panel recommends that patients with unresectable or inoperable lesions larger than 5 cm should be considered for treatment using arterially directed therapies or systemic therapy.

All HCC tumors, irrespective of location in the liver, may be amenable to arterially directed therapies, provided that the arterial blood supply to the tumor may be isolated.<sup>183,187,208,218</sup> An evaluation of the arterial

anatomy of the liver, patient’s performance status, and liver function is necessary prior to the initiation of arterially directed therapy. In addition, more individualized patient selection that is specific to the particular arterially directed therapy being considered is necessary to avoid significant treatment-related toxicity. General patient selection criteria for arterially directed therapies include unresectable or inoperable tumors not amenable to ablation therapy only, and the absence of large volume extrahepatic disease. Minimal extrahepatic disease is considered a “relative” contraindication for arterially directed therapies.

All arterially directed therapies are relatively contraindicated in patients with bilirubin greater than 3 mg/dL unless segmental treatment can be performed. Yttrium-90 microsphere therapy has an increased risk of radiation-induced liver disease in patients with bilirubin greater than 2 mg/dL.<sup>210</sup> Arterially directed therapies are relatively contraindicated in cases of main portal vein thrombosis and are contraindicated in Child-Pugh Class C patients. The angiographic endpoint of embolization may be chosen by the treating physician.

Sorafenib following arterially directed therapies may be appropriate in patients with adequate liver function once bilirubin returns to baseline, if there is evidence of residual or recurrent tumor not amenable to additional locoregional therapies.<sup>202-205</sup> The safety and efficacy of the concurrent use of sorafenib with arterially directed therapies is being investigated in ongoing clinical trials.<sup>206</sup>

### External Beam Radiation Therapy

External beam radiation therapy (EBRT) 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.<sup>231,232</sup> SBRT is an advanced technique of EBRT that delivers large ablative doses of

radiation in 1 week or less. There is growing evidence (primarily from non-randomized clinical trials) supporting the usefulness SBRT for patients with unresectable, locally advanced, or recurrent HCC.<sup>233-237</sup>

In a phase II trial of 50 patients with inoperable HCC treated with SBRT after incomplete TACE, SBRT induced complete and partial responses in 38.3% of patients within 6 months of completing SBRT.<sup>236</sup> The 2-year local control rate, OS, and PFS rates were 94.6%, 68.7%, and 33.8%, respectively. In another study that evaluated the long-term efficacy of SBRT for patients with primary small HCC ineligible for local therapy or surgery (42 patients), SBRT induced an overall complete response rate of 33%, with 1- and 3-year OS rates of 92.9% and 58.6%, respectively.<sup>233</sup> In patients with recurrent HCC treated with SBRT, tumor size, recurrent stage, and Child-Pugh were identified as independent prognostic factors for OS in multivariate analysis.<sup>235</sup> In a recent report from Princess Margaret Hospital on 102 patients treated with SBRT for locally advanced HCC in sequential phase I and phase II trials, Bujold et al reported a 1-year local control rate of 87% and a median survival of 17 months. The majority of these patients were at high risk with relatively advanced-stage tumors (55% of patients had tumor vascular thrombosis, and 61% of patients had multiple lesions with a median sum of largest diameter of almost 10 cm and a median diameter of 7.2 cm for the largest lesion).<sup>237</sup> SBRT has also been shown to be an effective bridging therapy for patients with HCC and cirrhosis awaiting liver transplant.<sup>238-240</sup>

All tumors irrespective of their location may be amenable to SBRT or 3D conformal RT. SBRT is often used for patients with 1 to 3 tumors with minimal or no extrahepatic disease. There is no strict size limit, so SBRT may be used for larger lesions if there is sufficient uninvolved liver and liver radiation tolerance can be respected. Patients with Child-Pugh A category are preferred. Those with Child-Pugh B cirrhosis

can safely be treated, but they may require dose modifications and strict dose constraint adherence. Child-Pugh C cirrhosis is a relative contraindication, and these patients should be considered for a clinical trial.

The panel recommends that SBRT can be considered as an alternative to ablation and/or embolization techniques or when these therapies have failed or are contraindicated (in patients with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation and those with local disease but are not considered candidates for surgery due to performance status or comorbidity). It is not included in the guidelines as an option for patients with metastatic disease. The panel encourages prospective clinical trials evaluating the role of SBRT in patients with unresectable, locally advanced, or recurrent HCC.

### 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 locoregional therapies available to treat patients with unresectable HCC confined to the liver, systemic therapy has often been only for 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, and evidence for a favorable impact of chemotherapy on OS in patients with HCC is lacking.<sup>241-243</sup> The panel recommends that systemic cytotoxic chemotherapy (single agent or combination), intra-arterial chemotherapy, and 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 that suppresses tumor cell proliferation and angiogenesis, has been evaluated in one phase II trial and two randomized, placebo-controlled, phase III trials for the treatment of patients with advanced or metastatic HCC.<sup>243-245</sup>

In the phase III trial (SHARP trial), 602 patients with advanced HCC were randomly assigned to sorafenib or best supportive care. In this study, advanced HCC was defined as patients not eligible for or those who had disease progression after surgical or locoregional therapies.<sup>243</sup> 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 ( $\geq 95\%$  of patients classified as Child-Pugh class A) and good performance status ( $>90\%$  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 OS was significantly longer in the sorafenib arm (10.7 months in the sorafenib arm vs. 7.9 months in the placebo group; HR, 0.69; 95% CI, 0.55 to 0.87;  $P < .001$ ). 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.<sup>243</sup>

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).<sup>244</sup> 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, to have symptomatic disease, and to have a higher number of tumor sites than patients in the SHARP study. The hazard ratio for the sorafenib arm compared with the placebo arm (HR, 0.68; CI, 0.50–0.93;  $P = .014$ ) was nearly identical to that reported for the SHARP study, although median OS was lower in both treatment and placebo groups in the Asia-Pacific study (6.5 months vs. 4.2 months).

Results of the subgroup analyses from the Asia-Pacific study and the SHARP study suggest that sorafenib is an effective treatment in patients with advanced HCC irrespective of the baseline ECOG performance status (0 to 2), tumor burden (presence or absence of macroscopic vascular invasion and/or extrahepatic spread), presence or absence of either lung or lymph node metastasis, tumor stage, prior therapy, and disease etiology (alcohol-related or HCV-related HCC).<sup>246,247</sup> Sorafenib is also an effective treatment irrespective of serum concentrations of ALT/AST/AFP, AFP, and total bilirubin levels; the hepatic function is not appreciably affected.<sup>247,248</sup>

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).<sup>249</sup> 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.<sup>245</sup> A subgroup analysis of data from this study showed lower median OS 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).<sup>250</sup> Other investigators have also reported lower median OS for Child-Pugh class B patients.<sup>251-255</sup> In a large retrospective study of 148 patients with advanced HCC treated with sorafenib, the median OS for Child-Pugh class B patients was 5.5 months compared to 11.3 months for Child-Pugh class A patients.<sup>251</sup> Among Child-Pugh class B patients, the baseline AST level was a

significant predictor of OS. The median OS was 6.5 months for patients with ALT levels less than 100 U/L compared to 2.1 months for those with ALT levels 100 U/L or more. In the GIDEON trial, the safety profile of sorafenib was generally similar for Child-Pugh class B and Child-Pugh class A patients. However, the median OS was shorter in the Child-Pugh class B patients, reflecting the poorer prognosis and natural history of liver disease in this patient population.<sup>254,256</sup> In the final analysis of the trial, in the intent-to-treat population (3,213 patients), the median OS was 13.6 months for the Child-Pugh class A patients compared to 5.2 months for the Child-Pugh class B patients.<sup>256</sup> The time-to-progression was, however, similar for the 2 groups (4.7 months and 4.4 months, respectively). The median OS was shorter in patients with a higher Child-Pugh B score.

In a phase II study that evaluated the efficacy and tolerability of sorafenib in the treatment of Asian patients with advanced HBV-related HCC (36 patients with Child-Pugh A cirrhosis, 13 patients with Child-Pugh B cirrhosis, and 2 patients with Child-Pugh C cirrhosis), there were no significant differences in OS (5.5 months vs. 5 months), grade 3 or 4 hematologic toxicities (17% vs. 33%;  $P = .18$ ), and nonhematologic toxicities (47% for Child-Pugh class A and Child-Pugh class B or C;  $P = .97$ ) between Child-Pugh class A and Child-Pugh class B or C patients.<sup>257</sup> However, the grade 3 or 4 liver toxicity, (although not statistically different) was 73% for Child-Pugh class B or C patients compared to 56% for the Child-Pugh class A patients.<sup>257</sup> More recently, Chiu et al also reported similar findings in a retrospective study exploring the tolerability and survival benefits of sorafenib in patients with underlying liver cirrhosis (108 patients with Child-Pugh class A and 64 patients with Child-Pugh class B).<sup>255</sup> However, in this study, although the median OS was similar in patients with Child-Pugh class A and Child-Pugh class B with a score of 7 (6.1 months and 5.4

months, respectively), the median OS was significantly lower for those with Child-Pugh class B with a score of 8 or 9 (2.7 months).

While more mature results from ongoing studies are needed to recommend sorafenib for Child-Pugh B or C patients, available evidence so far suggests that the Child-Pugh status is a strong predictor of OS for patients with unresectable HCC treated with sorafenib and it should be used with caution in Child-Pugh class B patients.

In addition to clinical outcome, liver function impairment may impact the dosing and toxicity of sorafenib. 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.<sup>250</sup> 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.<sup>258</sup> Finally, it is important to mention that validated criteria to evaluate tumor response to sorafenib are needed since true objective volumetric responses are rare.<sup>249</sup>

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. The panel recommends that best supportive care measures be administered to patients with unresectable/inoperable disease who are not candidates for other therapies.

In phase II studies, bevacizumab, a VEGF receptor inhibitor, has shown modest clinical activity (single agent or in combination with erlotinib or chemotherapy) in patients with advanced HCC.<sup>259-263</sup> Randomized trials are required to determine the role of bevacizumab in the management of patients with advanced HCC. At the present time, the consensus of the panel is that there are no mature data to support the use of bevacizumab in the treatment of patients with HCC.

### 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 every 6 to 12 months. AFP levels, if initially elevated, should be measured every 3 months for 2 years, then every 6 to 12 months. Re-evaluation according to the initial workup should be considered in the event of disease recurrence.

