Hepatobiliary Cancers
Version 1.2013
NCCN.org
Principles of Surgery: (Gallbladder Cancer, Intrahepatic and Extrahepatic Cholangiocarcinoma)

Michael I. D’Angelica, MD ¶/Lead
Memorial Sloan-Kettering Cancer Center

Chandrakanth Are, MD ¶
UNMC Eppley Cancer Center at The Nebraska Medical Center

Principles of Locoregional Therapy

Anne M. Covey, MD §
Memorial Sloan-Kettering Cancer Center

Daniel T. Chang, MD §
Stanford Cancer Institute
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.
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”.

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”.

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).
Gallbladder Cancer---continued

**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”.
- 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:\(^a\)
- Cirrhosis
  - Hepatitis B, C\(^b\)
  - Alcohol
  - Genetic hemochromatosis
  - Non-alcoholic steatohepatitis
  - Stage 4 primary biliary cirrhosis
  - Alpha1-antitrypsin deficiency
  - Other causes of cirrhosis\(^c\)
- Without cirrhosis
  - Hepatitis B carriers\(^d\)

Liver mass or nodule
(See HCC-2)

Mass confirmed
(See HCC-4)

Follow every 3 mo with AFP, liver imaging

Alfa-fetoprotein (AFP)/Ultrasound (US) every 6-12 mo

Rising AFP
Liver imaging studies\(^e,f\)

No mass\(^g\)


\(^b\)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.

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

\(^d\)Additional risk factors include patients with, family history of HCC, Asian males \(\geq 40\) y, Asian females \(\geq 50\) y, African/North American Blacks with hepatitis B.

\(^e\)If ultrasound is negative, CT/MRI should be performed.


\(^g\)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

#### CLINICAL PRESENTATION

- **Incidental liver mass or nodule found during screening**
- **Histologically confirmed HCC**

#### LIVER NODULE SIZE

<table>
<thead>
<tr>
<th>Size</th>
<th>Imaging: At least a 3-phase CT or MRI or CEUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>At least a 3-phase CT or MRI or CEUS every 3-6 mo</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>At least a 3-phase CT or MRI</td>
</tr>
</tbody>
</table>

#### ADDITIONAL IMAGING

- CEUS

#### FINDINGS

- **Stable**
  - Continue imaging every 3-6 mo using technique that first identified nodule(s)
- **Enlarging**
  - Proceed according to nodule size

#### HCC confirmed

- (See HCC-3)

---


**a** 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)

**f** Histologically confirmed HCC

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

**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.
**Hepatocellular Carcinoma (HCC)**

**DIAGNOSIS OF HCC**

**LIVER NODULE SIZE**

- **> 1 cm**
  - 0 or 1 classic enhancement
  - Perform 2nd type of contrast-enhanced (at least 3-phase) scan (CT or MRI)
  - 2 classic enhancements
  - Core biopsy (preferred) or FNA or Repeat imaging (at least 3-phase) in 3 mo and follow algorithm according to size and image findings
  - Positive for HCC

- **0 or 1 classic enhancement**
  - 1-2 cm
  - Core biopsy (preferred) or FNA
  - Non-diagnostic
  - Repeat imaging or Followup

- **> 2 cm**
  - Core biopsy (preferred) or FNA
  - Change in nodule size
  - Repeat imaging and/or biopsy

**ADDITIONAL IMAGING FINDINGS**

- **2 classic enhancements**
  - Positive

- **0 or 1 classic enhancement**
  - Negative

- **Perform 2nd type of contrast-enhanced (at least 3-phase) scan (CT or MRI)**

- **2 classic enhancements**

**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.

---


**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.**

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

**Classic imaging: Lesion shows arterial hyperenhancement and washes out in the venous phase.**

**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.**
**CLINICAL PRESENTATION**

Multidisciplinary evaluation (assess liver reserve\textsuperscript{1} and comorbidity):
- H&P
- Hepatitis panel\textsuperscript{m}
- Bilirubin, transaminases, alkaline phosphatase
- PT or INR, albumin, BUN, creatinine
- CBC, platelets
- AFP
- Chest CT
- Bone scan if clinically indicated

**WORKUP**

- HCC confirmed
  - Potentially resectable or transplantable, operable by performance status or comorbidity (See HCC-5)
  - Unresectable (See HCC-6)
  - Inoperable by performance status or comorbidity, local disease only (See HCC-7)
  - Metastatic disease (See HCC-7)

\textsuperscript{1}See Child-Pugh Score (HCC-A) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

\textsuperscript{m}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.

**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>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>SURGICAL ASSESSMENT\textsuperscript{n,o}</th>
<th>TREATMENT</th>
<th>SURVEILLANCE</th>
</tr>
</thead>
</table>
| Potentially resectable or transplantable, operable by performance status or comorbidity | • Child-Pugh Class A, B\textsuperscript{p}  
• No portal hypertension  
• Suitable tumor location  
• Adequate liver reserve  
• Suitable liver remnant | Resection, if feasible (preferred)\textsuperscript{s}  
or Locoregional therapy\textsuperscript{t} | • Imaging\textsuperscript{u} 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 |
| | • UNOS criteria\textsuperscript{q}  
  ➢ Patient has a tumor ≤ 5 cm in diameter or 2-3 tumors  
  ≤ 3 cm each  
  ➢ No macrovascular involvement  
  ➢ No extrahepatic disease | If ineligible for transplant |  |
| | If eligible for transplant,  
• Refer to liver transplant center\textsuperscript{q,r}  
• Consider bridge therapy as indicated\textsuperscript{r} |  |  |

\textsuperscript{n}Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.  
\textsuperscript{o}Patients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.  
\textsuperscript{p}In highly selected Child-Pugh Class B patients with limited resection.  
\textsuperscript{r}Many transplant centers consider bridge therapy for transplant candidates. (See Discussion)  
\textsuperscript{s}See Principles of Surgery (HCC-B).  
\textsuperscript{t}See Principles of Locoregional Therapy (HCC-C).  
\textsuperscript{u}MRI or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as 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.

For relapse, see initial Workup (HCC-4)
**Hepatocellular Carcinoma**

**Unresectable**

- Inadequate hepatic reserve[^u]
- Tumor location

**Evaluate whether patient a candidate for transplant** (See UNOS criteria under Surgical Assessment[^HCC-5])

**Transplant candidate**

- Refer to liver transplant center
- Consider bridge therapy as indicated[^r]

**Not a transplant candidate**

**Options:**[^w]
- Sorafenib (Child-Pugh Class A [category 1] or B)[^v][^x][^y]
- Chemotherapy ± RT only in the context of a clinical trial
  - Systemic chemotherapy
  - Intra-arterial chemotherapy
- Clinical trial
- Locoregional therapy[^l][^z]
- RT (conformal or stereotactic)[^aa] (category 2B)
- Supportive care

**Imaging[^u]**
- 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

---

[^u]: Many transplant centers consider bridge therapy for transplant candidates. (See Discussion)


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


[^r]: Order does not indicate preference.

[^x]: MRI or multi-phase CT scans for liver assessment are recommended. Consider chest imaging as clinically indicated.

[^y]: See Child-Pugh Score (HCC-A).

[^z]: See Principles of Locoregional Therapy (HCC-C).
Hepatocellular Carcinoma

**CLINICAL PRESENTATION**

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

Metastatic disease or Extensive liver tumor burden

**TREATMENT**

Options:
- Sorafenib (Child-Pugh Class A [category 1] or B)
- Clinical trial
- Locoregional therapy
- RT (conformal or stereotactic) (category 2B)
- Supportive care

**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.

---

1 See Principles of Locoregional Therapy (HCC-C).
2 See Child-Pugh Score (HCC-A).
3 Order does not indicate preference.
6 There are limited data to support the use of RT in this setting.
# Hepatocellular Carcinoma

## CHILD-PUGH SCORE

<table>
<thead>
<tr>
<th>Chemical and Biochemical Parameters</th>
<th>Scores (Points) for Increasing Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade)¹</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time prolonged (sec)²</td>
<td>1-4</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>• For primary biliary cirrhosis</td>
<td>&lt; 4</td>
</tr>
</tbody>
</table>

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


² Corresponding International Normalized Ratio (INR) measurements are Score points 1: < 1.7; Score points 2: 1.8 - 2.3; Score points 3: > 2.3 (van Rijn JL, Schmidt NA, Rutten WP. Correction of instrument- and reagent-based differences in determination of the International Normalized Ratio (INR) for monitoring anticoagulant therapy. Clin Chem 1989;35(5):840-843).

---

**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.
Patients must be medically fit for a major operation.

Hepatic resection is indicated as a potentially curative option in the following circumstances:
- Adequate liver function (generally Child-Pugh Class A without portal hypertension)
- Solitary mass without major vascular invasion
- Adequate future liver remnant (at least 20% without cirrhosis and at least 30% to 40% with Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)

Hepatic resection is controversial in the following circumstances, but can be considered:
- Limited and resectable multifocal disease
- Major vascular invasion

Patients with chronic liver disease being considered for major resection, pre-operative portal vein embolization should be considered. ¹

Patients meeting the UNOS criteria ([single lesion ≤ 5 cm, or 2 or 3 lesions ≤ 3 cm], http://www.unos.org) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside the UNOS guidelines and may be considered at some institutions for living or deceased donor.

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

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 ≤ 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.¹
• Unresectable/inoperable lesions > 5 cm should be considered for treatment using arterially directed or systemic therapy.²,³,⁴
• 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.⁵

Arterially directed therapies:
• All tumors irrespective of location may be amenable to arterially directed therapies (hepatic artery embolization [HAE], transarterial chemoembolization [TACE], drug-eluting beads [DEB], Yttrium-90 microspheres) provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.⁶-⁸
• All arterially directed therapies are relatively contraindicated in patients with bilirubin > 3 mg/dL unless segmental injections can be performed.⁹ Yttrium-90 microsphere therapy has an increased risk of radiation induced liver disease in patients with bilirubin over 2 mg/dL.¹⁰
• Arterially directed therapies are relatively contraindicated in cases of 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.¹¹
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.\(^{12}\) 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.\(^{13}\) Child-Pugh C cirrhosis is a relative contraindication, and these patients should be considered for a clinical trial.\(^{14,15}\)
PRINCIPLES OF LOCOREGIONAL THERAPY


**GALL-1**

### PRESENTATION
- Incidental finding at surgery
  - Intraoperative staging
  - Frozen section of gallbladder
  - Consider extended cholecystectomy

### POSTOPERATIVE WORKUP
- CT/MRI, chest CT
- Resectable
  - Cholecystectomy + en bloc hepatic resection + lymphadenectomy ± bile duct excision
- Unresectable

### PRIMARY TREATMENT
- Options:
  - Gemcitabine/cisplatin combination therapy (category 1)
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Fluoropyrimidine chemoradiation
  - Clinical trial
  - Supportive care

---

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

**b** See Principles of Surgery (GALL-A).

**c** Order does not indicate preference.

**d** 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, capcitabine/cisplatin, capcitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin and the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting. (Hezel AF and Zhu AX. Systemic therapy for biliary tract cancers. The Oncologist 2008;13:415-423)

**e** 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).
Hepatobiliary Cancers

**PRESENTATION**

- **Incidental finding on pathologic review**
  - T1a (with negative margins)
  - T1b or greater

**WORKUP**

- CT/MRI, chest CT
- Consider staging laparoscopy

**PRIMARY TREATMENT**

- Observe
- Observe
- Hepatic resection + lymphadenectomy ± bile duct excision

- Options:
  - Gemcitabine/cisplatin combination therapy (category 1)
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Fluoropyrimidine chemoradiation
  - Clinical trial
  - Supportive care

---

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

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

*Other Clinical Presentations (See GALL-3) and (GALL-4)*

---

*See Adjuvant Treatment and Surveillance (GALL-5)*

---

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

*b* See Principles of Surgery (GALL-A).