## Biliary Tract Cancers

### Gallbladder Cancer

Gallbladder cancer is the most common and aggressive type of all the biliary tract cancers. A vast majority of gallbladder cancers are adenocarcinomas and its incidence steadily increases with age; women are more likely to be diagnosed with gallbladder cancer than men and it is more common in white women.<sup>264,265</sup> Gallbladder cancer is

characterized by local and vascular invasion, extensive regional lymph node metastasis, and distant metastases. Gall bladder cancer is also associated with shorter median survival duration, a much shorter time to recurrence, and shorter survival duration after recurrence than hilar cholangiocarcinoma.<sup>266</sup>

### Risk Factors

Cholelithiasis with the presence of chronic inflammation is the most prevalent risk factor for gallbladder cancer and the risk increases with the stone size.<sup>267,268</sup> Calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been regarded as a risk factor for gallbladder cancer.<sup>267</sup> Recent reports, however, suggest that the risk of developing gallbladder cancer in patients with gallbladder calcification is much lower than anticipated (6% compared to 1% in patients without gallbladder calcifications).<sup>269,270</sup> Other risk factors include anomalous pancreaticobiliary duct junctions, gallbladder polyps (solitary and symptomatic polyps greater than 1 cm), chronic typhoid infection, adenomyomatosis of the gallbladder, and inflammatory bowel disease.<sup>268,271,272</sup> Prophylactic cholecystectomy may be beneficial for patients who are at high risk of developing gallbladder cancer.<sup>267</sup>

### Staging and Prognosis

In the AJCC staging system, gallbladder cancer is classified into 4 stages based on the depth of invasion into the gallbladder wall and the extent of spread to surrounding organs and lymph nodes. In the revised 2010 AJCC staging system, stage groupings have been changed to better correlate with the extent of cystic duct and lymph node involvement, resectability of the tumor, and patient outcome.<sup>76</sup> Lymph node metastasis is now classified as stage IIIB (N1) or stage IVB (N2), and locally unresectable T4 tumors have been reclassified as stage IV. An analysis of 10,705 patients diagnosed with gallbladder cancer

between 1989 and 1996 in the National Cancer Database demonstrated that this revised staging system provided an improved prognostic discrimination of patients with stage III and stage IV disease.<sup>273</sup>

Tumor stage is the strongest prognostic factor for patients with gallbladder cancer.<sup>264,274</sup> In an analysis of about 2500 patients with gallbladder cancer from hospital cancer registries throughout the United States, the 5-year survival rates were 60%, 39%, and 15% for patients with stage 0, stage I, and stage III disease, respectively, whereas the corresponding survival rates were only 5% and 1% for patients with stage III and stage IV disease, respectively.<sup>264</sup> Results from a retrospective analysis of 435 patients treated at a single center showed a median OS of 10.3 months for the entire cohort of patients.<sup>274</sup> The median survival was 12.9 months and 5.8 months for those presenting with stage IA-III and stage IV disease, respectively. In a recent report of 122 patients with gallbladder cancer identified in a prospectively maintained database, liver involvement was associated with decreased RFS and disease-specific survival for patients with T2 tumors (median RFS was 12 months vs. not reached for patients without liver involvement,  $P = .004$ ; median was 25 months vs. not reached for patients without liver involvement,  $P = .003$ ) but not in patients with T1b tumors.<sup>275</sup>

### Diagnosis

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 that mimics that of biliary colic or chronic cholecystitis. Hence, it is not uncommon for a diagnosis of gallbladder cancer to be an incidental finding at cholecystectomy for a benign gallbladder disease or, more frequently, on pathologic review following

cholecystectomy for symptomatic cholelithiasis. In a retrospective review of 435 patients diagnosed and treated with curative resection at a single center during the period of 1995 to 2005, 123 patients (47%) were diagnosed with gallbladder cancer as an incidental finding during laparoscopic cholecystectomy.<sup>274</sup> Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound or biliary tract obstruction with jaundice. The presence of jaundice in patients with gall bladder cancer is usually associated with a poor prognosis; patients with jaundice are more likely to have advanced-stage disease (96% vs. 60%;  $P < .001$ ) and significantly lower disease-specific survival (6 months vs. 16 months;  $P < .0001$ ) than those without jaundice.<sup>276</sup>

### Workup

The initial workup of patients presenting with a gallbladder mass or disease suspicious for gall bladder cancer should include liver function tests and an assessment of hepatic reserve. High-quality cross-sectional imaging (ultrasound, CT, or MRI) of the chest, abdomen, and pelvis is recommended to evaluate tumor penetration within the wall of the gallbladder to determine the presence of nodal and distant metastases and to detect the extent of direct tumor invasion of other organs/biliary system or major vascular invasion.<sup>277</sup> CT is more useful than ultrasound for the detection of lymph node involvement, adjacent organ invasion, and distant metastasis; MRI may be useful for distinguishing benign conditions from gallbladder cancer.<sup>265</sup> Although the role of PET scan has not been established in the evaluation of patients with gallbladder cancer, emerging evidence indicates that it may be useful for the detection of regional lymph node metastases and distant metastatic disease in patients with otherwise potentially resectable disease.<sup>278,279 280</sup>

For patients presenting with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor. Noninvasive magnetic resonance cholangiography (MRCP) is preferred over endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), unless a therapeutic intervention is planned.<sup>277</sup>

Carcinoembryonic antigen (CEA) and CA 19-9 testing could be considered as part of initial workup (in conjunction with imaging studies). Elevated serum CEA levels (higher than 4.0 ng/mL) or CA 19-9 levels (higher than 20.0 units/mL) could be suggestive of gallbladder cancer.<sup>281</sup> While CA 19-9 had higher specificity (92.7% vs. 79.2% for CEA), its sensitivity was lower (50% vs. 79.4% for CEA). However, these markers are not specific for gallbladder cancer and CA 19-9 could also be elevated in patients with jaundice from other benign causes.

### ***Surgical Management***

The surgical approach for the management of all patients with resectable gallbladder cancer is the same, with the exception that in patients with an incidental finding of cancer on pathologic review, the gallbladder has been removed. Complete surgical resection with negative margins remains the only curative treatment for patients with gallbladder cancer.<sup>282</sup> The optimal resection consists of cholecystectomy with a limited hepatic resection (segments IVB and V) and portal lymphadenectomy to encompass the tumor with negative margins.<sup>283</sup> Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct if possible. Extended hepatic resections (beyond segments IV B and V) and resection of the bile duct may be necessary in some patients to obtain negative margins, depending on the stage and location of the tumor, depth of tumor

invasion, proximity to adjacent organs, and the expertise of the surgeon.

A simple cholecystectomy is an adequate treatment for patients with T1a tumors, with the long-term survival rates approaching 100%.<sup>284</sup> While cholecystectomy combined with hepatic resection and lymphadenectomy is associated with an improved survival for patients with T2 or higher tumors, there is no definite evidence regarding the benefit of radical resection over simple cholecystectomy for patients with T1b tumors.<sup>285-290</sup> Some studies have demonstrated a significant improvement in cancer-specific survival for patients with T1b and T2 tumors, with no improvement in survival for patients with T3 tumors.<sup>286-288</sup> Other reports suggest that survival benefit associated with extended surgical resection and lymphadenectomy is seen only in patients with T2 tumors and some T3 tumors with localized hepatic invasion and limited regional node involvement.<sup>289,290</sup> Major hepatic resection and bile duct resection have also been shown to increase morbidity without improvement in survival.<sup>283,291</sup> An analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990 to 2002 showed that in a multivariate analysis, higher T and N stage, poor differentiation, and common bile duct involvement were independent predictors of poor disease-specific survival.<sup>291</sup> Major hepatectomy and common bile duct excision significantly increased overall perioperative morbidity (53%) and were not independently associated with long-term survival.<sup>291</sup> Fuks et al from the AFS-GBC-2009 study group also reported that bile duct resection resulted in a postoperative morbidity rate of 60% in patients with incidental finding of gallbladder cancer.<sup>283</sup> However, for patients with incidental finding of gallbladder cancer, Pawlik et al have reported that common duct resection should be performed at the time of re-resection

for those with positive cystic duct margins due to the presence of residual disease.<sup>292</sup>

With these data in mind, the guidelines recommend that extended hepatic resections (beyond segments IV B and V) and bile duct resections should be performed only when necessary to obtain negative margins (R0 resection) in certain clinical situations as discussed above.<sup>286,288-290</sup>

Among patients with an incidental finding of gallbladder cancer, there is some evidence that a delayed surgical resection due to referral to a tertiary cancer center or a radical resection following an initial noncurative procedure is not associated with a survival deficit compared with immediate resection.<sup>293,294</sup> However, these comparisons are difficult to interpret due to selection bias. Nevertheless, in all patients with a convincing clinical evidence of gallbladder cancer, the guidelines recommend that surgery should be performed by an experienced surgeon who is prepared to do a definitive resection of the tumor. If expertise is unavailable, patients should be referred to a center with available expertise. The panel is also of the opinion that surgery should not be performed in situations where the extent and resectability of the disease has not been established.

### **Management of Resectable Disease**

All patients should undergo cross-sectional imaging (ultrasound, CT, or MRI) of the chest, abdomen, and pelvis prior to surgery to evaluate for the presence of distant metastases. Staging laparoscopy has been shown to identify radiographically occult disseminated disease in patients with primary gallbladder cancer.<sup>295</sup> In a prospective study that evaluated the role of staging laparoscopy in 409 patients diagnosed with primary gallbladder cancer, Agarwal et al reported a significantly higher yield in locally advanced tumors compared with early-stage

tumors (25.2% vs.10.7%;  $P = .02$ ); the accuracy for detecting unresectable disease and a detectable lesion in locally advanced tumors (56.0% and 94.1%, respectively) was similar to that in early-stage tumors (54.6% and 100%, respectively).<sup>295</sup> The use of staging laparoscopy obviated the need for laparotomy in 55.9% of patients with unresectable disease. Staging laparoscopy, however, is of relatively low yield in patients with incidental finding of gallbladder cancer, since disseminated disease is relatively uncommon; higher yields may be obtained in patients who are at higher risk for disseminated metastases (those with poorly differentiated, T3 or higher tumors or margin-positive tumors at cholecystectomy).<sup>296</sup> Since the risk of peritoneal metastases is high for patients with primary gallbladder cancer, staging laparoscopy should be considered for this group of patients if no distant metastases are found on imaging or if there is any suspicion of metastatic disease on imaging that is not amenable to percutaneous biopsy.<sup>295</sup> In patients with incidental finding of gallbladder cancer, staging laparoscopy can be considered for patients who are at high risk for disseminated metastases.<sup>296</sup>

Radical cholecystectomy (cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision) is the preferred primary treatment for patients with incidental finding of gallbladder cancer at surgery. The guidelines also recommend intraoperative staging and procurement of frozen section of gallbladder for biopsy (in selected cases if the diagnosis is not clear) prior to definitive resection.

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.<sup>284</sup> Extended hepatic resection and lymphadenectomy



with or without bile duct excision is recommended for patients with T1b or greater lesions.<sup>286,288,289</sup> Aggressive re-resection to achieve negative margins is often performed for patients with an incidental finding of T1b, T2 or T3 gallbladder cancer since a significant percentage of these patients have been found to harbor residual disease within the liver and common bile duct.<sup>274,292</sup> Port site resection was not associated with improved survival or disease recurrence in patients with incidental findings of gallbladder cancer and should not be considered during definitive resection.<sup>297,298</sup>

For patients with a suspicious mass detected on imaging or in patients presenting with jaundice, the guidelines recommend cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision. A biopsy is not necessary and a diagnostic laparoscopy is recommended prior to definitive resection.<sup>295</sup> In selected cases where the diagnosis is not clear it may be reasonable to perform a cholecystectomy (including intra-operative frozen section) followed by the definitive resection during the same setting if pathology confirms cancer. However, jaundice in patients with gallbladder cancer is considered a relative contraindication to surgery and outcomes are generally poor in these patients; only a portion of those with node-negative disease potentially benefit from complete resection.<sup>276,299</sup> In patients with jaundice, if gallbladder cancer is suspected, surgery should only be performed with a curative intent. These patients should be carefully evaluated prior to surgery and referral to an experienced center should be considered.

The optimal adjuvant treatment strategy for patients with resected gallbladder cancer has not been determined and there are limited clinical trial data to support a standard regimen for adjuvant treatment. 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.<sup>300,301</sup> Results of these studies provide support for omitting adjuvant chemoradiation in the post-surgical treatment of patients with gallbladder cancer characterized as T1b, N0.

The guidelines have included consideration of fluoropyrimidine chemoradiation (except T1a or T1b, N0) and fluoropyrimidine or gemcitabine chemotherapy as options for adjuvant treatment. See the section on “Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers.”