*c* Order does not indicate preference.


*e* There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954.)
**GALL-3**

---

**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.

---

**GALL-3**

---

**NCCN Guidelines Index**

Hepatobiliary Cancers Table of Contents

Discussion

---

**GALL-3**

---

**NCCN Guidelines Version 1.2013**

Gallbladder Cancer

---

**PRESENTATION**

- Mass on imaging
  - H&P
  - CT/MRI
  - Liver function tests
  - Chest CT
  - Surgical consultation
  - Assessment of hepatic reserve
  - Consider CEA
  - Consider CA 19-9
  - Consider staging laparoscopy

---

**WORKUP**

- Resectable
  - Cholecystectomy
    - + en bloc hepatic resection
    - + lymphadenectomy ± bile duct excision

- Unresectable
  - Biopsy

---

**PRIMARY TREATMENT**

- Options:
  - Gemcitabine/cisplatin combination therapy (category 1)
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Fluoropyrimidine chemoradiation
  - Clinical trial
  - Supportive care

---

**See Adjuvant Treatment and Surveillance (GALL-5)**

---

**Other Clinical Presentations (See GALL-1, GALL-2, and GALL-4)**

---

**See Principles of Surgery (GALL-A)**

---

**Order does not indicate preference.**

---


---

**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).**
**PRESENTATION**

- Jaundice
- Metastatic disease

**WORKUP**

- H&P
- Liver function tests
- Chest CT
- CT/MRI
- Cholangiography
- Surgical consultation
- Consider CEA
- Consider CA 19-9
- Consider staging laparoscopy

**Resectable**

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

**Unresectable → Biopsy**

**Options:**

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

**Resectable**

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

**Unresectable → Biopsy**

**Options:**

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

**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.

**See Principles of Surgery (GALL-A).**

**Order does not indicate preference.**

**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).**

**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).**

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

**Consult with a multidisciplinary team.**

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

**See Adjuvant Treatment and Surveillance (GALL-5).**

**Other Clinical Presentations (See GALL-2) and GALL-3)**

**GALL-4**
Consider fluoropyrimidine chemoradiation (except T1a or T1b, N0)\(^f\)
or
Fluoropyrimidine or gemcitabine chemotherapy regimen\(^j\)

Consider imaging every 6 mo for 2 y\(^k\) if clinically indicated

Post resection

SURVEILLANCE

For relapse, see Workup of the following initial clinical presentations:

Mass on imaging (See GALL-3)

Jaundice (See GALL-4)

Metastases (See GALL-5)

\(^f\)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)

\(^j\)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.

\(^k\)There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.
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.¹
- 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.²³
- 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 to improve outcomes.⁴

### 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.¹,² 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.

---


---

**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.
**Isolated intrahepatic mass (biopsy proven adenocarcinoma) (See NCCN Guidelines for Occult Primary Cancers)**

- H&P
- CT/MRI
- Chest CT
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Surgical consultation
- Consider laparoscopy
- Consider esophagogastroduodenoscopy (EGD) and colonoscopy
- Consider viral hepatitis serologies

---

**Resectable**

- Options:
  - Gemcitabine/cisplatin combination therapy (category 1)
  - Clinical trial
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Fluoropyrimidine chemoradiation
  - Supportive care

**Unresectable**

- Options:
  -gemcitabine/cisplatin combination therapy (category 1)
  - Clinical trial
  - Fluoropyrimidine-based or other gemcitabine-based chemotherapy regimen
  - Supportive care

**Metastatic disease**

- Consider lymphadenectomy for accurate staging

---

**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 1.2013**

**Intrahepatic Cholangiocarcinoma**

### ADDITIONAL THERAPY

#### Post resection status

- **No residual local disease (R0 resection)**
  - Observe
  - Clinical trial
  - Fluoropyrimidine chemoradiation
  - Fluoropyrimidine-based or gemcitabine-based chemotherapy regimen

- **Microscopic margins (R1)** or Residual local disease (R2 resection)
  - Fluoropyrimidine chemoradiation
  - Fluoropyrimidine-based or gemcitabine-based chemotherapy regimen

### SURVEILLANCE

- Consider imaging every 6 mo for 2 y 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.

---

³Consult with multidisciplinary team.

¹There 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)

¹¹There 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)

¹²There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

---

PRINCIPLES OF SURGERY¹,²

- 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.


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

**WORKUP**
- 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

**PRIMARY TREATMENT**
**Unresectable**, see above
- 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

**Resectable**<sup>d</sup> → **Resection**<sup>d</sup> → **See Adjuvant Treatment and Surveillance (EXTRA-2)**
- 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/capecitabine the single agents gemcitabine, capecitabine, and 5-fluorouracil in the unresectable or metastatic setting.

(Hezelt 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 1.2013
Extrahepatic Cholangiocarcinoma

SECONDARY OR ADJUVANT TREATMENT

| Resected, negative margin (R0), Negative regional nodes or Carcinoma in situ at margin | Observe or Fluoropyrimidine chemoradiation or Fluoropyrimidine or gemcitabine chemotherapy or Clinical trial |
| Resected, positive margin (R1) or Resected gross residual disease (R2) or Positive regional nodes | Consider fluoropyrimidine chemoradiation followed by additional fluoropyrimidine or gemcitabine chemotherapy or Fluoropyrimidine based or gemcitabine based chemotherapy for positive regional lymph nodes |

SURVEILLANCE

Consider imaging every 6 mo for 2 y\textsuperscript{m} as clinically indicated

\textsuperscript{i}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)

\textsuperscript{j}R1 or R2 resections should be evaluated by a multidisciplinary team.

\textsuperscript{k}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)

\textsuperscript{m}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 pancreatoduodenectomy 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.1,2,3
• 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.4,5
• 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.
PRINCIPLES OF SURGERY
(References)

# Table 1

**American Joint Committee on Cancer (AJCC)**

### TNM Staging for Liver Tumors (7th ed., 2010)*

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Anatomic Stage/Prognostic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
<td>Stage I  T1  N0  M0</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>Stage II  T2  N0  M0</td>
</tr>
<tr>
<td>T1 Solitary tumor without vascular invasion</td>
<td>Stage IIIA T3a  N0  M0</td>
</tr>
<tr>
<td>T2 Solitary tumor with vascular invasion or multiple tumors none more than 5 cm</td>
<td>IIIB  T3b  N0  M0</td>
</tr>
<tr>
<td>T3a Multiple tumors more than 5 cm</td>
<td>IIIC  T4  N0  M0</td>
</tr>
<tr>
<td>T3b Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein</td>
<td>Stage IVA Any T  N1  M0</td>
</tr>
<tr>
<td>T4 Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum</td>
<td>Stage IVB Any T  Any N  M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th>Histologic Grade (G)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
<td>G1 Well differentiated</td>
</tr>
<tr>
<td>N0 No regional lymph node metastasis</td>
<td>G2 Moderately differentiated</td>
</tr>
<tr>
<td>N1 Regional lymph node metastasis</td>
<td>G3 Poorly differentiated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>Fibrosis Score (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0 No distant metastasis</td>
<td>F0 Fibrosis score 0-4 (none to moderate fibrosis)</td>
</tr>
<tr>
<td>M1 Distant metastasis</td>
<td>F1 Fibrosis score 5-6 (severe fibrosis or cirrhosis)</td>
</tr>
</tbody>
</table>

*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.**

---

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.
## Table 2

### American Joint Committee on Cancer (AJCC)

**TNM Staging for Gallbladder Cancer (7th ed., 2010)*

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX  Primary tumor cannot be assessed</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T0  No evidence of primary tumor</td>
<td>M1 Distant metastasis</td>
</tr>
<tr>
<td>Tis  Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T1  Tumor invades lamina propria or muscular layer</td>
<td></td>
</tr>
<tr>
<td>T1a Tumor invades lamina propria</td>
<td></td>
</tr>
<tr>
<td>T1b Tumor invades muscle layer</td>
<td></td>
</tr>
<tr>
<td>T2  Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>T4  Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures</td>
<td></td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes (N)

| N0  No regional lymph node metastasis                                               | Anatomic Stage/Prognostic Groups                                                   |
| N1  Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein | Stage 0 Tis N0 M0                                                                       |
| N2  Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes | Stage I T1 N0 M0                                                                       |
| N3  Metastases to lymph nodes in the liver, portal vein, or hepatic artery | Stage II T2 N0 M0                                                                       |
| N4  Metastases to lymph nodes in the portal vein, hepatic artery, or superior mesenteric artery | Stage IIIA T3 N0 M0                                                                  |
| N5  Metastases to lymph nodes in the superior mesenteric artery, inferior mesenteric artery, or celiac artery | Stage IIIB T1-3 N1 M0                                                                |
| N6  Metastases to lymph nodes in the inferior mesenteric artery or porta hepatica       | Stage IVA T4 N0-1 M0                                                                   |
| N7  Metastases to lymph nodes in the porta hepatica, caval lymph nodes, or superior mesenteric artery, or splenic artery | Stage IVB Any T N2 M0                                                               |

### Histologic Grade (G)

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

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.
# NCCN Guidelines Version 1.2013 Staging Hepatobiliary Cancers

## Table 3

**American Joint Committee on Cancer (AJCC)**

**TNM Staging for Intrahepatic Bile Ducts (7th ed., 2010)**

### Primary Tumor (T)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (intraductal tumor)</td>
</tr>
<tr>
<td>T1</td>
<td>Solitary tumor without vascular invasion</td>
</tr>
<tr>
<td>T2a</td>
<td>Solitary tumor with vascular invasion</td>
</tr>
<tr>
<td>T2b</td>
<td>Multiple tumors, with or without vascular invasion</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with periductal invasion</td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis present</td>
</tr>
</tbody>
</table>

### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

### Anatomic Stage/Prognostic Groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IVA</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
</tbody>
</table>

### Histologic Grade (G)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

---

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.
### Table 4

**American Joint Committee on Cancer (AJCC)**

**TNM Staging for Perihilar Bile Duct Tumors (7th ed., 2010)***

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Anatomic Stage/Prognostic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TX</strong> Primary tumor cannot be assessed</td>
<td><strong>Stage 0</strong> Tis N0 M0</td>
</tr>
<tr>
<td><strong>T0</strong> No evidence of primary tumor</td>
<td><strong>Stage I</strong> T1 N0 M0</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
<td><strong>Stage II</strong> T2a-b N0 M0</td>
</tr>
<tr>
<td><strong>T1</strong> Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue</td>
<td><strong>Stage IIIA</strong> T3 N0 M0</td>
</tr>
<tr>
<td><strong>T2a</strong> Tumor invades beyond the wall of the bile duct to surrounding adipose tissue</td>
<td><strong>Stage IIIB</strong> T1-3 N1 M0</td>
</tr>
<tr>
<td><strong>T2b</strong> Tumor invades adjacent hepatic parenchyma</td>
<td><strong>Stage IVA</strong> T4 N0-1 M0</td>
</tr>
<tr>
<td><strong>T3</strong> Tumor invades unilateral branches of the portal vein or hepatic artery</td>
<td><strong>Stage IVB</strong> Any T N2 M0</td>
</tr>
<tr>
<td><strong>T4</strong> 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</td>
<td>Any T Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional Lymph Nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NX</strong> Regional lymph nodes cannot be assessed</td>
<td></td>
</tr>
<tr>
<td><strong>N0</strong> No regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td><strong>N1</strong> Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)</td>
<td></td>
</tr>
<tr>
<td><strong>N2</strong> Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

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

**Histologic Grade (G)**

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

*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.*
### Table 5

<table>
<thead>
<tr>
<th>American Joint Committee on Cancer (AJCC)</th>
<th>TNM Staging for Distal Bile Ducts Tumors (7th ed., 2010)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to the bile duct histologically</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades beyond the wall of the bile duct</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis, or the superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis, or the superior mesenteric artery</td>
</tr>
<tr>
<td><strong>Regional Lymph Nodes (N)</strong></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td><strong>Distant Metastasis (M)</strong></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anatomic Stage/Prognostic Groups</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis  N0  M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1   N0  M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2   N0  M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3   N0  M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1   N1  M0</td>
</tr>
<tr>
<td></td>
<td>T2   N1  M0</td>
</tr>
<tr>
<td></td>
<td>T3   N1  M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4   Any N M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T  Any N M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histologic Grade (G)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>
Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/28/11

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.

Overview

Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma; HCC), bile ducts (intrahepatic and extrahepatic cholangiocarcinoma) and gallbladder. Cholangiocarcinomas and gallbladder cancer are collectively known as biliary tract cancers. In the United States, an estimated 26,190 and 9,250 cases will be diagnosed with liver or intrahepatic bile duct cancer and gallbladder cancer or other biliary tract cancer, respectively in 2011 with approximately 19,590 deaths from liver or intrahepatic bile duct cancer, and 3,300 deaths due to gallbladder cancer or other biliary tract cancer occurring during that year.1

The NCCN Guidelines for Hepatobiliary Cancers presented here are the work of the members of the NCCN Hepatobiliary Cancers Clinical Practice Guidelines Panel. The types of hepatobiliary cancers covered in these guidelines include: HCC; gallbladder cancer; 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.2 For example, chronic hepatitis B viral infection is the leading cause of HCC in Asia and Africa, while hepatitis C viral infection is the leading cause of HCC in Europe, Japan, and North America.3,4 A retrospective analysis of patients at liver transplantation centers in the U.S. found that nearly 50% and about 15% of patients were infected with the hepatitis C or B virus, respectively, with approximately 5% of patients having markers of both hepatitis B and hepatitis C infection.5

Seropositivity for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) are associated with an increased risk of HCC in patients with chronic hepatitis B viral infection.6,7 Data from large population-based studies have also identified high serum HBV DNA and HCV RNA viral load as independent risk factors for developing HCC in patients with chronic infection.8,11
Non-viral causes associated with an increased risk of HCC include alcoholic cirrhosis, inherited errors of metabolism (relatively rare) such as hereditary hemochromatosis, porphyria cutanea tarda, alpha1-antitrypsin deficiency, Wilson’s disease, and stage IV primary biliary cirrhosis. 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. 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.

Alcoholic cirrhosis is clearly a risk factor for HCC, 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.

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

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 histological findings of hepatic steatosis with inflammation in individuals who consume little or no alcohol) in the setting of metabolic syndrome or diabetes mellitus and the development of HCC. Estimations of the prevalence of NASH in the United States are in the range of 3-5%, indicating that this sizable subpopulation is at risk for cirrhosis and development of HCC. 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%. 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.

In most cases, the risk factors for HCC are also risk factors for liver cirrhosis. It has been estimated that 60-80% of persons with HCC have underlying cirrhosis, possibly approaching 90% in the U.S. 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. Importantly, certain populations chronically infected with the HBV (ie, hepatitis B carriers) have been identified as being at increased risk of HCC in the absence of cirrhosis, especially when other risk factors are present, and it has been estimated that 30-50% of patients with chronic hepatitis B viral infection who develop HCC do not have underlying cirrhosis. 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 ≥40 years, Asian females ≥ 50 years, and African/North American blacks with hepatitis. 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. 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.\(^2\)

The incidence of HCC is increasing in the United States, particularly in the population infected with the hepatitis C virus. Approximately 4 million individuals in the United States are chronically infected with the HCV,\(^27\) and the annual incidence rate of HCC among patients with HCV-related cirrhosis has been estimated to be between 2% and 8%.\(^4\) Although it has been reported that the number of cases of hepatitis C infection diagnosed per year in the United States is declining, it is likely that the observed increase in the number of cases of HCV-related HCC is associated with the often prolonged period between viral infection and the manifestation of HCC.\(^28,29\) Approximately 1.5 million people in the United States are chronically infected with HBV.\(^30,31\) 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,\(^32\) although studies have shown wide variation in the annual incidence rate of HCC among individuals with chronic hepatitis B infection.\(^4\)

**Screening for HCC**

The purpose of a cancer screening test is to identify the presence of a specific cancer in an asymptomatic individual in a situation where early detection has the potential to favorably impact patient outcome. The panel supports the recommendation by the American Association for the Study of Liver Disease (AASLD) that HCC screening should be “offered in the setting of a program or a process in which screening tests and recall procedures have been standardized and in which quality control procedures are in place.”\(^4\)

Support for enrolling individuals at high-risk of HCC in a screening program comes from a large randomized controlled trial of 18,816 men and women with hepatitis B infection or a history of chronic hepatitis in China. In this study, screening with serum alpha-fetoprotein (AFP) testing and ultrasonography every 6 months was shown to result in a 37% reduction in HCC mortality, despite the fact that less than 60% of individuals in the screening arm completed the screening program.\(^33\) In a recent prospective study of 638 patients with HCC in Singapore carried out over a 9 year period, patients 40 years or younger were more likely than older patients to be hepatitis B carriers and to have more advanced disease at diagnosis.\(^34\) Although survival did not differ in the 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 ultrasonography are the most widely used methods of screening for HCC.\(^35\) In a screening study involving a large population of patients in China infected with the hepatitis B virus or those with chronic hepatitis, the detection rate, false positive rate, and positive predictive value was 84%, 2.9%, and 6.6% for ultrasound alone; 69%, 5.0%, and 3.3% for AFP alone, and 92%, 7.5%, and 3.0% for the combination of AFP and ultrasound.\(^36\) These results demonstrate that ultrasound imaging alone is a better HCC screening approach than AFP testing alone. Nevertheless, since ultrasonography is highly operator dependent, 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.\(^37,39\)

In these guidelines, the populations considered to be “at risk” for HCC and likely to benefit from participation in an HCC screening program...
include patients with liver cirrhosis induced by viral (Hepatitis B, C) as well as non-viral causes (alcoholic cirrhosis, genetic hemochromatosis, NASH, stage IV primary biliary cirrhosis and alpha1 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 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.

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 ultrasonography and AFP testing every 6-12 months for patients at risk for HCC. Additional imaging [at least a 3-phase contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)] is recommended (as described in the following section on Diagnosis and Initial Workup) in the setting of a rising serum AFP or following identification of a liver mass nodule on ultrasound. It is reasonable to study patients with cross-sectional imaging (CT or MRI) and this is probably the most commonly employed method in the United States, although not well studied.

**Diagnosis**

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

**Imaging**

HCC lesions are characterized by arterial hypervascularity, deriving most of their blood supply from the hepatic artery unlike the surrounding liver which receives most of its supply of blood from the portal vein. Diagnostic HCC imaging involves the use of one or more of the following modalities: 4-phase helical CT; 4-phase dynamic contrast-enhanced MRI or contrast-enhanced ultrasonography (CEUS), although the latter modality is not commonly available in the U.S. Positron emission tomography (PET)/CT is not considered to be adequate. The term 4-phase refers to the phases of scanning: unenhanced phase, an arterial phase, a portal venous phase, and the venous phase after a delay. 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.

The results of a prospective study evaluating the accuracy of CEUS and dynamic contrast-enhanced MRI for the diagnosis of liver nodules 2 cm or smaller observed on screening ultrasonography, demonstrated that the diagnosis of HCC can be established without biopsy confirmation if both imaging studies are conclusive. However, as noted earlier, CEUS is not commonly utilized in the US. Other investigators have suggested that a finding of classical arterial enhancement using a single imaging technique is sufficient to diagnose HCC in patients with cirrhosis and 1-2 cm liver nodules detected during surveillance, thereby reducing the need for a biopsy. In the updated AASLD guidelines, the algorithms for the liver nodules 1-2 cm in size have been changed to reflect these considerations.
Recommendations for imaging included in the NCCN guidelines if clinical suspicion for HCC is high (e.g., following identification of a liver nodule on ultrasonography or in the setting of rising a serum AFP level) are adapted from the updated guidelines developed by the AASLD. 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 is 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 3-6 months, with enlarging lesions evaluated according to size. Patients with lesions stable in size should be followed with imaging every 3-6 months using the same imaging modality that was first used to identify the nodules.

Liver nodules greater than 1 cm in size should be first evaluated with 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 1-2 cm in size or greater 2 cm. For patients with liver nodules 1-2 cm in size, the NCCN guidelines have included repeat 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 enhancements is observed by the recommended imaging method. If transplant is a consideration, patients should be referred to a transplant center before biopsy.

Both core biopsy and FNAB have advantages and disadvantages in this setting. For example, FNAB may be associated with a lower complication rate when sampling deeply situated lesions or those located near major blood vessels. In addition, the ability to rapidly stain and examine cytological samples can provide for immediate determinations of whether sufficient sample has been obtained, as well as the possibility of an upfront tentative diagnosis. However, FNAB is highly dependent on the skill of the cytopathologist, and there are reports of high false-negative rates as well as the possibility of false-positive findings with this procedure. Although a core biopsy is a more invasive procedure, it has the advantage of providing pathologic information on both cytology and tissue architecture. Further, additional histological and immunohistochemical tests can be performed on the paraffin wax embedded sample. However, recent evidence
indicates that a core biopsy does not provide an accurate determination of tumor grade.\(^{51}\)

Nevertheless, use of biopsy to diagnose HCC is limited by a number of factors including sampling error, particularly when lesions are greater than 1 cm.\(^{4,24}\) Patients for whom a nondiagnostic biopsy result is obtained should be followed closely, and subsequent additional imaging and/or biopsy is recommended if a change in nodule size is observed.

**Serum biomarkers**

Although serum AFP has long been used as a marker for HCC, it is not a sensitive or specific diagnostic test for HCC. Serum AFP levels of more than 400 ng/ml are considered diagnostic of HCC, however, such high values are observed only in a small percentage of patients with HCC. In a series of 1,158 patients with HCC, only 18% of patients had values greater than 400 ng/ mL and 46% of patients had normal serum AFP levels of less than 20 ng/ mL.\(^{52}\) In patients with chronic liver disease, an elevated AFP could be more indicative of HCC in non-infected patients.\(^{53}\) Furthermore, AFP can also be elevated in intrahepatic cholangiocarcinoma and some metastases from colon cancer.\(^{4}\) AFP testing can be useful in conjunction with other test results to guide the management of patients for whom a diagnosis of HCC is suspected. An elevated AFP level in conjunction with imaging results showing the presence of a larger liver mass has been shown to have a high positive predictive value for HCC in 2 retrospective analyses involving small numbers of patients,\(^{54,55}\) although the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institutions.