### **Management of Unresectable or Metastatic Disease**

Preoperative evaluation and a biopsy to confirm the diagnosis is recommended for patients with unresectable (includes tumors with distant lymph node metastases in the celiac axis or aorto-caval groove) or metastatic disease (includes distant metastases, nodal metastases beyond the porta hepatis, and extensive involvement of the porta hepatis causing jaundice or vascular encasement). Primary options for these patients include: 1) clinical trial; 2) fluoropyrimidine-based or gemcitabine-based chemotherapy; or 3) best supportive care. In addition, fluoropyrimidine chemoradiation is included as an option for patients with unresectable disease. See section on “Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers.”

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.<sup>299</sup> Biliary drainage followed by chemotherapy can result in improved quality of life. CA 19-9 testing can be considered after biliary decompression.

### 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 workup should be considered in the event of disease relapse or progression.

### Cholangiocarcinomas

Cholangiocarcinomas encompass all tumors originating in the epithelium of the bile duct. More than 90% of cholangiocarcinomas are adenocarcinomas and are broadly divided into 3 histologic types based on their growth patterns: mass-forming; periductal-infiltrating; and intraductal-growing.<sup>302</sup> Cholangiocarcinomas are diagnosed throughout the biliary tree and are typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas.

Intrahepatic cholangiocarcinomas (also known as “peripheral cholangiocarcinomas”) are located within the hepatic parenchyma and have also been called “peripheral cholangiocarcinomas” (Figure 1). Extrahepatic cholangiocarcinomas occur anywhere within the common hepatic duct; at or near the junction of the right and left hepatic ducts or the common bile duct, including the intrapancreatic portion (Figure 1); and are further classified into hilar or distal tumors. Hilar cholangiocarcinomas (also called Klatskin tumors) occur at or near the junction of the right and left hepatic ducts; distal cholangiocarcinomas are extrahepatic lesions arising in the extrahepatic bile ducts above the ampulla of Vater.<sup>303</sup> Hilar cholangiocarcinomas are the most common type of extrahepatic cholangiocarcinomas.

The NCCN Guidelines discuss the clinical management of patients with intrahepatic cholangiocarcinomas and extrahepatic cholangiocarcinomas including the hilar cholangiocarcinomas and the distal bile duct tumors. Tumors of the ampulla of Vater are not included in the NCCN Guidelines.

### Risk Factors

No predisposing factors have been identified in most patients diagnosed with cholangiocarcinoma,<sup>304</sup> 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. Primary sclerosing cholangitis, chronic calculi of the bile duct (hepatolithiasis), choledochal cysts, and liver fluke infections are well-established risk factors for cholangiocarcinoma. Unlike gallbladder cancer, however, cholelithiasis is not thought to be closely linked with cholangiocarcinoma.<sup>305</sup> Other potential but less established risk factors include inflammatory bowel disease, HCV, HBV, cirrhosis, diabetes, obesity, alcohol, and tobacco. Recently, several case-controlled studies from Asian and Western countries have reported hepatitis C viral infection as a significant risk factor for intrahepatic cholangiocarcinoma.<sup>306-309</sup> This may be responsible for the increased incidence of intrahepatic cholangiocarcinoma recently observed at some centers, although future studies are needed to further explore this putative association.<sup>310</sup>

### Staging and Prognosis

#### *Intrahepatic Cholangiocarcinoma*

In the 6th edition of the AJCC staging system, intrahepatic cholangiocarcinoma was staged identically to HCC. However, this staging system did not include predictive clinicopathologic features (multiple hepatic tumors, regional nodal involvement, and large tumor

size) that are specific to intrahepatic cholangiocarcinoma.<sup>311</sup> In more recent reports, tumor size had no effect on survival in patients undergoing surgery.<sup>312,313</sup> In a SEER database analysis of 598 patients with intrahepatic cholangiocarcinoma who had undergone surgery, Nathan et al first reported that multiple lesions and vascular invasion predicted adverse prognosis following resection; lymph node status was of prognostic significance among patients without distant metastases.<sup>312</sup> In this study, tumor size had no independent effect on survival. These findings were confirmed in a subsequent multi-institutional international study of 449 patients undergoing surgery for intrahepatic cholangiocarcinoma.<sup>313</sup> The 5-year survival rate was higher for patients who lacked all three risk factors (multiple tumors, vascular invasion, and N1 disease) than those with one or more risk factors (38.3%, 27.3%, and 18.1%, respectively) and, more importantly, tumor number and vascular invasion were of prognostic significance only in patients with N0 disease. Although tumor size was associated with survival in the univariate analysis, it was not of prognostic significance in the multivariate analysis.

In the revised 7th edition of the AJCC staging system, intrahepatic cholangiocarcinoma has a new staging classification that is independent of the staging classification used for HCC.<sup>76</sup> The new classification 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.<sup>314</sup> The revised classification was useful in predicting survival according to the TNM staging. With a median 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 ( $P = .01$ ) and 16 months for those with stage III disease ( $P < .0001$ ).

### *Extrahepatic Cholangiocarcinoma*

In the previous AJCC classification, extrahepatic cholangiocarcinomas (hilar, middle, and distal tumors) were grouped together as a single entity. The 7<sup>th</sup> Edition of AJCC staging system includes a separate TNM classification for hilar and distal bile duct tumors, based on the extent of liver involvement and distant metastatic disease.<sup>76</sup> Although the depth of tumor invasion is not part of the TNM classification, it has been identified as an independent predictor of outcome in patients with distal as well as hilar cholangiocarcinomas.<sup>315,316</sup>

The modified Bismuth-Corlette staging system<sup>317</sup> and the Blumgart staging system<sup>318</sup> are used for the classification of hilar cholangiocarcinomas. The modified Bismuth-Corlette staging system classifies hilar cholangiocarcinomas into 4 types based on the extent of biliary duct involvement. However, this does not include other clinicopathologic features such as vascular encasement, lymph node involvement, distant metastases, and liver atrophy. In addition, both the AJCC and the Bismuth-Corlette staging systems are not useful for predicting resectability or survival. The Blumgart staging system developed by Jarnagin and colleagues is a useful preoperative staging system that predicts resectability, likelihood of metastatic disease, and survival.<sup>318,319</sup> In this staging system, the hilar cholangiocarcinomas are classified into 3 stages (T1-T3) based on the location and extent of bile duct involvement, the presence or absence of portal venous invasion, and hepatic lobar atrophy.<sup>318</sup> Negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after resection; increasing T-stage significantly correlated with reduced R0 resection rate, distant metastatic disease, and lower median survival.<sup>319</sup>

### Diagnosis

Early-stage cholangiocarcinomas are typically asymptomatic. Patients with intrahepatic cholangiocarcinoma are 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.<sup>43</sup> In contrast, patients with extrahepatic cholangiocarcinoma are likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.

### Workup

The initial workup should include liver function tests. CEA and CA 19-9 testing can be considered, although these markers are not specific for cholangiocarcinoma; they are also associated with other malignancies and benign conditions.<sup>320</sup> Early surgical consultation with a multidisciplinary team is recommended as part of the initial workup for assessment of resectability in intrahepatic and extrahepatic cholangiocarcinomas.

Direct visualization of the bile duct with directed biopsies is the ideal technique for the workup of cholangiocarcinoma. Delayed contrast CT/MRI to assess the involvement of the liver, major vessels, nearby lymph nodes, and distant sites is also recommended when extrahepatic cholangiocarcinoma is suspected.<sup>321</sup> 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, and lymph node involvement, if present.<sup>321</sup> In addition, chest imaging should be performed, and laparoscopy may be done in conjunction with surgery if

no distant metastasis is found. Endoscopic ultrasound may be useful for distal common bile duct cancers for defining a mass or abnormal thickening, which can direct biopsies. Upper and lower endoscopy should be considered to exclude extrahepatic primary gastrointestinal tumors. However, this may not be necessary if immunohistochemistry is conclusive of intrahepatic cholangiocarcinoma. Immunostaining with cytokeratins (CK) 7 and 20 have been found to be helpful in distinguishing intrahepatic cholangiocarcinoma (CK7+, CK20-, and CDX2-) from metastasis from colon cancer (CDX2+, CK20+).<sup>322</sup> 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).

Since many of the patients with extrahepatic cholangiocarcinoma present with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of the tumor.<sup>321</sup> MRCP is noninvasive and is considered to be a safer alternative to direct cholangiography; hence, it is preferred over ERCP PTC, unless a therapeutic intervention is planned. For distal bile duct tumors in which a diagnosis is needed or where palliation is indicated, an ERCP allows for complete imaging of the bile duct and stenting of the obstruction. In addition, brushes of the bile duct can be obtained for pathologic evaluation. PTC approach can be used for hilar tumors.

Although the role of PET scanning has not been established in the evaluation of patients with cholangiocarcinoma, emerging evidence indicates that it may be useful for the detection of regional lymph node metastases and distant metastatic disease in patients with otherwise potentially resectable disease.<sup>278-280,323,324</sup>

### **Management of Intrahepatic Cholangiocarcinoma**

Complete surgical resection is the only potentially curative treatment for patients with resectable disease, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis. The optimal surgical margin associated with improved survival and reduced risk of recurrence in patients undergoing surgery remains uncertain, with some reports documenting R0 resection as a significant predictor of survival and recurrence,<sup>325-330</sup> while others suggest that margin status is not a significant predictor of outcome.<sup>331,332</sup> Ribero et al from the Italian Intrahepatic Cholangiocarcinoma Study Group reported that margin-negative resection was associated with significantly higher survival rates (the estimated 5-year survival rates were 39.8% vs. 4.7% for patients with a positive margin) and significantly lower recurrence rates (53.9% vs. 73.6% for those with a positive margin); however, in patients resected with negative margins, the margin width had no long-term impact on survival ( $P = .61$ ) or recurrence ( $P > .05$ ) following resection.<sup>330</sup> Farges et al from the AFC-IHCC-2009 study group reported that although R1 resection was the strongest independent predictor of poor outcome in pN0 patients undergoing surgery, its survival benefit was very low in pN+ patients (median survival was 18 months and 13 months, respectively, after R0 and R1 resections;  $P = .1$ ).<sup>332</sup> In this study, a margin width  $>5$  mm was an independent predictor of survival among pN0 patients with R0 resections, which is in contrast to the findings reported by Ribero et al.<sup>330</sup>

Available evidence (although not conclusive) supports the recommendation that hepatic resection with negative margins (wedge resections and segmental resections) should be the goal of surgical therapy for patients with potentially resectable disease.<sup>333</sup> More extensive hepatic resections are often necessary to achieve clear

margins.<sup>330</sup> Initial surgical exploration should include assessment of multi-focal liver disease, lymph node metastases, and distant metastases. A preoperative biopsy is not always necessary prior to definitive and potentially curative resection. Although multifocal liver tumors, lymph node metastases to the porta hepatis, and distant metastases are considered contraindications to surgery, surgical approaches can be considered in highly selected patients. Patient selection for surgery is facilitated by careful preoperative staging, which may include laparoscopy to identify patients with unresectable or disseminated metastatic disease.<sup>334,335</sup> Staging laparoscopy has been shown to identify peritoneal metastases and liver metastases with a yield of 36% and 67% accuracy in patients with potentially resectable intrahepatic cholangiocarcinoma.<sup>334</sup> A portal lymphadenectomy is reasonable as this provides accurate staging information. However, there are very little data to support the therapeutic benefit of routine lymph node dissection in patients undergoing surgery, particularly in those with no lymph node involvement.<sup>336-339</sup> However, since lymph node metastasis is an important prognostic indicator of survival, lymphadenectomy could be considered for patients with lymph node metastases.<sup>313,330</sup>

The optimal adjuvant treatment strategy for patients with resected intrahepatic cholangiocarcinoma has not been determined and there are limited clinical trial data to support a standard regimen for adjuvant treatment. Lymphovascular and perineural invasion, lymph node metastasis, and tumor size  $\geq 5$  cm have been reported as independent predictors of recurrence and reduced OS following resection.<sup>340-342</sup> Since recurrence following resection is common, these tumor-specific risk factors could be considered as criteria for selection of patients for adjuvant treatment in clinical trials. Patients who have undergone an R0 resection may be followed with observation alone. For patients found to

have microscopic positive tumor margins (R1) or residual local disease (R2) after resection, it is essential for a multidisciplinary team to review the available options on a case-by-case basis. Although the optimal treatment strategy has not been determined, adjuvant treatment options include fluoropyrimidine chemoradiation or fluoropyrimidine-based or gemcitabine-based chemotherapy. See the section on “Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers.”