The updated AASLD guidelines no longer recommend AFP testing as part of diagnostic evaluation.\(^{4}\) The panel considers an imaging finding of classic enhancement to be more definitive in this setting since the level of serum AFP may be elevated in those with certain nonmalignant conditions, as well as within normal limits in a substantial percentage of patients with HCC,\(^{56}\) which is in agreement with the updated AASLD guidelines recommendation.\(^{4}\) Additional imaging studies (CT or MRI) are recommended for patients with a rising serum AFP level in the absence of a liver mass. If no liver mass is detected following measurement of an elevated AFP level, the patient should be followed with AFP testing and liver imaging every 3 months.

Other serum biomarkers being studied in this setting include des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence-II (PIVKA-II), and lens culinaris agglutinin-reactive AFP (AFP-L3), an isoform of AFP.\(^{24,57,58}\) Although AFP was found to be more sensitive than DCP or AFP-L3 in detecting early-stage and very early-stage HCC in a recent retrospective case control study, none of these biomarkers were considered optimal in this setting.\(^{59}\) 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.\(^{58}\)

**Initial workup**

The foundation of the initial workup of the patient diagnosed with HCC is a multidisciplinary evaluation involving investigations into the etiological origin of liver disease, including a hepatitis panel for detection of hepatitis B and/or C viral infection (HBsAg, hepatitis B surface antibody, 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 hepatologist for appropriate antiviral therapy.\textsuperscript{14,60}

Common sites of HCC metastasis include the lung, abdominal lymph nodes, peritoneum and the bone.\textsuperscript{61,62} 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 are also used in the evaluation of the HCC tumor burden, to detect the presence of metastatic disease, nodal disease, and vascular invasion, to assess whether evidence of portal hypertension is present, to provide an estimate of the size and location of HCC and the extent of chronic liver disease, and, in the case of patients being considered for resection, to provide an estimate of the future liver remnant in relation to the total liver volume.\textsuperscript{43} Enlarged lymph nodes are seen commonly in patients with viral hepatitis, primary biliary cirrhosis, and other underlying liver disorders that predispose patients to HCC\textsuperscript{63} 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 (CBC) and tests of kidney function (blood urea nitrogen [BUN] and creatinine) which are established prognostic markers in patients with liver disease.\textsuperscript{64}

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.\textsuperscript{65,66} The Child-Pugh classification provides a rough estimate of liver function by classifying patients as having compensated (class A) or decompensated (class B and C) cirrhosis. The Child-Pugh score is an empirical score which incorporates laboratory measurements (ie, serum albumin, bilirubin, and PT) as well as more subjective clinical assessments of encephalopathy and ascites. More recently, a version of the Child-Pugh score which includes INR has come into use. Advantages of the Child-Pugh score include ease of performance (ie, can be done at the bedside) and the inclusion of clinical parameters. An important additional assessment of liver function not included in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension (ie, esophagogastric varices, splenomegaly, abdominal collaterals, and thrombocytopenia). Evidence of portal hypertension may also be evident on CT/MRI. Measurement of hepatic venous pressure gradient (HVPG) is an evolving tool for the assessment of portal hypertension.\textsuperscript{67-70}

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.\textsuperscript{71} The MELD score has since been adopted by the United Network for Organ Sharing (UNOS; www.unos.org) to stratify patients on the liver transplantation waiting list according to their risk of death within 3 months.\textsuperscript{72} 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.66

Pathology and Staging

Pathology

Three gross morphologic types of HCC have been identified: nodular, massive and diffuse.73 Nodular HCC is often associated with cirrhosis and is characterized by well circumscribed nodules. The massive type of HCC, usually associated with a noncirrhotic liver, occupies a large area with or without satellite nodules in the surrounding liver. The less common diffuse type is characterized by diffuse involvement of many small indistinct tumor nodules throughout the liver.

Staging

Clinical staging systems for the cancer patient can provide a more accurate prognostic assessment before and after a particular treatment intervention, and may be used to guide treatment decision-making. Therefore, staging can have a critical impact on treatment outcome by facilitating appropriate patient selection for specific therapeutic interventions, and by providing risk stratification information following treatment. The key factors affecting prognosis in patients with HCC are the clinical stage, aggressiveness and growth rate of the tumor, the general health of the patient, the liver function of the patient and the treatments administered.42 A number of staging systems for patients with HCC have been devised.75,76 Each of the staging systems includes variables which evaluate one or more of the factors listed above. For example, the Child-Pugh65 and MELD scores77 can be considered to be staging systems which evaluate aspects of liver function only.

The American Joint Committee on Cancer (AJCC) TNM staging system (Table 1) provides information on pathologic characteristics of resected specimens only,78 whereas the Okuda system incorporates aspects of liver function and tumor characteristics.79 The French classification (GRETCH) system incorporates the Karnofsky performance score as well as measurements of liver function and serum AFP.80 Several staging systems include all parameters from other staging systems as well as additional parameters. For example, the Chinese University Prognostic Index (CUPI) system81 and the Japanese Integrated Staging (JIS)42 scores incorporate the TNM staging system and the Cancer of the Liver Italian Program (CLIP),83 Barcelona Clinic Liver Cancer (BCLC),84 SLiDe,85 and JIS systems include the Child-Pugh score (with modified versions of CLIP and JIS substituting the MELD score for the Child-Pugh score.86-88 In addition, the BCLC system also incorporates the Okuda system, as well other tumor characteristics, measurements of liver function, and patient performance status.89

Although some of these systems have been found to have use in all stages of HCC (eg, BCLC),24,89,90 limitations of all of these systems have been identified. For example, the AJCC TNM classification system has limited usefulness since most patients with HCC do not undergo surgery. A number of studies have shown that particular staging systems perform well for specific patient populations likely related to differing etiologies. Furthermore, staging systems may be used to direct treatment and/or to predict survival outcomes following a particular type of therapeutic intervention. For example, the AJCC TNM system has recently been shown to accurately predict survival for patients who underwent orthotopic liver transplantation.91 The CLIP, CUPI and
GRETSCH staging systems have been shown to perform well in predicting survival in patients with advanced disease.\textsuperscript{92}

The CLIP system has been specifically identified as being useful for staging patients who underwent transarterial chemoembolization and those treated in a palliative setting.\textsuperscript{93,94} 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.\textsuperscript{95} 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.\textsuperscript{76} Furthermore, the BCLC staging system was recently shown to be very useful for predicting outcome in patients following radiofrequency ablation therapy.\textsuperscript{96} 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.\textsuperscript{97} In addition, another study showed tumor size > 2 cm, multifocal tumors, and vascular invasion to be independent predictors of poor survival in patients with early HCC following liver resection or liver transplantation,\textsuperscript{98} and this staging system has been retrospectively validated in a population of patients with early HCC.\textsuperscript{99}

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.

The selection characteristics of these patient populations are described in more detail in the section on Management, below.

**Management**

The patient with HCC should be carefully evaluated for HCC treatment consideration. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, it is possible that the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome.\textsuperscript{100} 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.\textsuperscript{24}

**Surgery**

Partial hepatectomy (ie, liver resection) is a potentially curative therapy for patients with early-stage HCC (solitary tumor ≤5 cm in size, or ≤3 tumors each ≤3 cm in size and no evidence of gross vascular invasion) who are eligible to undergo the procedure.\textsuperscript{101,102} Partial hepatectomy for selected patients with HCC can now be performed with low operative morbidity and mortality (in the range of 5% or less).\textsuperscript{103,104} Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC,\textsuperscript{104-106} 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%. However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.

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

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

With respect to tumor characteristics and estimates of the future liver remnant following resection, preoperative imaging is essential for surgical planning. 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. However, in one study, no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors of 10 cm or larger. Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence. The role of liver resection for patients with limited and resectable multifocal disease and/or signs of major vascular invasion is controversial, although results of a recent retrospective analysis showed a 5-year overall survival rate of 81% for selected patients with single tumor of 5 cm or less or 3 or fewer tumors of 3 cm or less undergoing liver resection.

Another critical preoperative assessment includes evaluation of the postoperative future liver remnant (FLR) as an indicator of postoperative liver function. CT is used to measure the FLR directly and estimates of the total liver volume can be calculated. The ratio of future remnant/total liver volume (subtracting tumor volume) is then determined. The panel recommends that this ratio be at least 20% in patients without cirrhosis and at least 30-40% in patients with a Child-Pugh A score. For patients with an estimated FLR/total liver volume ratio below recommended values who are otherwise suitable candidates for liver resection, pre-operative portal vein embolization (PVE) should be considered. PVE is a safe and effective procedure for...
redirecting blood flow toward the portion of the liver which will remain following surgery. Hypertrophy is induced in these segments of the liver while the embolized portion of the liver undergoes atrophy.\(^{118}\)

**Liver Transplantation**

Liver transplantation is an attractive, potentially curative therapeutic option for patients with early HCC.\(^{101}\) 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, Mazzaferrro et al. proposed the Milan criteria (single tumors 5 cm or less in diameter or no more than three tumor nodules 3 cm or less in diameter in patients with multiple tumors) for patients with unresectable HCC and cirrhosis.\(^{119}\) The 4-year overall and recurrence-free survival rates were 85% and 92%, respectively, when liver transplantation was restricted to a subgroup of patients meeting the Milan selection criteria. These results have been supported by more recent studies in which patient selection for liver transplantation was based on these criteria.\(^{120}\) These selection criteria were adopted by UNOS, because they identify a subgroup of patients with HCC for whom liver transplantation results are similar to those in patients who underwent liver transplantation for end-stage cirrhosis without HCC.

The UNOS criteria (radiologic evidence of a single tumor ≤ 5 cm in diameter, or 2-3 tumors ≤ 3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease) 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.\(^{121-124}\)

The MELD score as a measure of liver function is also used as measure of pre-transplant mortality. In 2002 it was adopted by UNOS to provide an estimate of risk of death within 3 months for patients on the waiting list for cadaveric liver transplant. According to the current UNOS policy, patients with T2 HCC tumors (defined by UNOS as 1 nodule 2-5 cm or 2 or 3 nodules all less than 3 cm) receive an additional 22 priority MELD points (also called a “MELD-exception”).\(^{72}\) In a retrospective analysis of data provided by UNOS of 15,906 patients undergoing first-time liver transplantation during 1997-2002 and 19,404 patients undergoing the procedure during 2002-2007, 4.6% of liver transplant recipients had HCC compared with 26% in 2002-2007, with most of patients in the latter group receiving an “HCC MELD exception”.\(^{125}\) In 2002-2007, patients with an “HCC MELD-exception” had similar survival to patients without HCC. Important predictors of poor posttransplantation survival for patients with HCC were MELD score ≥ 20, and serum AFP level ≥ 455 ng/mL,\(^{125}\) although the reliability of the MELD score as a measure of posttransplantation mortality is controversial. Survival was also significantly lower for the subgroup of patients with HCC tumors in the size range of 3-5 cm.

Expansion of the Milan/UNOS criteria to provide patients who have marginally larger HCC tumors with liver transplant eligibility is an active area of debate.\(^{89,120,126,127}\) An expanded set of criteria including patients with a single HCC tumor ≤ 6.5 cm, with a maximum of 3 total tumors with no tumor > 4.5 cm (and cumulative tumor size <8 cm) as liver transplant candidates has been proposed by Yao et al at the University of California at San Francisco (UCSF).\(^{128}\) Studies evaluating the
posttransplantation survival of patients who exceed the Milan criteria but meet the UCSF criteria show wide variation in 5-year survival rates (range of 38% to 93%). 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. Some support for the former objection comes from a large retrospective analysis of the UNOS database showing significantly lower survival for the subgroup of patients with tumors 3-5 cm in size compared with those who had smaller tumors.

**Resectable disease**

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

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. 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 2-3 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. See the section on “Treatment before Liver transplantation” below. If transplant is not feasible, the panel recommends hepatic resection for this group of patients.

**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 systemic therapy with sorafenib (see the section on “Systemic therapy”), locoregional therapy (see the section on “Locoregional therapies”), conformal or stereotactic RT, best supportive care, systemic chemotherapy with or without RT or intra-arterial chemotherapy in the context of clinical trial.

**Treatment before Liver Transplantation**

**Bridge therapy**

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list. It is considered for patients who meet the transplant criteria. A number of studies have investigated the role of locoregional treatment as a bridge to liver transplantation in patients on a waiting list. These studies included radiofrequency ablation (RFA), chemoembolization, conformal radiation therapy, transarterial chemoembolization (TACE) and sorafenib 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. Nevertheless, use of bridge therapy in this setting is increasing, and it is administered at some NCCN centers.

**Downstaging Therapy**

Downstaging therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) that are beyond the accepted transplant criteria. Recent prospective studies have demonstrated that downstaging (prior to transplant) with percutaneous ethanol injection (PEI), RFA, TACE and transarterial radioembolization (TARE) with yttrium 90 microspheres improves disease-free survival following transplant. However, such studies have used different selection criteria for the downstaging therapy and different transplant criteria after successful downstaging. In some studies response to locoregional therapy has been associated with good outcomes after transplantation. Further validation is needed to define the end-points for successful downstaging prior to transplant.

**Ablation**

Induction of HCC tumor necrosis can be achieved by direct exposure of the tumor to a particular chemical substance (eg, ethanol, acetic acid) or an alteration in temperature (RFA, cryoablation or microwave ablation). Any ablative therapy can be performed by laparoscopic, percutaneous or open approaches. The 2 most commonly used methods of ablation therapy are RFA and PEI. Selection criteria for ablative therapy include patients with local disease only characterized as being completely amenable to ablative therapy according to the size and location of the tumor(s). The complication rate associated with ablative therapy in the treatment of HCC has been reported to be relatively low. For example, in a randomized controlled trial comparing treatment of patients with HCC using RFA or PEI, the major complication and mortality rates were 4.8% and 0%, respectively. The effectiveness of RFA and PEI therapy in the treatment of Child-Pugh class A patients with HCC has also been compared in a number of randomized controlled trials. RFA was shown to be superior to PEI with respect to complete response rate (65.7% vs. 36.2% respectively; P=0.0005), and rate of local recurrence. In addition, in one study patients in the RFA arm were shown to require fewer treatment sessions. However, the benefit of RFA compared with PEI on overall survival was demonstrated only in 2 studies, but not in a third study, which showed no significant overall survival differences between the two treatment arms. The results of a retrospective analysis of 5 randomized trials also showed that RFA was superior to PEI in the treatment of small HCC with respect to overall survival.
survival and tumor response; RFA was also associated with a significantly smaller risk of local recurrence.\textsuperscript{163}

RFA has also been compared with liver resection in a prospective randomized controlled studies.\textsuperscript{163,164} In one study, there were no differences in recurrence-free survival or overall survival between the two treatment arms, although limitations of the study include the small number of patients and the lack of a noninferiority design.\textsuperscript{163} The results of a recent randomized trial showed survival benefit with surgical resection over RFA in 235 patients with small HCC conforming to the Milan criteria.\textsuperscript{164} The 5-year overall survival rates were 54.8% and 75.6% respectively for the RFA group and surgical resection. The corresponding recurrence-free survival rates for the 2 groups were 28.7% and 51.3% respectively. In a retrospective analysis, Vivarelli et al reported that overall and disease-free survival were significantly higher with surgery compared to percutaneous RFA.\textsuperscript{158} 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.

There is a wide range of reported rates of local recurrence following ablative therapy for HCC which may reflect differences in patient selection criteria and treatment protocols. For example, in the study of Shiina et al. 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 (≤ 3 cm).\textsuperscript{162} However, another study found less than 3% of patients with single HCC tumors ≤ 2 cm who underwent repeated applications of RFA to have a recurrence of disease at 31 months.\textsuperscript{165} Results of some long-term studies show survival rates of over 50% at 5 years for patients with successful HCC tumor necrosis following ablative therapy.\textsuperscript{166,167} Nevertheless, reported rates of overall survival vary widely across studies of patients treated with ablation.\textsuperscript{160-163,166-168}

This is likely to reflect differences in specific disease characteristics (eg, size and number of tumors) and, perhaps more importantly, the extent of underlying liver function in the patient populations studied.\textsuperscript{167,168}

Available evidence from retrospective analyses and prospective trials suggest that tumor size is a critical factor in determining the effectiveness of ablation therapy for patients with HCC.\textsuperscript{135,136,169} In a study of 218 patients with single HCC lesion 2.0 cm or less, RFA induced complete necrosis in 214 patients (98%; 86% with 1 session of RFA and 12% with 2 sessions).\textsuperscript{165} There were 2 local recurrences after a median follow-up of 31 months, resulting in a sustained complete response rate of 97% (212 of 218 cases). In a series of 126 patients with cirrhosis or chronic hepatitis, Livraghi et al showed that RFA was a safe and effective procedure for the treatment of medium (3.1-5.0 cm) and large (5.1- 9.5 cm) tumors.\textsuperscript{169} Complete and partial necrosis rates were 47.6% and 20.6% respectively. Nearly complete necrosis was seen in 31.7% of patients. Tumor size was highly significant in predicting treatment success. Smaller tumors (3.1-5.0 cm) were successfully treated significantly more often than tumors greater than 5.0 cm. In a retrospective analysis of 40 mostly Child-Pugh class A or B patients with HCC liver nodules treated with RFA, PEI, or a combination of both methods while awaiting liver transplantation, complete and partial necrosis rates were 47% and 53%, respectively, when RFA was used, and 23% and 46%, respectively, following PEI therapy with 31% of tumors showing no evidence of necrosis with PEI therapy.\textsuperscript{135} The overall rate of complete necrosis was 53% for HCC tumors < 3 cm and 14% for tumors ≥ 3 cm (P=0.033). However, this rate increased to 62% when the subset of tumors less than 3 cm treated by RFA was evaluated. The study of Mazzaferro et al. provides additional support for the use of ablation therapy in the treatment of HCC tumors ≤ 3 cm.\textsuperscript{136} In this prospective study of 50 consecutive patients with liver
cirrhosis undergoing RFA while awaiting liver transplantation, the rate of complete tumor necrosis was 55% overall and 63% when only tumors ≤ 3 cm were considered. \(^{136}\) A recent retrospective study of 1,061 patients with Child-Pugh A cirrhosis also confirmed that surgical resection was superior to RFA in terms of OS and tumor-free survival (TFS) in patients with solitary HCC ≤ 3 cm as well as for OS, RFS, and TFS in patients with solitary tumors larger than 3 cm but less than 5 cm, or with two or three lesions each less than 5 cm. \(^{170}\) There was no significant difference in RFS between the two treatments in patients with solitary HCC ≤ 3 cm.

It should be emphasized that ablative techniques are limited by anatomic location. Lesions in certain portions of the liver (eg, dome) may not be accessible to a percutaneous approach. Similarly, ablative treatment of tumors located on the liver capsule may cause tumor rupture with track seeding. Major vessels in close proximity to the tumor can absorb large amounts of heat (known as the ‘heat sink effect’) when methods such as radiofrequency ablation is performed which decrease the effectiveness and significantly increase local recurrence rates. \(^{24}\) The panel emphasizes that caution should be exercised when ablating lesions near major bile ducts, and other intra-abdominal organs such as the colon, stomach, diaphragm, heart and gallbladder and these organs can be damaged.

**Embolization**

Arterial embolization therapy (chemoembolization, bland embolization, radioembolization) in the treatment of HCC is based on selective catheter-based infusion of particles targeted to the arterial branch of the hepatic artery feeding the portion of the liver in which the tumor is located. \(^{171}\) Embolization therapy is made possible by the dual blood supply to the liver; whereas the majority of the blood supply to normal liver tissue comes from the portal vein, blood flow to liver tumors is mainly from the hepatic artery. \(^{41}\) Furthermore, HCC tumors are characterized by hypervascularity resulting in increased blood flow to tumor relative to normal liver tissue.

Prior to performance of the embolization procedure, a careful evaluation of the arterial anatomy of the liver of each patient is necessary. Because non-target embolization of the liver can result in serious injury, arterial embolization is limited to a segment, subsegment, or lobe of the liver. All HCC tumors, irrespective of location in the liver, may be amenable to embolization therapy provided that the arterial blood supply to the tumor may be isolated. \(^{172-175}\) Tumor necrosis induced by embolic therapy is typically estimated by the extent to which contrast uptake on dynamic CT/MRI is diminished at some specified point following treatment when compared with pre-treatment imaging findings.

General patient selection criteria for embolization procedures include unresectable/inoperable disease with tumors not amenable to ablation therapy only, and the absence of large volume extrahepatic disease. Minimal extrahepatic disease is considered a ‘relative’ contraindication for embolization procedures. An evaluation of performance status and liver function (ie, Child-Pugh score) should also be performed. In addition, more individualized patient selection that is specific to the particular embolization procedure being considered is necessary to avoid significant treatment-related toxicity (see sections on Bland embolization and chemoembolization and Radioembolization, below).

**Bland embolization and chemoembolization**

The principle of bland embolization, also called transarterial embolization (TAE), and TACE is a reduction in blood flow to the tumor, resulting in tumor ischemia followed by tumor necrosis. Gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres...
have been used to block arterial flow.\textsuperscript{173,176,177} TACE is distinguished from TAE by the catheter-based administration of a concentrated dose of chemotherapy (eg, doxorubicin or cisplatin) combined with an emulsifying agent, usually administered prior to the embolic particles.\textsuperscript{176} Results of two randomized clinical trials have shown a survival benefit for use of TACE therapy vs. supportive care in patients with unresectable HCC.\textsuperscript{175,178} In one study patients were randomly assigned to TAE, TACE, and supportive care treatment arms.\textsuperscript{175} One- and 2-year survival rates were 82\%, and 63\%, 75\% and 50\%, and 63\% and 27\% for patients in the TACE, TAE, and supportive care arms, respectively. The majority of the patients in the study had liver function classified as Child-Pugh A, a performance status of 0 and main tumor nodule size of about 5 cm. For the group of evaluable patients receiving either TACE or TAE, partial and complete response rates sustained for at least 6 months of approximately 30\% and 1\%, respectively, were observed. Limitations of this study include its early termination, and lack of power to detect a difference between TACE and TAE treatment arms. In the other study which randomized patients with unresectable HCC to TACE or best supportive care, the actuarial survival was significantly better in the TACE group (1 year, 57\%; 2 years, 31\%; 3 years, 26\%) than in the control group (1 year, 32\%; 2 years, 11\%; 3 years, 3\%; \(P = .002\)).\textsuperscript{178} Although death from liver failure was more frequent in patients who received TACE, the liver functions of the survivors were not significantly different between the two groups.