For patients with unresectable or metastatic disease, the primary treatment options include: 1) clinical trial; 2) fluoropyrimidine-based or gemcitabine-based chemotherapy; or 3) best supportive care. In addition, fluoropyrimidine chemoradiation is included as an option for patients with unresectable disease. See section on “Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers.”

Locoregional therapies such as RFA,<sup>343,344</sup> TACE,<sup>345-350</sup> DEB-TACE, or TACE drug-eluting microspheres<sup>350-352</sup> and TARE with yttrium microspheres<sup>353-356</sup> have been shown to be safe and effective in a small series of patients with unresectable intrahepatic cholangiocarcinomas. In a series of 17 patients with primary unresectable intrahepatic cholangiocarcinoma, RFA resulted in a median PFS of 32 months and OS of 38.5 months.<sup>344</sup> The results of two independent prospective studies showed that the efficacy of TACE with irinotecan DEBs was similar to that of gemcitabine and oxaliplatin but was superior to that of TACE with mitomycin in terms of PFS and OS for patients with unresectable intrahepatic cholangiocarcinoma.<sup>350</sup> In another series of 24 patients with unresectable intrahepatic cholangiocarcinoma, TARE with yttrium-90 microspheres induced >50% tumor necrosis and 100% tumor necrosis in 77% and 9% of patients, respectively, with a median OS of 14.9 months.<sup>353</sup> However, none of these approaches has been evaluated in randomized clinical trials. Ablation might be considered in

patients with intrahepatic cholangiocarcinoma following R1 or R2 resection.

Photodynamic therapy (PDT) is a relatively new ablative therapy that involves 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. The combination of PDT with biliary stenting was reported to improve the OS of patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.<sup>357,358</sup>

### **Management of Extrahepatic Cholangiocarcinoma**

Complete resection with negative margins is the only potentially curative treatment for patients with resectable disease. The reported 5-year survival rates following radical surgery are in the range of 20% to 42% and 16% to 52%, respectively, for patients with hilar and distal cholangiocarcinomas.<sup>359</sup>

Surgical margin status and lymph node metastases are independent predictors of survival following resection.<sup>329,360</sup> Regional lymphadenectomy of the porta hepatis should be considered along with curative resections.<sup>361,362</sup> Since these surgical procedures are associated with morbidity and postoperative complications, they should be carried out in patients without comorbidities and should be considered in the proper clinical setting. Surgery is contraindicated in patients with distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis.

The type of surgical procedure for a resectable tumor is based on its anatomic location on the biliary tract. Hilar resection of the involved biliary tract and en bloc liver resection is recommended for hilar tumors. Major bile duct excision with frozen section assessment of proximal and

distal bile duct margins and pancreaticoduodenectomy are recommended for mid and distal tumors, respectively. Very rare cases of small mid bile duct tumors can be resected with an isolated bile duct resection. A pancreaticoduodenectomy and a hepatic resection would be required, in rare instances, for a bile duct tumor with an extensive biliary tract involvement. Combined hepatic and pancreatic resections to clear distant nodal disease are not recommended.

In patients with hilar cholangiocarcinoma, extended hepatic resection (to encompass the biliary confluence) with caudate lobectomy is strongly encouraged, since hilar tumors, by definition, abut or invade the central portion of the liver. The recommendation for extended liver resection is supported by retrospective analyses showing a survival benefit and decreased hepatic recurrence associated with extended hepatic resections.<sup>363-367</sup> 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 extended liver resection was performed, although some reports suggest that extended hepatic resections result in higher probability of R0 resection.<sup>365,368</sup> Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection, especially in patients with more advanced disease.<sup>369,370</sup>

Patient selection for surgery is facilitated by careful preoperative staging, surgical exploration, biopsy, and laparoscopy to identify patients with unresectable or distant metastatic disease. However, surgery may be performed without a biopsy if the index of suspicion is high. Laparoscopy can identify the majority of patients with unresectable hilar cholangiocarcinoma, albeit with a lower yield.<sup>371,372</sup> Connor et al reported that the yield of laparoscopy alone was 24% in identifying patients with unresectable hilar tumors, which increased to 42% with an overall accuracy of 53%, with the addition of intraoperative

ultrasound.<sup>371</sup> In another report, Weber et al reported a higher yield for T2/T3 tumors (36%) than T1 tumors (9%), suggesting that staging laparoscopy may be more useful for patients who are at higher risk for occult unresectable disease.<sup>372</sup>

While not routinely used in all patients undergoing resection, the consensus of the panel is that in patients with hilar cholangiocarcinoma, preoperative treatments including biliary drainage (using an endoscopic [ERCP] or percutaneous approach [PTC])<sup>373-376</sup> and contralateral PVE<sup>377,378</sup> should be considered for patients with very low FLR volumes.

Among patients with resectable disease, those who have undergone an R0 resection and who have negative regional nodes or those with carcinoma in situ at margin may be followed with observation alone, receive fluoropyrimidine chemoradiation, or receive fluoropyrimidine or gemcitabine chemotherapy. However, there are limited clinical trial data to define a standard regimen, and enrollment in a clinical trial is encouraged. Patients with microscopic positive tumor margins (R1), gross residual local disease (R2), or positive regional lymph nodes after resection should be evaluated by a multidisciplinary team to review the available treatment options on a case-by-case basis. Although the optimal treatment strategy has not been established, treatment options include: fluoropyrimidine chemoradiation 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 “Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers”).

Patients with unresectable or metastatic 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.<sup>379-382</sup> Biopsy is recommended to confirm the diagnosis prior to the initiation of further treatment. Primary treatment options include: 1) clinical trial; 2) fluoropyrimidine-based or gemcitabine-based chemotherapy; or 3) best supportive care. In addition, fluoropyrimidine chemoradiation is included as an option for patients with unresectable disease. Data to support particular chemoradiation and chemotherapy regimens are limited. See section on “Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers.”

Liver transplantation is the only other potentially curative option for selected patients with non-disseminated cholangiocarcinomas, with the 5-year survival rates ranging from 25% to 42%.<sup>383-386</sup> There is retrospective evidence suggesting that neoadjuvant chemoradiation followed by liver transplantation is highly effective for selected patients with hilar cholangiocarcinoma.<sup>387-389</sup> Results from two studies suggest that the combination of liver transplantation and neoadjuvant and/or adjuvant chemoradiation is associated with higher RFS than a potentially curative resection.<sup>390,391</sup> However, in one of these studies there were substantial differences in the characteristics of patients in the two treatment groups.<sup>390</sup> The panel encourages continuation of clinical research in this area. Liver transplantation should be considered only for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. 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 workup should be considered in the event of disease progression.

### Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers

Local recurrence following surgery is a primary limitation for cure in patients with biliary tract cancers, which provides an important justification for the use of adjuvant therapy. Nevertheless, the role of adjuvant chemotherapy or chemoradiation therapy in patients with resected biliary tract cancers is poorly defined.<sup>392</sup>

Due to the low incidence of biliary tract cancers, the efficacy and safety of adjuvant chemotherapy or chemoradiation therapy in these patients has been evaluated mostly in retrospective studies that have included only a small number of patients; these studies often combined patients with gallbladder and bile duct cancers, with a few exceptions. Despite the challenges associated with the accrual of large numbers of patients with biliary tract cancer for randomized phase III trials, it is widely recognized that efforts should be made to conduct such studies in which the individual disease entities are evaluated separately. Retrospective studies that have combined patients with gallbladder cancer and cholangiocarcinomas provide conflicting evidence regarding the role of adjuvant therapy.<sup>266,393</sup> A retrospective analysis of 177 patients with resected gallbladder cancer and hilar cholangiocarcinoma concluded that based on the pattern of initial recurrence, adjuvant treatment may not have a significant impact in the management of patients with gallbladder cancer, whereas it could be a reasonable approach for patients with hilar cholangiocarcinoma. The initial recurrence rate involving a distant site was significantly higher for



patients with gallbladder cancer than for those with hilar cholangiocarcinoma (85% and 41%, respectively;  $P < .001$ ).<sup>266</sup> In a more recent retrospective review of a prospective database of 157 patients with resected gallbladder cancer ( $n = 63$ ) and cholangiocarcinoma ( $n = 94$ ), the authors reported that adjuvant therapy did not significantly prolong survival for this group of patients but identified an early surgical resection with 1 cm tumor-free margins as the best predictor of long-term survival.<sup>393</sup> Conversely, in a recent systematic review and meta-analysis of 6,712 patients with biliary tract cancers, Horgan et al reported an improvement in OS (although nonsignificant) with adjuvant therapy compared with surgery alone, with no difference between patients with gallbladder cancer and bile duct cancers.<sup>394</sup> Chemotherapy or chemoradiation therapy was associated with statistically greater benefit than radiation therapy alone, with the greatest benefit observed in patients with lymph node-positive disease and macroscopic residual disease (R1 resection).

In the only phase III randomized trial that evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer, 508 patients (139 patients had cholangiocarcinoma and 140 patients had gallbladder cancer) were randomly assigned to adjuvant chemotherapy with fluorouracil and mitomycin C or to a control arm.<sup>395</sup> Results from the subgroup analyses showed a significantly better 5-year DFS for patients with gallbladder cancer treated with chemotherapy (20.3% compared to 11.6% in the control group;  $P = .021$ ), although no significant differences between the two treatment arms were observed for patients with biliary duct cancers, suggesting that patients with gallbladder cancer undergoing noncurative resection may derive survival benefit with adjuvant chemotherapy.

Among the retrospective studies that included only the patients with gallbladder cancer, two large retrospective analyses did not show a

clear benefit for adjuvant chemotherapy alone,<sup>274,396</sup> although in one study the number of patients who received adjuvant chemotherapy was very limited (only 24 of 123 patients who underwent curative resection received adjuvant chemotherapy or chemoradiation or both),<sup>274</sup> and the other study, which included patients treated during 1988 to 1997, did not include chemotherapy with newer agents.<sup>396</sup> In contrast, more recent retrospective studies have concluded that adjuvant chemoradiation following R0 resection might improve OS in selected patients with T2 or T3 tumors and lymph node-positive gallbladder cancer.<sup>397-399</sup> In a series of 47 patients with gallbladder cancer who underwent surgical resection followed by adjuvant chemoradiation, the 5-year OS rate was significantly higher following R0 resection (52.8% vs. 20.0%, and 0% for those with R1 and R2 resections, respectively;  $P = .0038$ ).<sup>399</sup> Adjuvant chemoradiation after R0 resection was associated with good long-term survival rate even in patients with lymph node metastases.