Many of the clinical studies evaluating the effectiveness of TAE and/or TACE in the treatment of patients with HCC are confounded by use of a wide range of treatment strategies, including type of embolic particles, type of chemotherapy and type of emulsifying agent (for studies involving TACE), and number of treatment sessions.\textsuperscript{173,177} In a recent retrospective analysis of patients undergoing TAE for the treatment of HCC in which a standardized technique was used, 1-, 2- and 3-year overall survival rates of 66\%, 46\%, and 33\%, respectively, were observed. These 1-, 2-, and 3-year survival rates were increased to 84\%, 66\%, and 51\%, respectively, when only the subgroup of patients without extrahepatic spread or portal vein involvement by tumor was considered.\textsuperscript{173}

In the study of Maluccio et al., predictors of poor prognosis on multivariate analysis following TAE were tumor size \(\geq 5\) cm, 5 or more tumors and extrahepatic disease; portal vein occlusion was not found to be an independent predictor of survival.\textsuperscript{173} However, there is evidence showing portal vein obstruction,\textsuperscript{179,180} liver function categorized as Child-Pugh class C and total serum bilirubin level of > 3 mg/mL\textsuperscript{180,181} to be significant predictors of poor prognosis in patients treated with TACE.

Complications of TAE and TACE can include acute portal vein thrombosis, cholecystitis, and bone marrow suppression, in addition to other toxicities, although the reported frequencies of serious adverse events vary across studies.\textsuperscript{35,182} A post-embolization syndrome involving fever, abdominal pain, and intestinal ileus has been reported to be relatively common in patients undergoing these procedures.\textsuperscript{35,182} Reported rates of TAE and TACE treatment-associated mortality for are usually less than 5\%.\textsuperscript{35,173,175,182}

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,\textsuperscript{176} the panel recommends that a total bilirubin level > 3 mg/mL should be considered as a relative contraindication for TACE or
TAE unless segmental injections can be performed. Furthermore, patients with previous biliary-enteric bypass have an increased risk of intrahepatic abscess following TACE. 176

Recent studies have evaluated TACE with drug-eluting-beads in patients with unresectable HCC. 183-187 In a randomized study (PRECISION V), TACE with doxorubicin-eluting embolic beads (DEB-TACE) 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) in 212 patients with Child-Pugh A/B cirrhosis and localized, unresectable HCC without nodal involvement. Although, DEB-TACE was not superior to conventional TACE with doxorubicin (P = 0.11), patients with Child-Pugh B, ECOG performance status 1, bilobar disease, and recurrent disease showed a significant increase in objective response (P = 0.038) compared to conventional TACE. The former approach was also associated with improved tolerability with a significant reduction in serious liver toxicity and a significantly lower rate of doxorubicin-related side effects. 185 However, in other prospective randomized studies DEB-TACE was associated with survival advantage, better local response, fewer recurrences and a longer time-to-progression. 186,187 These results need to be confirmed in large prospective studies.

TACE causes increased hypoxia leading to an upregulation of vascular endothelial growth factor (VEGF) and insulin-like growth factor-2 (IGF-2). 188 Increased plasma levels of VEGF and IGF-2 have been associated with the development of metastasis after TACE. 189,190 These findings suggest that sorafenib may be an appropriate option following TACE or ablation therapy in patients with adequate liver function if there is evidence of residual or recurrent tumor not amenable to additional local therapies. In non-randomized phase II studies, the use of sorafenib concomitantly with TACE or DEB-TACE was well tolerated and effective in patients with unresectable HCC. 191-193 However, in a phase III randomized trial, sorafenib when given after treatment with TACE did not significantly prolong time to progression or overall survival 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. 194 Ongoing 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.

Radioembolization

Radioembolization is a newer embolization method that provides for the internal delivery of high-dose radiation to the tumor-associated capillary bed. 171,195 TARE is accomplished through the catheter-based administration of microspheres in which yttrium-90, an emitter of beta radiation, is embedded. This method allows for limited penetration of radiation, thereby sparing the normal liver tissue. The microspheres are available in 2 formulations: TheraSpheres (glass microspheres) and SIR-Spheres (resin microspheres). Although radioembolization, like TAE and TACE, involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia. 174

A partial response rate of 42.2% was observed in a phase II study of 108 patients with unresectable HCC with and without portal vein thrombosis treated with radioembolization and followed for up to 6 months. 174 Grade 3/4 adverse events were more common in patients
with main portal vein thrombosis. However, patients with branch portal vein thrombosis experienced a similar frequency of adverse events related to elevated bilirubin levels as patients without portal vein thrombosis. Results from a recent single-center, prospective longitudinal cohort study of 291 patients with HCC treated with radioembolization therapy showed a significant difference in median survival times based on liver function level (Child-Pugh A [17.2 months]; Child-Pugh B [7.7 months]; P=0.002).196 Median survival for patients with disease characterized by Child-Pugh class B liver function and portal vein thrombosis was 5.6 months. In a recent comparative effective analysis, patients with HCC treated with chemoembolization or radioembolization with yttrium-90 microspheres had similar survival times.197 However, radioembolization resulted in a longer time-to-progression and less toxicity than chemoembolization. Reported complications of radioembolization therapy include cholecystitis/bilirubin toxicity and abscess formation.174,196,198 Randomized controlled studies of the use of radioembolization in the treatment of patients with HCC are needed.

**Combinations of local therapies**

Recently, a number of studies have evaluated the effectiveness of using a combination of local therapies in the treatment of patients with unresectable or inoperable HCC. The principle behind the combination of RFA and TAE is that the focused heat delivery of RFA may be enhanced by vessel occlusion through TAE since blood circulation inside the tumor may interfere with the transfer of heat to the tumor. Recent evidence suggests that combination of transarterial embolization with RFA or PEI may be effective especially for larger lesions that do not respond to either procedure alone.

A retrospective review of selected patients with a single HCC tumor up to 7 cm treated with either the combination of TAE and ablation or liver resection showed 1-, 3-, and 5-year actuarial survival rates of 97%, 77%, and 56% for patients receiving combination therapy and 81%, 70%, and 58% for the patients undergoing surgery.172 In another study of similar design the 1-, 3-, and 5-year survival rates of patients with tumors meeting UNOS criteria with respect to number and size were 98%, 94%, and 75% for the combination group and 97%, 93%, and 81% for the surgery group.115 In another retrospective analysis, combination of TACE with PEI or RFA was more effective (both in terms of tumor response and overall survival) than TACE, PEI or RFA alone in patients with multiple tumors fulfilling the Milan criteria.199 However, in a randomized trial, the combination of RFA and TACE was associated with lower local tumor progression rate but no significant difference in overall survival rates in patients with intermediate-sized (3.1-5.0 cm) HCC tumors.200 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 overall survival 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.201

**Recommendations for locoregional therapies**

The effectiveness of local regional approaches in the treatment of HCC has not been established to be comparable to that of liver resection or transplantation. The consensus of the panel is that liver resection, if feasible is preferred for patients who meet surgical selection criteria. Locoregional therapy can be considered if patients are not amenable to surgery. The panel considers percutaneous ablation to be a very good option for well selected patients with small tumors who are not candidates for surgery.
The consensus of the panel is that ablation therapy alone for the treatment of HCC performs optimally when tumors are ≤ 3 cm, and that lesions between 3 and 5 cm may be treated using a combination of ablation and embolization methods, as long as tumor location is favorable. The panel recommends that patients with unresectable or inoperable disease who are eligible to undergo embolization therapy and have tumor lesions > 5 cm should be considered for treatment using arterial embolic approaches or systemic therapy.

**External beam radiation therapy**

External-beam radiation therapy (3-D conformal or stereotactic) allows focal administration of high dose radiation to HCC tumors while sparing surrounding liver tissue, thereby limiting the risk of radiation-induced liver damage in patients with unresectable or inoperable liver disease. There is growing evidence supporting the usefulness of conformal or stereotactic body radiation therapy (SBRT) for patients with unresectable disease. The panel encourages prospective clinical trials evaluating the role of SBRT in patients with unresectable HCC.

All tumors irrespective of their location may be amenable to conformal or SBRT. SBRT is often used for patients in the Child-Pugh A category with 1-3 tumors with a cumulative diameter of less than 6 cm and with minimal or no extrahepatic disease. It could be considered for larger lesions if there is at least 800 cc of uninvolved liver and liver radiation tolerance can be respected. The panel recommends that radiation therapy can be considered (category 2B) as an alternative to ablation/embolization techniques or when these therapies have failed in patients with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation and those with local disease only who are not operable due to performance status or comorbidity. It is not included in the guidelines as an option for patients with metastatic disease.

**Systemic therapy**

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

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

Sorafenib, an oral multikinase inhibitor which suppresses tumor cell proliferation and angiogenesis, has been evaluated in one phase II trial and two randomized placebo controlled phase III trials for the treatment of patients with advanced or metastatic HCC. In the phase III trial [Sorafenib in Advanced Hepatocellular Carcinoma (SHARP) study], 602 patients with advanced HCC were randomly assigned to sorafenib or best supportive care. In this study, advanced HCC was defined as patients not eligible for or those who had disease progression after surgical or locoregional therapies. 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 (≥ 95% of patients classified as Child-Pugh 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 overall survival was significantly longer in the sorafenib arm (10.7 months in the sorafenib arm vs. 7.9 months in the placebo group; hazard ratio=0.69; 95% CI, 0.55 to 0.87; P<0.001).

In the Asia-Pacific study, another phase III trial with a similar design to the SHARP study, 226 patients were randomly assigned to sorafenib or placebo arms (150 and 76 in sorafenib and placebo arms, respectively).210 Although inclusion/exclusion criteria and the percentage of patients with Child-Pugh A liver function (97%) were similar in the Asia-Pacific and SHARP studies, there were significant differences in patient and disease characteristics between the two studies. Only Asian patients were enrolled in the Asia-Pacific study and these patients were more likely to be younger, to have HBV-related disease (ie, over 70%), symptomatic disease, and a higher number of tumor sites than patients in the SHARP study. The hazard ratio for the sorafenib arm compared with the placebo arm (0.68; CI, 0.50-0.93; P=0.014) was nearly identical to that reported for the SHARP study, although median overall survival was lower in both treatment and placebo groups in the Asia-Pacific study (6.5 months vs. 4.2 months).

Using data from the SHARP study, a number of analyses have been performed to investigate the efficacy of sorafenib in particular patient subgroups. Results of these analyses suggest that sorafenib is an effective treatment in patients with advanced HCC irrespective of baseline ECOG performance status (0-2) and presence or absence of macroscopic vascular invasion and/or extrahepatic spread212 and those with alcohol-related213 and hepatitis C viral-related HCC,214 and it is an effective treatment irrespective of ALT/AST/AFP levels, and that hepatic function is not appreciably affected.215 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.209

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).216 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.211 A subgroup analysis of data from this study showed lower median overall survival for patients in the Child-Pugh class B group compared with those in the Child-Pugh class A group (3.2 months vs. 9.5 months).217 In another large retrospective study by Pinter et al., the median overall survival for Child-Pugh class B patients was 4.3 months compared to 8.3 months for Child-Pugh class A patients and it was only 1.5 months for Child-Pugh class C patients.218 219 In the GIDEON trial (global, prospective, noninterventional study of patients with HCC suitable for systemic therapy and receiving sorafenib in real-life practice), 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 (5 months vs. 10.5 months), reflecting the poorer prognosis and natural history of liver disease in this patient population. In a phase II study by Yau et al., which included 36 patients with Child-Pugh A cirrhosis, 13 patients had Child-Pugh B cirrhosis and 2 had Child-Pugh C cirrhosis, there were no significant differences between Child-Pugh A and Child-Pugh B/C patients in overall survival (5.5 months vs. 5 months), grade 3 or 4 hematologic (17% vs. 33%; P =
0.18) and nonhematologic toxicities (47% for Child-Pugh A and Child-Pugh B/C; P = 0.97). However, the grade 3 or 4 liver toxicity, although not statistically different was 73% for Child-Pugh B/C patients compared to 56% for the Child-Pugh A patients. Similar findings were also reported recently by Chiu et al in a study exploring the tolerability and survival benefits of sorafenib in Child-Pugh class B patients. Therefore, more mature results from ongoing studies are needed to recommend sorafenib for Child-Pugh B or C 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. 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. Finally, it is important to mention that validated criteria to evaluate tumor response to sorafenib are needed since true objective volumetric responses are rare.

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.

In phase II studies, bevacizumab, a vascular endothelial growth factor receptor (VEGFR) inhibitor, has shown modest clinical activity (single agent or in combination with erlotinib or chemotherapy) in patients with advanced HCC. 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 is no mature data to support the use of bevacizumab in the treatment of patients with HCC.

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

**Surveillance**
Although data on the role of surveillance in patients with resected HCC are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends high-quality cross-sectional imaging every 3-6 months for 2 years, then every 6-12 months. AFP levels, if initially elevated, should be measured every 3 months for 2 years, then every 6-12 months. Re-evaluation according to the initial work-up should be considered in the event of disease recurrence.

**Biliary Tract Cancers**

**Gallbladder Cancer**

**Risk Factors and Epidemiology**
Gallbladder cancer is the most common and aggressive type of all the biliary tract cancers, with the shortest median survival duration. It is more common in whites than in blacks and its incidence steadily...
increases with age and women are 2-6 times more likely to be diagnosed with gallbladder cancer than men. Gallbladder cancer is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement, and distant metastases.228

Risk factors for gallbladder cancer, of which cholelithiasis is the most prevalent, are associated with the presence of chronic inflammation. Calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been associated with gallbladder cancer.229,230

**Diagnosis and Initial Workup**

Gallbladder cancer is often diagnosed at an advanced stage due to the aggressive nature of the tumor which can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation which mimics that of biliary colic or chronic cholecystitis.229

Hence, it is not uncommon for a diagnosis of gallbladder cancer to be an incidental finding at surgery or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis.

Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound or in patients presenting with jaundice. The initial workup of these patients should include liver function tests, and an assessment of hepatic reserve. CEA and CA 19-9 testing can be considered although these markers are not specific for gallbladder cancer.229 High-quality imaging is recommended to evaluate tumor penetration within the wall of the gallbladder, to detect direct tumor invasion of other organs/biliary system, to determine whether major vascular invasion is present, and to evaluate for the presence of nodal and distant metastases.229 In addition, chest imaging should be performed. Staging laparoscopy should be considered if no distant metastases are found on imaging since the risk of peritoneal metastases is high in this disease.230,231

For patients presenting with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor.43 Noninvasive magnetic resonance cholangiography (MRCP) is preferred over endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), unless a therapeutic intervention is planned. Although the role of PET scanning has not been established in the evaluation of patients with gallbladder cancer, emerging evidence indicates that it is useful for detecting the presence of distant metastatic disease in patients with otherwise potentially resectable disease.232,233

**Pathology and Staging**

Approximately 80% of gallbladder cancers are adenocarcinomas.229,234 Gallbladder cancer is often characterized by early spread to lymph tissue and the bloodstream.229,235 The AJCC TNM staging criteria for gallbladder cancer are shown in Table 2. A review of about 2500 patients with gallbladder cancer from hospital cancer registries throughout the U.S. showed tumor stage to be closely associated with survival; 5-year survival rates were 60%, 39%, 15%, 5% and 1% for patients with stage 0 - stage IV disease, respectively.236 Results from a recent retrospective single center analysis showed a 10.3 month median survival for the overall population of patients diagnosed with gallbladder cancer.234 Median survival was 12.0 months and 5.8 months for those with stage IA-III and stage IV disease, respectively.234

**Management**

Surgery remains the only curative modality for gallbladder cancer. In a retrospective review covering the period of 1995-2005, 123 patients of 435 patients treated for gallbladder cancer at a single center underwent
curative resection, and 47% were diagnosed with gallbladder cancer as an incidental finding during laparoscopic cholecystectomy. Factors determining gallbladder tumor resectability include the stage of the tumor according to AJCC TNM staging criteria as well as tumor location. Nodal disease outside of this area (most commonly, celiac, retropancreatic or in the interaortocaval groove) should be considered unresectable.

An analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990-2002 showed that while major hepatectomy and common bile duct excision significantly increased the surgical complication rate, they were not independently associated with survival, leading the authors to conclude that these procedures should be performed only when necessary to remove disease. Another study which retrospectively evaluated data from 115 patients who underwent re-resection for incidental gallbladder cancer showed that achievement of R0 resection margins strongly correlated with long-term survival. In a retrospective analysis of patients with gallbladder cancer treated at a single institution, 74% of patients who underwent surgical re-exploration following an incidental diagnosis of gallbladder cancer following laparoscopic cholecystectomy were found to have residual cancer.

With these data in mind the optimal resection (extended cholecystectomy) is a limited hepatic resection and portal lymphadenectomy to encompass the tumor with negative margins. Major hepatic resections and bile duct resections should be performed when necessary to achieve an R0 resection.

**Resectable disease**

Although the initial management of patients discovered to have gallbladder cancer at the time of cholecystectomy or on pathologic review following cholecystectomy differs from the initial management of patients with a diagnosis of gallbladder cancer prior to surgery (see below), the surgical approach for patients found to have resectable gallbladder cancer is the same, with the exception that the gallbladder has been removed in the case of an incidental finding of cancer on pathologic review. In all cases, surgery to treat gallbladder cancer should be performed by a surgeon who is prepared to do a cancer operation.

All patients should undergo CT/MRI and chest imaging prior to surgery to evaluate for the presence of distant metastases. Furthermore, since staging laparoscopy has a high yield in this disease, it should be considered before laparotomy for a potentially curative resection of gallbladder cancer.

In the event that gallbladder cancer is found at the time of surgery, the panel recommends intraoperative staging, and procurement of a frozen section of gallbladder. An extended cholecystectomy, as described above, can be considered depending on the expertise of the surgeon and the establishment of disease resectability. For patients with an incidental finding of gallbladder cancer at the time of surgery or for those with a suspicious mass detected on imaging or in patients presenting with jaundice, the panel recommends that patients with resectable disease should undergo cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision. Lymphadenectomy should include lymph nodes in the porta hepatitis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct if possible. However, jaundice in patients with gallbladder cancer is considered a relative contraindication to surgery and outcomes are generally poor in these patients and only a portion of those with node-negative disease potentially benefit from complete resection. 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 experienced center should be considered.

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. Among patients with T1b or greater lesions, extended cholecystectomy is recommended for resectable lesions, after CT/MRI, chest imaging, and laparoscopy confirm the absence of metastatic disease. This recommendation is supported by findings of residual disease within the liver in a significant percentage of these patients and an association between increasing risk of metastasis to locoregional lymph nodes and increasing T stage. Therefore, if resectable, patients should undergo hepatic resection and lymphadenectomy with or without bile duct excision. The consensus of the panel is that surgery should not be performed in situations where the resectability of disease has not been established nor should it be performed by surgeons untrained in this procedure. There is evidence that a delayed open laparotomy due to referral following an incidental diagnosis of gallbladder is not associated with a survival deficit compared with immediate resection, although these comparisons are difficult to interpret due to selection bias. Nevertheless, given the option, upfront surgical resection of gallbladder cancer by a surgeon experienced in this procedure is the approach preferred by the panel.

Although the role of adjuvant treatment strategy for patients with resected gallbladder cancer has not been determined, options include consideration of fluoropyrimidine chemotherapy (except T1b, N0) and fluoropyrimidine or gemcitabine chemotherapy (see section on “Chemoradiation and chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”).

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

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

Cholangiocarcinomas
Risk Factors and Epidemiology
The term cholangiocarcinoma encompasses all tumors originating in the epithelium of the bile duct. Although cholangiocarcinomas are diagnosed throughout the biliary tree, they are distinguished by...
anatomic site and typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Intrahepatic cholangiocarcinomas are located within the hepatic parenchyma and have also been called “peripheral cholangiocarcinomas” (Figure 1). Cholangiocarcinomas occurring anywhere within the common hepatic duct, the region of the junction of the right and left hepatic ducts, or the common bile duct (including the intrapancreatic portion of the common bile duct) are classified as extrahepatic (Figure 1). Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas and perihilar cholangiocarcinoma is most common type of extrahepatic cholangiocarcinoma. In these Guidelines, extrahepatic cholangiocarcinomas include perihilar cholangiocarcinomas (also called Klatskin tumors) which occur at or near the junction of the right and left hepatic ducts and the distal bile duct tumors arising in the extrahepatic bile ducts above the ampulla of Vater. The guidelines do not include tumors of the ampulla of Vater.

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

**Diagnosis and Initial Workup**

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

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

Delayed contrast CT/MRI is recommended as part of the workup of patients with intrahepatic cholangiocarcinoma. Although there are no pathognomonic CT/MRI features associated with intrahepatic cholangiocarcinoma, CT/MRI is used to help determine tumor resectability by characterizing the primary tumor, its relationship to nearby major vessels and the biliary tree, the presence of satellite lesions and distant metastases in the liver, as well as lymph node involvement, if present. In addition, chest imaging should be performed, and laparoscopy may be done in conjunction with surgery if no distant metastasis is found. Upper and lower endoscopy should be considered to exclude extrahepatic primary gastrointestinal tumors. However, this may not be necessary if immunohistochemistry/pathology is conclusive of intrahepatic cholangiocarcinoma. Immunostaining with...
cytokeratins 7 and 20 have been found to be helpful in distinguishing intrahepatic cholangiocarcinoma (CK7+, CK20- and CDX2-) from metastasis from colon cancer (CDX2+, CK20+). The panel emphasizes that a multidisciplinary review of imaging studies involving experienced radiologists and surgeons is necessary to stage the disease and determine potential treatment options (ie, resection or other approach).

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

Pathology and Staging
More than 90% of cholangiocarcinomas are adenocarcinomas. Cholangiocarcinomas can be divided into 3 types depending on macroscopic appearance: mass-forming; periductal-infiltrating; and intraductal-growing.