Retrospective studies that included only patients with resected extrahepatic cholangiocarcinoma suggest that adjuvant chemoradiation may improve local control and survival, although distant metastases was the most common pattern of failure.<sup>400-403</sup> In one retrospective study of 168 patients with extrahepatic cholangiocarcinoma treated with curative resection followed by adjuvant chemoradiation, the 5-year local control (58.5% vs. 44.4%;  $P = .007$ ), DFS (32.1% vs. 26.1%,  $P = .041$ ), and OS rates (36.5% vs. 28.2%,  $P = .049$ ) were significantly better for patients who received chemoradiation than for those who were treated with surgery alone.<sup>403</sup> Other studies have suggested that adjuvant chemoradiation may have a significant survival benefit only in a subgroup of patients with T3 or T4 tumors or those with a high risk of locoregional recurrence (R1 resection or positive lymph nodes).<sup>402,404,405</sup> A non-randomized, single-center study of 120 patients with curatively

resected extrahepatic cholangiocarcinoma also showed that 5-FU–based adjuvant concurrent chemoradiation followed by 5-FU–based adjuvant chemotherapy resulted in a significant survival benefit, especially in patients with R1 resection or negative lymph nodes compared to 5-FU–based adjuvant concurrent chemoradiation alone.<sup>402</sup> The 3-year DFS rates for concurrent chemoradiation therapy alone and concurrent chemoradiation therapy followed by adjuvant chemotherapy were 27% and 45.2% ( $P = .04$ ), respectively. The corresponding OS rates were 31% and 63% ( $P < .01$ ), respectively. However, this was not observed for patients with R0 resection or positive lymph nodes as well as those with T1 or T2 tumors.

Most of the collective experience of chemoradiation in biliary tract cancers involves concurrent chemoradiation and fluorouracil. More recently, concurrent chemoradiation with capecitabine has also been used.<sup>402,406</sup> Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.<sup>407</sup> Due to the limited data and the heterogeneity of patient populations included in many of the published studies, in most cases the recommendations in the NCCN Guidelines on the use of adjuvant chemotherapy or chemoradiation therapy are not specific to the particular type of biliary tract cancer. Specific recommendations for fluoropyrimidine-based or gemcitabine-based chemotherapy listed in the NCCN Guidelines are based on the extrapolation of data from studies of patients with advanced disease. Additionally, some of the recommendations are primarily based on practice patterns at NCCN Member Institutions and retrospective studies from single center experiences.

### Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers

The prognosis of patients with advanced biliary tract cancers is poor and the median survival for those undergoing supportive care alone is short.<sup>408</sup> The survival benefit of chemotherapy (fluorouracil, leucovorin, and etoposide) over best supportive care for patients with advanced biliary tract cancers was initially suggested in a phase III trial of 90 patients with advanced pancreatic and biliary tract cancers, 37 of whom had advanced biliary tract cancers.<sup>409</sup> In a recent single-center randomized study of 81 patients with unresectable gallbladder cancer, Sharma et al reported that modified gemcitabine and oxaliplatin (GEMOX) improved PFS and OS compared to best supportive care or fluorouracil.<sup>410</sup> Median OS was 4.5, 4.6, and 9.5 months, respectively, for the best supportive care, fluorouracil and modified GEMOX arms ( $P = .039$ ). The corresponding PFS was 2.8, 3.5, and 8.5 months ( $P < .001$ ).

Several phase II studies have also demonstrated the efficacy of chemotherapy for the treatment of patients with advanced biliary tract cancers.<sup>411,412</sup> The results of a pooled analysis of 104 trials that have included 2810 patients with advanced biliary tract cancers showed that response rates and tumor control were higher for the subgroup of patients receiving a combination of gemcitabine and platinum-based agents.<sup>413</sup> In a retrospective study of 304 patients with unresectable biliary tract cancers who were treated with gemcitabine alone, a cisplatin-based regimen, or a fluoropyrimidine-based regimen, patients receiving gemcitabine were shown to have a lower risk of death.<sup>414</sup> Most importantly, the support for the use of gemcitabine-based or fluoropyrimidine-based chemotherapy for patients with advanced biliary tract cancers comes from 4 randomized studies.<sup>415-418</sup>

In a randomized phase II study of 51 patients, Kornek et al established the efficacy and tolerance of mitomycin in combination with gemcitabine or capecitabine in previously untreated patients with advanced biliary tract cancers.<sup>415</sup> Mitomycin and capecitabine was associated with superior complete response rate (31% vs. 20%), median PFS (5.3 months vs. 4.2 months) and OS (9.25 months vs. 6.7 months). The results of the 40955 EORTC trial showed that cisplatin and fluorouracil was more active than high-dose fluorouracil in terms of overall response rates (19% and 7.1%, respectively) and OS (8 months and 5 months, respectively), but the PFS was similar in both treatment arms (3.3 months).<sup>416</sup> The 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 OS and PFS by 30% over gemcitabine alone.<sup>417</sup> Median OS was 11.7 months and 8.1 months (HR, 0.64; 95% CI, 0.52–0.80;  $P < .001$ ), and median PFS was 8.0 months vs. 5.0 months (HR, 0.63; 95% CI, 0.51–0.77;  $P < .001$ ), 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. Okusaka et al also reported similar findings in a phase II randomized study of 84 patients with advanced biliary tract cancers.<sup>418</sup> Based on these results, 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. Examples of other gemcitabine-based or fluoropyrimidine (fluorouracil or capecitabine)-based regimens with demonstrated activity in phase II trials include: gemcitabine and cisplatin or oxaliplatin;<sup>419-427</sup> gemcitabine and fluoropyrimidine;<sup>428-433</sup> and fluoropyrimidine and oxaliplatin or cisplatin.<sup>434-437</sup> Triple-drug chemotherapy regimens also have been

shown to be effective in patients with advanced biliary tract cancers, albeit in a very small number of patients.<sup>438-440</sup> The phase III trial that evaluated fluorouracil, leucovorin, and etoposide versus fluorouracil, cisplatin, and epirubicin did not show one regimen to be significantly superior with respect to OS (12 months vs. 9 months, respectively) in patients with advanced biliary tract cancers, although the trial was underpowered to detect such a difference.<sup>438</sup>

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; fluorouracil with cisplatin or oxaliplatin; and single-agent fluorouracil, capecitabine, and gemcitabine. The combination of gemcitabine and fluorouracil is not included due to the increased toxicity and decreased efficacy observed with this regimen<sup>428</sup> when compared with results of studies of the gemcitabine and capecitabine regimen in the setting of advanced biliary tract cancer.

Chemoradiation in the setting of advanced biliary tract cancer can provide control of symptoms due to local tumor effects, and may prolong OS, although there are limited clinical trial data to define a standard regimen or definitive benefit. In a retrospective analysis of 37 patients treated with chemoradiation for unresectable extrahepatic cholangiocarcinoma, the actuarial OS rates at 1 and 2 years were 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).<sup>441</sup> The most



extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers has been fluorouracil,<sup>442,443</sup> although capecitabine has been substituted for fluorouracil in some studies.<sup>406</sup> The panel recommends that concurrent chemoradiation should be limited to either fluorouracil 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 the 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 class 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. The combination of gemcitabine and cisplatin is included as a category 1 recommendation for this group of patients.

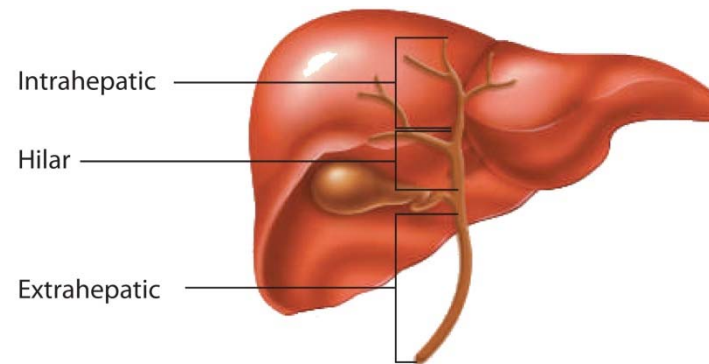
Liver transplantation is the best available curative option for patients with early-stage HCC who meet the Milan criteria and for patients with cholangiocarcinoma. Bridge therapy can be considered for patients with

HCC to decrease tumor progression and the dropout rate from the liver transplantation waiting list.

Locoregional therapies (ablation and arterially directed therapies) can be considered for patients who are not candidates for surgery or liver transplantation. Ablation alone may be a curative treatment for tumors  $\leq 3$  cm, and tumors between 3 and 5 cm may be treated with a combination of ablation and arterially directed therapies. Arterially directed therapies (TACE, DEB-TACE, or TARE with yttrium microspheres) may be appropriate for patients with unresectable or inoperable tumors that are not amenable to ablation therapy. SBRT can be considered as an alternative to ablation and/or embolization techniques (especially for patients with 1–3 tumors and minimal or no extrahepatic disease) or when these therapies have failed or are contraindicated.

It is essential that all patients should be evaluated prior to initiation of 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. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63:11-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23335087>.
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. 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>.
14. 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>.
15. 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>.
16. 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>.

17. 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>.
18. 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>.
19. 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>.
20. 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>.
21. 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>.
22. 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>.
23. 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>.
24. 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>.
25. 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>.
26. National Health and Nutrition Examination Survey - Viral hepatitis: Department of Health and Human Services. Centers for Disease Control and Prevention. National center for health statistics. Available at: <http://www.cdc.gov/nchs/data/nhanes/databriefs/viralhep.pdf>.
27. 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>.
28. 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>.
29. 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>.
30. 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>.
31. 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>.
32. 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>.

33. 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>.

34. 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>.

35. Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasound 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>.

36. 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>.

37. 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>.

38. 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>.

39. Schiff ER, Sorrell MF, Maddrey WC. *Schiff's Diseases of the Liver*. Philadelphia: Lippincott Williams & Wilkins (LWW); 2007.

40. Luo JC, Hwang SJ, Wu JC, et al. Clinical characteristics and prognosis of hepatocellular carcinoma patients with paraneoplastic syndromes. *Hepatogastroenterology* 2002;49:1315-1319. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12239934>.

41. 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>.

42. 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>.

43. 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>.

44. 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>.

45. 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>.

46. 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>.

47. 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>.

48. 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>.

49. 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>.

50. 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>.

51. 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>.

52. 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>.

53. 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>.

54. 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>.

55. 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>.

56. 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>.

57. 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>.

58. 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>.

59. 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>.

60. 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>.

61. Katyal 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>.

62. 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>.
63. 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>.
64. 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>.
65. 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>.
66. 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>.
67. 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>.
68. 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>.
69. 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>.
70. 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>.
71. 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>.
72. 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>.
73. 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>.
74. 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>.
75. 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>.
76. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual* (ed 7). New York, NY: Springer; 2010.

77. 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>.
78. 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>.
79. 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>.
80. 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>.
81. 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>.
82. 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>.
83. 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>.
84. 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>.
85. 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>.
86. 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>.
87. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-1236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16250051>.
88. 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>.
89. 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>.
90. 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>.

91. 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>.
92. 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>.
93. 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>.
94. 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>.
95. Vitale A, Morales RR, Zanusi G, et al. Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. *The Lancet Oncology* 2011;12:654-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21684210>.
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. 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>.
100. 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>.
101. 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>.
102. 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>.
103. 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>.
104. 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>.

105. 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>.

106. 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>.

107. 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>.

108. 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>.

109. 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>.

110. 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>.

111. 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>.

112. 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>.

113. 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>.

114. 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>.

115. 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>.

116. 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>.

117. 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>.

118. 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>.

119. 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>.

120. 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>.

121. 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>.

122. 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>.

123. 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>.

124. 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>.

125. 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>.

126. 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>.

127. 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>.

128. Fujiki M, Aucejo F, Kim R. General overview of neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: necessity or option? *Liver Int* 2011;31:1081-1089. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22008644>.

129. 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>.

130. 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>.

131. 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>.

132. 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>.

133. 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>.

134. 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>.

135. 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>.

136. 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>.

137. 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>.

138. Kulik LM, Atassi B, van Holsbeeck L, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006;94:572-586. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17048240>.

139. 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>.

140. 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>.

141. 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>.

142. 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>.

143. 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>.

144. 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>.

145. 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>.

146. 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>.

147. 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>.

148. 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>.

149. 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>.

150. 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>.

151. 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>.

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. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003;228:235-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12759473>.

158. 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>.

159. 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>.

160. 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>.

161. 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>.



162. Giorgio A, Di Sarno A, De Stefano G, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma compared to percutaneous ethanol injection in treatment of cirrhotic patients: an Italian randomized controlled trial. *Anticancer Res* 2011;31:2291-2295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21737654>.

163. Cho YK, Kim JK, Kim MY, et al. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology* 2009;49:453-459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19065676>.

164. Orlando A, Leandro G, Olivo M, et al. Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. *Am J Gastroenterol* 2009;104:514-524. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19174803>.

165. Germani G, Pleguezuelo M, Gurusamy K, et al. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta-analysis. *J Hepatol* 2010;52:380-388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20149473>.

166. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation as first-line treatment for small solitary hepatocellular carcinoma: long-term results. *Eur J Surg Oncol* 2010;36:1054-1060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20846819>.

167. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol* 2012;107:569-577. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22158026>.

168. Brunello F, Cantamessa A, Gaia S, et al. Radiofrequency ablation: technical and clinical long-term outcomes for single hepatocellular carcinoma up to 30 mm. *Eur J Gastroenterol Hepatol* 2013;25:842-849. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23442417>.

169. Francica G, Saviano A, De Sio I, et al. Long-term effectiveness of radiofrequency ablation for solitary small hepatocellular carcinoma: a retrospective analysis of 363 patients. *Dig Liver Dis* 2013;45:336-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23245589>.

170. Huang G-T, Lee P-H, Tsang Y-M, et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. *Ann Surg* 2005;242:36-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15973099>.

171. 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>.

172. 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>.

173. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012;57:794-802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22634125>.

174. Xu G, Qi F-Z, Zhang J-H, et al. Meta-analysis of surgical resection and radiofrequency ablation for early hepatocellular carcinoma. *World J Surg Oncol* 2012;10:163-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22897815>.

175. 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>.

176. Peng ZW, Lin XJ, Zhang YJ, et al. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. *Radiology* 2012;262:1022-1033. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22357902>.
177. 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>.
178. 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>.
179. Ruzzenente A, Guglielmi A, Sandri M, et al. Surgical resection versus local ablation for HCC on cirrhosis: results from a propensity case-matched study. *J Gastrointest Surg* 2012;16:301-311; discussion 311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22095524>.
180. 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>.
181. Rand T, Loewe C, Schoder M, et al. Arterial embolization of unresectable hepatocellular carcinoma with use of microspheres, lipiodol, and cyanoacrylate. *Cardiovasc Intervent Radiol* 2005;28:313-318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15886943>.
182. Huang YH, Chen CH, Chang TT, et al. The role of transcatheter arterial embolization for patients with unresectable hepatocellular carcinoma: a nationwide, multicentre study evaluated by cancer stage. *Aliment Pharmacol Ther* 2005;21:687-694. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15771754>.
183. 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>.
184. Bonomo G, Pedicini V, Monfardini L, et al. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. *Cardiovasc Intervent Radiol* 2010;33:552-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19957182>.
185. 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>.
186. 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>.
187. 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>.
188. Morse MA, Hanks BA, Suhocki P, et al. Improved time to progression for transarterial chemoembolization compared with transarterial embolization for patients with unresectable hepatocellular carcinoma. *Clin Colorectal Cancer* 2012;11:185-190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22280845>.
189. 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>.

190. 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>.

191. Kim W, Clark TW, Baum RA, Soulen MC. Risk factors for liver abscess formation after hepatic chemoembolization. *J Vasc Interv Radiol* 2001;12:965-968. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11487677>.

192. Mezhir JJ, Fong Y, Fleischer D, et al. Pyogenic abscess after hepatic artery embolization: a rare but potentially lethal complication. *J Vasc Interv Radiol* 2011;22:177-182. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21195630>.

193. 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>.

194. 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>.

195. 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>.

196. 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>.

197. 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>.

198. Sergio A, Cristofori C, Cardin R, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. *Am J Gastroenterol* 2008;103:914-921. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18177453>.

199. Xiong ZP, Yang SR, Liang ZY, et al. Association between vascular endothelial growth factor and metastasis after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2004;3:386-390. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15313674>.

200. Song BC, Chung YH, Kim JA, et al. Association between insulin-like growth factor-2 and metastases after transcatheter arterial chemoembolization in patients with hepatocellular carcinoma: a prospective study. *Cancer* 2001;91:2386-2393. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11413529>.

201. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011;47:2117-2127. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21664811>.

202. Erhardt A, Kolligs FT, Dollinger MM, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: Final results of the multicenter SOCRATES trial [abstract]. *J Clin Oncol*

2011;29(15\_suppl):Abstract 4107. Available at:  
[http://meeting.ascopubs.org/cgi/content/abstract/29/15\\_suppl/4107](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/4107).

203. Pawlik TM, Reyes DK, Cosgrove D, et al. Phase II Trial of Sorafenib Combined With Concurrent Transarterial Chemoembolization With Drug-Eluting Beads for Hepatocellular Carcinoma. *J Clin Oncol* 2011;29:3960-3967. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21911714>.

204. Park JW, Koh YH, Kim HB, et al. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. *J Hepatol* 2012;56:1336-1342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22314421>.

205. Chung Y-H, Han G, Yoon J-H, et al. Interim analysis of START: study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma trial. *Int J Cancer* 2013;132:2448-2458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23129123>.

206. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial. *ASCO Meeting Abstracts* 2012;30:LBA154. Available at: [http://meeting.ascopubs.org/cgi/content/abstract/30/4\\_suppl/LBA154](http://meeting.ascopubs.org/cgi/content/abstract/30/4_suppl/LBA154).

207. 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>.

208. 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>.

209. Woodall CE, Scoggins CR, Ellis SF, et al. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? *J Am Coll Surg* 2009;208:375-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19317999>.

210. 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>.

211. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011;54:868-878. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21618574>.

212. Mazzaferro V, Spósito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013;57:1826-1837. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22911442>.

213. 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>.

214. Lance C, McLennan G, Obuchowski N, et al. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2011;22:1697-1705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21983055>.

215. 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>.

216. Moreno-Luna LE, Yang JD, Sanchez W, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013;36:714-723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23093355>.

217. Kirikoshi H, Saito S, Yoneda M, et al. Outcome of transarterial chemoembolization monotherapy, and in combination with percutaneous ethanol injection, or radiofrequency ablation therapy for hepatocellular carcinoma. *Hepatol Res* 2009;39:553-562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19527484>.

218. 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>.

219. Elnekave E, Erinjeri JP, Brown KT, et al. Long-Term Outcomes Comparing Surgery to Embolization-Ablation for Treatment of Solitary HCC <7 cm. *Ann Surg Oncol* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23563960>.

220. Koda M, Murawaki Y, Mitsuda A, et al. Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma: a randomized control study. *Cancer* 2001;92:1516-1524. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11745230>.

221. Becker G, Soezgen T, Olschewski M, et al. Combined TACE and PEI for palliative treatment of unresectable hepatocellular carcinoma. *World J Gastroenterol* 2005;11:6104-6109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16273634>.

222. Peng Z-W, Zhang Y-J, Chen M-S, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. *J Clin Oncol* 2013;31:426-432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23269991>.

223. Shibata T, Isoda H, Hirokawa Y, et al. Small hepatocellular carcinoma: is radiofrequency ablation combined with transcatheter arterial chemoembolization more effective than radiofrequency ablation alone for treatment? *Radiology* 2009;252:905-913. Available at: <http://radiology.rsna.org/content/252/3/905.full.pdf>.

224. Kim JH, Won HJ, Shin YM, et al. Medium-sized (3.1-5.0 cm) hepatocellular carcinoma: transarterial chemoembolization plus radiofrequency ablation versus radiofrequency ablation alone. *Ann Surg Oncol* 2011;18:1624-1629. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21445671>.

225. Peng ZW, Zhang YJ, Liang HH, et al. Recurrent hepatocellular carcinoma treated with sequential transcatheter arterial chemoembolization and RF ablation versus RF ablation alone: a prospective randomized trial. *Radiology* 2012;262:689-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22157201>.

226. Wang W, Shi J, Xie WF. Transarterial chemoembolization in combination with percutaneous ablation therapy in unresectable hepatocellular carcinoma: a meta-analysis. *Liver Int* 2010;30:741-749. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20331507>.

227. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology* 2001;33:1124-1129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11343240>.

228. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology* 2003;226:441-451. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12563138>.

229. Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005;234:961-967. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15665226>.

230. Zhang Y-J, Liang H-H, Chen M-S, et al. Hepatocellular carcinoma treated with radiofrequency ablation with or without ethanol injection: a prospective randomized trial. *Radiology* 2007;244:599-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17641378>.

231. 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>.

232. 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>.

233. Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. *Stereotactic radiotherapy for liver cancer*. *BMC Cancer* 2010;10:475-475. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20813065>.

234. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2011;81:e447-453. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21645977>.

235. Huang W-Y, Jen Y-M, Lee M-S, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2012;84:355-361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22342300>.

236. Kang J-K, Kim M-S, Cho CK, et al. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. *Cancer*

2012;118:5424-5431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22570179>.

237. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 2013;31:1631-1639. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23547075>.

238. Facciuto ME, Singh MK, Rochon C, et al. Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: evaluation of radiological and pathological response. *J Surg Oncol* 2012;105:692-698. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21960321>.

239. Katz AW, Chawla S, Qu Z, et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. *Int J Radiat Oncol Biol Phys* 2012;83:895-900. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22172906>.

240. O'Connor JK, Trotter J, Davis GL, et al. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 2012;18:949-954. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22467602>.

241. 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>.

242. 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>.

243. 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>.

244. 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>.

245. 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>.

246. Bruix J, Raoul J-L, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012;57:821-829. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22727733>.

247. Cheng A-L, Guan Z, Chen Z, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer* 2012;48:1452-1465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22240282>.

248. Raoul J-L, Bruix J, Greten TF, et al. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. *J Hepatol* 2012;56:1080-1088. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22245896>.

249. 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>.

250. 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>.

251. Pinter M, Sieghart W, Hucke F, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. *Aliment Pharmacol Ther* 2011;34:949-959. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21883324>.

252. Hollebecque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. *Aliment Pharmacol Ther* 2011;34:1193-1201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21958438>.

253. Kim JE, Ryoo BY, Ryu MH, et al. Sorafenib for hepatocellular carcinoma according to Child-Pugh class of liver function. *Cancer Chemother Pharmacol* 2011;68:1285-1290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21445543>.

254. Lencioni R, Kudo M, Ye SL, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib) non-interventional study. *Int J Clin Pract* 2012;66:675-683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22698419>.

255. Chiu J, Tang YF, Yao T-J, et al. The use of single-agent sorafenib in the treatment of advanced hepatocellular carcinoma patients with underlying Child-Pugh B liver cirrhosis: a retrospective analysis of efficacy, safety, and survival benefits. *Cancer* 2012;118:5293-5301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22517493>.

256. Marrero JA, Lencioni R, Ye S-L, et al. Final analysis of GIDEON (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma [HCC] and of its treatment with sorafenib [sor]) in >3000 sor-treated patients (pts): Clinical findings in pts with liver dysfunction [abstract]. *J Clin Oncol* 2013;31:Abstract 4126. Available at: [http://meeting.ascopubs.org/cgi/content/abstract/31/15\\_suppl/4126](http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/4126).

257. 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>.

258. 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>.

259. Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:1898-1903. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16622265>.

260. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008;26:2992-2998. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18565886>.

261. Thomas MB, Morris JS, Chadha R, et al. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. *J Clin Oncol* 2009;27:843-850. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19139433>.

262. Hsu CH, Yang TS, Hsu C, et al. Efficacy and tolerability of bevacizumab plus capecitabine as first-line therapy in patients with advanced hepatocellular carcinoma. *Br J Cancer* 2010;102:981-986. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20160718>.

263. Sun W, Sohal D, Haller DG, et al. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. *Cancer* 2011;117:3187-3192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21264839>.

264. 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>.

265. Levy AD, Murakata LA, Rohrmann CA, Jr. Gallbladder carcinoma: radiologic-pathologic correlation. *Radiographics* 2001;21:295-314; questionnaire, 549-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11259693>.

266. 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>.

267. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. *Am J Gastroenterol* 2000;95:1402-1410. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10894571>.

268. Tazuma S, Kajiyama G. Carcinogenesis of malignant lesions of the gall bladder. The impact of chronic inflammation and gallstones. *Langenbecks Arch Surg* 2001;386:224-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11382326>.

269. Khan ZS, Livingston EH, Huerta S. Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: case series and systematic review of the literature. *Arch Surg* 2011;146:1143-1147. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22006872>.

270. Schnelldorfer T. Porcelain Gallbladder: A Benign Process or Concern for Malignancy? *J Gastrointest Surg* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23423431>.

271. Elnemr A, Ohta T, Kayahara M, et al. Anomalous pancreaticobiliary ductal junction without bile duct dilatation in



gallbladder cancer. *Hepatogastroenterology* 2001;48:382-386.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11379314>.

272. 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>.

273. Fong Y, Wagman L, Gonen M, et al. Evidence-based gallbladder cancer staging: changing cancer staging by analysis of data from the National Cancer Database. *Ann Surg* 2006;243:767-771; discussion 771-764. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16772780>.

274. 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>.

275. Ito H, Ito K, D'Angelica M, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. *Ann Surg* 2011;254:320-325. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21617582>.

276. Hawkins WG, DeMatteo RP, Jarnagin WR, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. *Ann Surg Oncol* 2004;11:310-315. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14993027>.

277. Furlan A, Ferris JV, Hosseinzadeh K, Borhani AA. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. *AJR Am J Roentgenol* 2008;191:1440-1447. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18941083>.

278. 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>.

279. 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>.

280. Lee SW, Kim HJ, Park JH, et al. Clinical usefulness of 18F-FDG PET-CT for patients with gallbladder cancer and cholangiocarcinoma. *J Gastroenterol* 2010;45:560-566. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20035356>.

281. Strom BL, Maislin G, West SL, et al. Serum CEA and CA 19-9: potential future diagnostic or screening tests for gallbladder cancer? *Int J Cancer* 1990;45:821-824. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/2335386>.

282. Dixon E, Vollmer CM, Jr., Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. *Ann Surg* 2005;241:385-394. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15729060>.

283. Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. *World J Surg* 2011;35:1887-1897. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21547420>.

284. Lee SE, Jang JY, Lim CS, et al. Systematic review on the surgical treatment for T1 gallbladder cancer. *World J Gastroenterol* 2011;17:174-180. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21245989>.

285. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. *Ann Surg Oncol* 2007;14:833-840. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17103074>.

286. Coburn NG, Cleary SP, Tan JC, Law CH. Surgery for gallbladder cancer: a population-based analysis. *J Am Coll Surg* 2008;207:371-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18722943>.

287. You DD, Lee HG, Paik KY, et al. What is an adequate extent of resection for T1 gallbladder cancers? *Ann Surg* 2008;247:835-838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18438121>.

288. 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>.

289. Downing Sr CKOG, et al. Early-stage gallbladder cancer in the surveillance, epidemiology, and end results database: Effect of extended surgical resection. *Archives of Surgery* 2011;146:734-738. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21690451>.

290. Shirai Y, Sakata J, Wakai T, et al. "Extended" radical cholecystectomy for gallbladder cancer: long-term outcomes, indications and limitations. *World J Gastroenterol* 2012;18:4736-4743. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23002343>.

291. 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>.

292. 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; discussion 1486-1477. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17846848>.

293. 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>.

294. 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>.

295. Agarwal AK, Kalayarsan R, Javed A, et al. Role of Staging Laparoscopy in Primary Gall Bladder Cancer-An Analysis of 409 Patients: A Prospective Study to Evaluate the Role of Staging Laparoscopy in the Management of Gallbladder Cancer. *Ann Surg* 2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23059504>.

296. Butte JM, Gonen M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. *HPB (Oxford)* 2011;13:463-472. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21689230>.

297. Maker AV, Butte JM, Oxenberg J, et al. Is port site resection necessary in the surgical management of gallbladder cancer? *Ann Surg Oncol* 2012;19:409-417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21698501>.

298. Fuks D, Regimbeau JM, Pessaux P, et al. Is port-site resection necessary in the surgical management of gallbladder cancer? *J Visc Surg* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23665059>.

299. Regimbeau JM, Fuks D, Bachellier P, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC-GBC-2009 study group. *Eur J Surg Oncol* 2011;37:505-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21514090>.

300. 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>.

301. Wang SJ, Lemieux A, Kalpathy-Cramer J, et al. Nomogram for Predicting the Benefit of Adjuvant Chemoradiotherapy for Resected Gallbladder Cancer. *Journal of Clinical Oncology* 2011;29:4627-4632. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22067404>.

302. 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>.

303. 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>.

304. 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>.

305. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011;54:173-184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21488076>.

306. Donato F, Gelatti U, Tagger A, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. *Cancer Causes Control* 2001;12:959-964. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11808716>.

307. 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>.

308. Shaib YH, El-Serag HB, Davila JA, et al. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. *Gastroenterology* 2005;128:620-626. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15765398>.

309. Welzel TM, Mellekjaer L, Gloria G, et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. *Int J Cancer* 2007;120:638-641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17109384>.

310. 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>.

311. 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>.

312. 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>.

313. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol* 2011;29:3140-3145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21730269>.

314. 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>.

315. de Jong MC, Hong S-M, Augustine MM, et al. Hilar cholangiocarcinoma: tumor depth as a predictor of outcome. *Arch Surg* 2011;146:697-703. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21690446>.

316. Hong S-M, Pawlik TM, Cho H, et al. Depth of tumor invasion better predicts prognosis than the current American Joint Committee on

Cancer T classification for distal bile duct carcinoma. Surgery 2009;146:250-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19628081>.

317. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1309988>.

318. 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>.

319. Matsuo K, Rocha FG, Ito K, et al. The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. J Am Coll Surg 2012;215:343-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22749003>.

320. 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>.

321. Sainani NI, Catalano OA, Holalkere NS, et al. Cholangiocarcinoma: current and novel imaging techniques. Radiographics 2008;28:1263-1287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18794305>.

322. 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>.

323. Kim JY, Kim M-H, Lee TY, et al. Clinical role of 18F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging. Am J

Gastroenterol 2008;103:1145-1151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18177454>.

324. Ruys AT, Bennink RJ, van Westreenen HL, et al. FDG-positron emission tomography/computed tomography and standardized uptake value in the primary diagnosis and staging of hilar cholangiocarcinoma. HPB (Oxford) 2011;13:256-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21418131>.

325. 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>.

326. Konstadoulakis MM, Roayaie S, Gomatos IP, et al. Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome. Surgery 2008;143:366-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18291258>.

327. Paik KY, Jung JC, Heo JS, et al. What prognostic factors are important for resected intrahepatic cholangiocarcinoma? J Gastroenterol Hepatol 2008;23:766-770. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17868336>.

328. 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>.

329. Murakami Y, Uemura K, Sudo T, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. Ann Surg Oncol 2011;18:651-658. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20945107>.

330. Ribero D, Pinna AD, Guglielmi A, et al. Surgical Approach for Long-term Survival of Patients With Intrahepatic Cholangiocarcinoma: A Multi-institutional Analysis of 434 Patients. Arch Surg

2012;147:1107-1113. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22910846>.

331. Tamandl D, Herberger B, Gruenberger B, et al. Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2008;15:2787-2794. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18685896>.

332. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. *Ann Surg* 2011;254:824-829; discussion 830. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22042474>.

333. Carpizo DR, D'Angelica M. Management and extent of resection for intrahepatic cholangiocarcinoma. *Surg Oncol Clin N Am* 2009;18:289-305, viii-ix. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19306813>.

334. Goere D, Wagholikar GD, Pessaux P, et al. Utility of staging laparoscopy in subsets of biliary cancers : laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. *Surg Endosc* 2006;20:721-725. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16508808>.

335. Joseph S, Connor S, Garden OJ. Staging laparoscopy for cholangiocarcinoma. *HPB (Oxford)* 2008;10:116-119. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18773068>.

336. Shimada M, Yamashita Y, Aishima S, et al. Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma. *Br J Surg* 2001;88:1463-1466. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11683741>.

337. Choi S-B, Kim K-S, Choi J-Y, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node

dissection with survival. *Ann Surg Oncol* 2009;16:3048-3056. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19626372>.

338. Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, et al. Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. *HPB (Oxford)* 2011;13:612-620. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21843261>.

339. Morine Y, Shimada M, Utsunomiya T, et al. Clinical impact of lymph node dissection in surgery for peripheral-type intrahepatic cholangiocarcinoma. *Surg Today* 2012;42:147-151. Available at:

340. Fisher SB, Patel SH, Kooby DA, et al. Lymphovascular and perineural invasion as selection criteria for adjuvant therapy in intrahepatic cholangiocarcinoma: a multi-institution analysis. *HPB (Oxford)* 2012;14:514-522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22762399>.

341. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. *Surgery* 2013;153:811-818. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23499016>.

342. Ribero D, Rosso S, Pinna AD, et al. Postoperative nomogram for predicting survival after resection for intrahepatic cholangiocarcinoma [abstract]. *J Clin Oncol* 2013;31:Abstract 4129. Available at: [http://meeting.ascopubs.org/cgi/content/abstract/31/15\\_suppl/4129](http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/4129).

343. Carrafiello G, Lagana D, Cotta E, et al. Radiofrequency ablation of intrahepatic cholangiocarcinoma: preliminary experience. *Cardiovasc Intervent Radiol* 2010;33:835-839. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20411389>.

344. Kim JH, Won HJ, Shin YM, et al. Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. *AJR Am J Roentgenol* 2011;196:W205-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21257864>.

345. Mambrini A, Guglielmi A, Pacetti P, et al. Capecitabine plus hepatic intra-arterial epirubicin and cisplatin in unresectable biliary cancer: a phase II study. *Anticancer Res* 2007;27:3009-3013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17695488>.

346. Shitara K, Ikami I, Munakata M, et al. Hepatic arterial infusion of mitomycin C with degradable starch microspheres for unresectable intrahepatic cholangiocarcinoma. *Clin Oncol (R Coll Radiol)* 2008;20:241-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18222071>.

347. Inaba Y, Arai Y, Yamaura H, et al. Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301). *Am J Clin Oncol* 2011;34:58-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20177362>.

348. Kemeny NE, Schwartz L, Gonen M, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: does the addition of systemic bevacizumab improve results? *Oncology* 2011;80:153-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21677464>.

349. Kiefer MV, Albert M, McNally M, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol: a 2-center study. *Cancer* 2011;117:1498-1505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21425151>.

350. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol* 2012;24:437-443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22261548>.

351. Poggi G, Quaretti P, Minoia C, et al. Transhepatic arterial chemoembolization with oxaliplatin-eluting microspheres (OEM-TACE)

for unresectable hepatic tumors. *Anticancer Res* 2008;28:3835-3842. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19192637>.

352. Schiffman SC, Metzger T, Dubel G, et al. Precision hepatic arterial irinotecan therapy in the treatment of unresectable intrahepatic cholangiocellular carcinoma: optimal tolerance and prolonged overall survival. *Ann Surg Oncol* 2011;18:431-438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20862554>.

353. 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>.

354. 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>.

355. Hoffmann R-T, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovasc Intervent Radiol* 2012;35:105-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21431970>.

356. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc Intervent Radiol* 2013;36:440-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22956045>.

357. 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>.

358. 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>.

359. Akamatsu N, Sugawara Y, Hashimoto D. Surgical strategy for bile duct cancer: Advances and current limitations. *World J Clin Oncol* 2011;2:94-107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21603318>.

360. Qiao Q-L, Zhang T-P, Guo J-C, et al. Prognostic factors after pancreatoduodenectomy for distal bile duct cancer. *Am Surg* 2011;77:1445-1448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22196654>.

361. Schwarz RE, Smith DD. Lymph node dissection impact on staging and survival of extrahepatic cholangiocarcinomas, based on U.S. population data. *J Gastrointest Surg* 2007;11:158-165. Available at:

362. Ito K, Ito H, Allen PJ, et al. Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma. *Ann Surg* 2010;251:675-681. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20224368>.

363. Nishio H, Nagino M, Nimura Y. Surgical management of hilar cholangiocarcinoma: the Nagoya experience. *HPB (Oxford)* 2005;7:259-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18333203>.

364. 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>.

365. van Gulik TM, Kloek JJ, Ruys AT, et al. Multidisciplinary management of hilar cholangiocarcinoma (Klatskin tumor): extended resection is associated with improved survival. *Eur J Surg Oncol* 2011;37:65-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21115233>.

366. Cheng QB, Yi B, Wang JH, et al. Resection with total caudate lobectomy confers survival benefit in hilar cholangiocarcinoma of Bismuth type III and IV. *Eur J Surg Oncol* 2012;38:1197-1203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22992326>.

367. Cho MS, Kim SH, Park SW, et al. Surgical outcomes and predicting factors of curative resection in patients with hilar cholangiocarcinoma: 10-year single-institution experience. *J Gastrointest Surg* 2012;16:1672-1679. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22798185>.

368. Lee SG, Song GW, Hwang S, et al. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. *J Hepatobiliary Pancreat Sci* 2010;17:476-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19851704>.

369. de Jong MC, Marques H, Clary BM, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. *Cancer* 2012;118:4737-4747. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22415526>.

370. Wu XS, Dong P, Gu J, et al. Combined Portal Vein Resection for Hilar Cholangiocarcinoma: A Meta-analysis of Comparative Studies. *J Gastrointest Surg* 2013;17:1107-1115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23592188>.

371. Connor S, Barron E, Wigmore SJ, et al. The utility of laparoscopic assessment in the preoperative staging of suspected hilar cholangiocarcinoma. *J Gastrointest Surg* 2005;9:476-480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15797226>.

372. Weber SM, DeMatteo RP, Fong Y, et al. Staging laparoscopy in patients with extrahepatic biliary carcinoma. Analysis of 100 patients. *Ann Surg* 2002;235:392-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11882761>.

373. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). *HPB (Oxford)* 2008;10:130-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18773090>.

374. Kennedy TJ, Yopp A, Qin Y, et al. Role of preoperative biliary drainage of liver remnant prior to extended liver resection for hilar cholangiocarcinoma. *HPB (Oxford)* 2009;11:445-451. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768150>.

375. Liu F, Li Y, Wei Y, Li B. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: whether or not? A systematic review. *Dig Dis Sci* 2011;56:663-672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20635143>.

376. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. *Br J Surg* 2013;100:274-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23124720>.

377. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg* 2008;247:49-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18156923>.

378. Shindoh J, Vauthey J-N, Zimmitti G, et al. Analysis of the Efficacy of Portal Vein Embolization for Patients with Extensive Liver Malignancy and Very Low Future Liver Remnant Volume, Including a Comparison with the Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy Approach. *J Am Coll Surg* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23632095>.

379. 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>.

380. 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>.

381. 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>.

382. Paik WH, Park YS, Hwang JH, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. *Gastrointest Endosc* 2009;69:55-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18657806>.

383. Robles R, Figueras J, Turrion VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004;239:265-271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14745336>.

384. Becker NS, Rodriguez JA, Barshes NR, et al. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. *J Gastrointest Surg* 2008;12:117-122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17963015>.

385. Kaiser GM, Sotiropoulos GC, Jauch KW, et al. Liver transplantation for hilar cholangiocarcinoma: a German survey. *Transplant Proc* 2008;40:3191-3193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19010230>.

386. Friman S, Foss A, Isoniemi H, et al. Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results. *Scand J Gastroenterol* 2011;46:370-375. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21073376>.

387. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology*



- 2012;143:88-98. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22504095>.
388. Panjala C, Nguyen JH, Al-Hajjaj AN, et al. Impact of neoadjuvant chemoradiation on the tumor burden before liver transplantation for unresectable cholangiocarcinoma. *Liver Transpl* 2012;18:594-601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22140024>.
389. Duignan S, Maguire D, Ravichand CS, et al. Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience. *HPB (Oxford)* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23600750>.
390. 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>.
391. Hong JC, Jones CM, Duffy JP, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. *Arch Surg* 2011;146:683-689. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21690444>.
392. Cereda S, Belli C, Reni M. Adjuvant treatment in biliary tract cancer: to treat or not to treat? *World J Gastroenterol* 2012;18:2591-2596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22690066>.
393. Glazer ES, Liu P, Abdalla EK, et al. Neither neoadjuvant nor adjuvant therapy increases survival after biliary tract cancer resection with wide negative margins. *J Gastrointest Surg* 2012;16:1666-1671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22777053>.
394. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis. *Journal of Clinical Oncology* 2012;30:1934-1940. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22529261>.
395. 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>.
396. 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>.
397. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. *Int J Radiat Oncol Biol Phys* 2009;75:150-155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19297105>.
398. Cho SY, Kim SH, Park S-J, et al. Adjuvant chemoradiation therapy in gallbladder cancer. *J Surg Oncol* 2010;102:87-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20578085>.
399. Kim K, Chie EK, Jang JY, et al. Postoperative chemoradiotherapy for gallbladder cancer. *Strahlenther Onkol* 2012;188:388-392. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22402869>.
400. 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>.
401. 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>.
402. 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>.

403. Kim TH, Han SS, Park SJ, et al. Role of adjuvant chemoradiotherapy for resected extrahepatic biliary tract cancer. *Int J Radiat Oncol Biol Phys* 2011;81:e853-859. Available at:

404. 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>.

405. Park J-h, Choi EK, Ahn SD, et al. Postoperative chemoradiotherapy for extrahepatic bile duct cancer. *Int J Radiat Oncol Biol Phys* 2011;79:696-704. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20510541>.

406. 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>.

407. 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>.

408. 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>.

409. 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>.

410. Sharma A, Dwary AD, Mohanti BK, et al. Best Supportive Care Compared With Chemotherapy for Unresectable Gall Bladder Cancer: A Randomized Controlled Study. *Journal of Clinical Oncology* 2010;28:4581-4586. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20855823>.

411. 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>.

412. Geynisman DM, Catenacci DV. Toward personalized treatment of advanced biliary tract cancers. *Discov Med* 2012;14:41-57. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22846202>.

413. 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>.

414. 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>.

415. Kornek GV, Schuell B, Laengle F, et al. Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. *Ann Oncol* 2004;15:478-483. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/14998852>.

416. Ducreux M, Van Cutsem E, Van Laethem JL, et al. A randomised phase II trial of weekly high-dose 5-fluorouracil with and without folinic acid and cisplatin in patients with advanced biliary tract carcinoma: results of the 40955 EORTC trial. *Eur J Cancer* 2005;41:398-403. Available at:

417. 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>.

418. Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. *Br J Cancer* 2010;103:469-474. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20628385>.

419. Doval DC, Sekhon JS, Gupta SK, et al. A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. *Br J Cancer* 2004;90:1516-1520. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15083178>.

420. 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>.

421. Giuliani F, Gebbia V, Maiello E, et al. Gemcitabine and cisplatin for inoperable and/or metastatic biliary tree carcinomas: a multicenter phase II study of the Gruppo Oncologico dell'Italia Meridionale (GOIM). *Ann Oncol* 2006;17 Suppl 7:73-77. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16760299>.

422. Lee J, Kim T-Y, Lee MA, et al. Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. *Cancer Chemother Pharmacol* 2008;61:47-52. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17364190>.

423. Meyerhardt JA, Zhu AX, Stuart K, et al. Phase-II study of gemcitabine and cisplatin in patients with metastatic biliary and gallbladder cancer. *Dig Dis Sci* 2008;53:564-570. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17597402>.

424. Andre T, Reyes-Vidal JM, Fartoux L, et al. Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. *Br J Cancer* 2008;99:862-867. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19238628>.

425. Harder J, Riecken B, Kummer O, et al. Outpatient chemotherapy with gemcitabine and oxaliplatin in patients with biliary tract cancer. *Br J Cancer* 2006;95:848-852. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16969352>.

426. Kim HJ, Lee NS, Lee S-C, et al. A phase II study of gemcitabine in combination with oxaliplatin as first-line chemotherapy in patients with inoperable biliary tract cancer. *Cancer Chemother Pharmacol* 2009;64:371-377. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19142638>.

427. Jang J-S, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. *Cancer Chemother Pharmacol* 2010;65:641-647. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19652971>.

428. 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>.

429. Cho JY, Paik YH, Chang YS, et al. Capecitabine combined with gemcitabine (CapGem) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. *Cancer* 2005;104:2753-2758. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16294346>.

430. 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>.

431. Riechelmann RP, Townsley CA, Chin SN, et al. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. *Cancer* 2007;110:1307-1312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17628484>.

432. 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>.

433. Iqbal S, Rankin C, Lenz H-J, et al. A phase II trial of gemcitabine and capecitabine in patients with unresectable or metastatic gallbladder cancer or cholangiocarcinoma: Southwest Oncology Group study S0202. *Cancer Chemother Pharmacol* 2011;68:1595-1602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21556747>.

434. Nehls O, Klump B, Arkenau HT, et al. Oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas: a prospective phase II trial. *Br J Cancer* 2002;87:702-704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12232749>.

435. 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>.

436. 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>.

437. 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>.

438. 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>.

439. Yamashita Y-i, Taketomi A, Fukuzawa K, et al. Gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients with advanced biliary tree cancers: a pilot study. *Anticancer Res* 2006;26:771-775. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16739352>.

440. Wagner AD, Buechner-Steudel P, Moehler M, et al. Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials. *Br J Cancer* 2009;101:1846-1852. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19904267>.

441. 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>.

442. 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>.

443. 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>.