The AJCC has developed staging systems for cholangiocarcinomas. In the 6th edition of the AJCC staging system, intrahepatic cholangiocarcinoma was staged identical to HCC. However, this staging system did not include predictive clinicopathologic features that are specific to intrahepatic cholangiocarcinoma. Other more practical staging systems for intrahepatic cholangiocarcinoma have been used. In the revised 7th edition of the AJCC staging classification, intrahepatic cholangiocarcinoma has a new staging system that is independent of the staging system used for HCC. The 7th AJCC staging classification is based on the data from the SEER program on 598 patients with intrahepatic cholangiocarcinoma who had undergone surgery. In this study by Nathan et al., tumor size had no independent effect on survival. In addition, multiple tumors and vascular invasion had similar effects on prognosis, but the presence of both of these factors did not confer additional risk compared to the presence of either one. Based on the results of this study, the new staging system focuses on multiple tumors, vascular invasion and lymph node metastasis. Farges et al from the AFC-IHCC study group validated the new staging classification in 163 patients with resectable intrahepatic cholangiocarcinoma. The revised classification was useful in predicting survival according to the TNM staging. With an average follow-up of 34 months, the median survival was not reached for patients with stage I disease, 53 months for those with stage II disease (P = 0.01) and 16 months for stage III disease (P < 0.0001).

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

**Management of Intrahepatic cholangiocarcinoma**

Complete resection is the only potentially curative therapy for patients with intrahepatic cholangiocarcinoma, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis. Endo et al reported that multiple hepatic tumors, regional nodal involvement and large tumor size independently predicted poor recurrence-free survival following resection. More recently, Nathan et al. reported that multiple lesions and vascular invasion predicted adverse prognosis following resection; lymph node status was of prognostic significance among patients without distant metastases. The 3- and 5-year survival rates were 40% and 25% respectively for patients with N0M0 disease compared to 21% and 4% respectively for those with N1M0 disease. Multifocal tumors and lymph node metastases are considered contraindications to surgery due to the poor survival after resection but surgical approaches can be considered in highly selected cases.

Surgery involves hepatic resection whose extent is dictated by what is necessary to achieve clear margins (eg. removal of hepatic lobe or segment along the bile duct in which the tumor is located). Patient selection for surgery is facilitated by careful pre-operative staging which may include laparoscopy to identify patients with unresectable or metastatic disease. There is evidence that an R0 resection is associated with significantly longer survival rates in patients undergoing surgery for intrahepatic cholangiocarcinoma. Five-year survival rates in the range of 20% to 43% have been reported.

Although the optimal treatment strategy for patients with resected intrahepatic cholangiocarcinoma has not been determined, patients who have undergone an R0 resection with or without ablation may be followed with observation alone. Adjuvant chemotherapy can be administered if appropriate clinical trials are available. For patients found to have microscopic positive tumor margins (R1) or residual local disease (R2) after resection, it is essential for a multidisciplinary team to review the available options on a case-by-case basis. These patients should also be evaluated by an experienced hepatobiliary surgeon to determine if re-resection (although uncommon) may be considered. Although the optimal treatment strategy has not been determined, options include (1) consideration of additional resection; (2) ablative therapy (See the section on “Locoregional Therapies for cholangiocarcinomas”); (3) fluoropyrimidine chemoradiation; or (4) fluoropyrimidine-based or gemcitabine-based chemotherapy. (See section on “Chemoradiation and Chemotherapy for treatment of gallbladder cancer and cholangiocarcinoma”).

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

**Management of Extrahepatic cholangiocarcinoma**

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

Patient selection for surgery is facilitated by careful pre-operative staging which may include surgical exploration and laparoscopy to identify patients with unresectable or metastatic disease. However, the consensus of the panel is that surgery may be performed without a biopsy if the index of suspicion is high. The consensus of the panel is that biliary drainage should be considered prior to surgery, although there is controversy regarding the risks and benefits of such an approach. Pre-operative biliary drainage is accomplished by ERCP or PTC.

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

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

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

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

**Locoregional therapies for cholangiocarcinomas**

Locoregional therapies such as RFA, TACE and transarterial radioembolization have been shown to be safe and effective in small series of patients with intrahepatic cholangiocarcinomas.\(^{275-280}\) In a series of 20 patients with recurrent cholangiocarcinoma after curative resection, RFA resulted in a median overall survival rate of 27.4 months.\(^{277}\) In a series of 24 patients with unresectable intrahepatic cholangiocarcinoma, radioembolization with yttrium-90 microspheres induced >50% tumor necrosis and 100% tumor necrosis in 77% and 9% of patients respectively, with a median overall survival of 14.9 months.\(^{275}\) However, none of these approaches have been evaluated in randomized clinical trials.\(^{247}\) Ablation might be considered in patients with intrahepatic cholangiocarcinoma following R1 or R2 resection. Hepatic arterial infusion chemotherapy has also been shown to be effective and feasible for patients with unresectable intrahepatic cholangiocarcinoma.\(^{281-285}\)

Photodynamic therapy (PDT) is a relatively new ablative therapy, involving intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation, and has been used for palliation in patients with cholangiocarcinoma.\(^ {247}\) The combination of PDT with biliary stenting was reported to improve the overall survival of patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.\(^ {286,287}\)

**Liver Transplantation for cholangiocarcinomas**

Liver transplantation is the only other potentially curative option for patients with extrahepatic cholangiocarcinoma.\(^ {288,289}\) This option is only recommended for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. There is retrospective evidence showing selected patients with hilar cholangiocarcinoma receiving preoperative chemoradiation therapy followed by liver transplantation to have significantly improved overall survival compared with patients undergoing resection.\(^ {290}\) Nevertheless, there were substantial differences in the characteristics of patients in the two treatment groups in this study. The panel encourages continuation of clinical research in this area.

**Surveillance**

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

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

Chemotherapy and Chemoradiation in the Adjuvant Setting

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

Studies evaluating the use of adjuvant chemotherapy alone in patients with biliary tract cancer are few; hence, there are limited clinical trial data to define a standard regimen or definitive clinical benefit of such therapy. No clear benefit of adjuvant chemotherapy alone was seen in 2 large retrospective analyses of patients with biliary tract cancer, although the number of patients who received such therapy was very limited in one study, and chemotherapy did not include newer agents in the latter study which covered the period from 1988-1997. A phase III trial evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer. About 50% of the eligible patients in this study had a diagnosis of either cholangiocarcinoma or gallbladder cancer. Patients were randomly assigned to adjuvant chemotherapy with 5-fluorouracil (5-FU)/mitomycin C or to a control arm. Subgroup analyses showed a significantly better 5-year survival in the chemotherapy group for patients with gallbladder cancer although no significant differences in the 2 treatment arms were observed when the subgroup of patients with biliary tract cancer was considered. A retrospective analysis of 177 patients with resected biliary tract cancer showed that initial recurrence involving a distant site occurred in 41% and 85% of patients with hilar cholangiocarcinoma and gallbladder cancer, respectively, arguing for the development of active adjuvant systemic therapy in gallbladder cancer. Due to very limited data on use of chemotherapy in the adjuvant setting, specific recommendations for fluoropyrimidine-based or gemcitabine-based chemotherapy listed in the Guidelines primarily represent an extrapolation from studies of patients with advanced disease.

A primary limitation for cure in patients with biliary tract cancer following surgery is local failure, thereby providing an important justification for
use of adjuvant radiation therapy. Useful reviews on the use of radiation therapy in biliary tract cancers are available and include specific citations to a number of relevant studies.\textsuperscript{295-297} In a retrospective study of 2325 patients who had undergone surgery for gallbladder cancer from the SEER database during the period 1992-2002, median survival was 14 months and 8 months in the groups receiving adjuvant chemoradiation versus not, respectively (P<0.0001). The survival benefit of adjuvant chemoradiation was even more pronounced (16 months vs 5 months; P<0.0001) when only the group of patients with positive regional lymph nodes was considered.\textsuperscript{292} Retrospective analyses from single center experiences for patients with resected extrahepatic cholangiocarcinoma who received fluoropyrimidine-based chemoradiation therapy also suggested that chemoradiation may offer a local control benefit, although distant failure was commonly observed.\textsuperscript{298,299} Results from a recent population-based analysis of patients with locoregional extrahepatic cholangiocarcinoma included in the SEER database covering the period from 1973 to 2005 suggested that while adjuvant radiotherapy was associated with an initial improvement in survival within 1-2 years following surgery, this benefit was no longer evident at long-term (> 5 years) follow-up.\textsuperscript{300}

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.\textsuperscript{301} Results of these studies provide support for omitting adjuvant chemoradiation in the post-surgical treatment of patients with gallbladder cancer characterized as T1b, N0.

Some support for use of adjuvant chemoradiation in the treatment of patients with intrahepatic cholangiocarcinoma comes from a retrospective analysis of patients in the SEER database.\textsuperscript{302} In this study, overall survival was significantly improved when patients received chemoradiation in addition to surgery (P=0.014). In a retrospective study of patients with extrahepatic cholangiocarcinoma, no significant survival differences when seen when patients with R0 margins following surgery who did not undergo adjuvant therapy were compared with patients with R1 margins following surgery who received chemoradiation, suggesting that chemoradiation may have a survival benefit in the latter group.\textsuperscript{303} In another retrospective analysis of patients with curatively extrahepatic cholangiocarcinoma, adjuvant concurrent chemoradiation (CCRT) followed by adjuvant chemotherapy was found to have a survival benefit especially in patients with R1 resection or negative lymph node compared to adjuvant CCRT alone.\textsuperscript{304}

The 3-year disease-free survival rates for CCRT alone and CCRT followed by adjuvant chemotherapy were 27% and 45.2% (p = 0.04), respectively. The corresponding overall survival rates were 31% and 63% (p < 0.01), respectively. These results provide support for the recommendation of consideration of fluoropyrimidine chemoradiation followed by additional fluoropyrimidine or gemcitabine chemotherapy for patients with extrahepatic cholangiocarcinoma with either positive margins or positive regional lymph nodes.

Most of the collective experience of chemoradiation in biliary tract cancer involves concurrent chemoradiation and 5-FU.\textsuperscript{295,296} More recently, concurrent chemoradiation with capecitabine has also been used.\textsuperscript{303,305} Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.\textsuperscript{306}

Chemotherapy and Chemoradiation in the Advanced Setting

The prognosis of patients with advanced biliary tract cancers is poor and the median survival time for those undergoing supportive care is generally short.
alone is short. The survival benefit of chemotherapy in patients with advanced biliary tract cancer was suggested in a trial comparing the regimen of 5-FU, leucovorin and etoposide versus best supportive care. A subsequent phase III trial evaluating patients with advanced biliary tract cancer randomly assigned to receive either 5-FU, leucovorin and etoposide or 5-FU, cisplatin and epirubicin did not show one regimen to be significantly superior with respect to overall survival (12 months vs. 9 months, respectively), although the trial was underpowered to detect such a difference. A number of other chemotherapy combinations as well as single agents have been evaluated in clinical studies for the treatment of advanced biliary tract cancers as reviewed by Hezel and Zhu. Examples of chemotherapy combinations demonstrated in phase II trials to have activity in the treatment of advanced biliary tract cancers include: gemcitabine and cisplatin, gemcitabine and capecitabine, gemcitabine and oxaliplatin, capcitabine and oxaliplatin, capecitabine and cisplatin and 5-FU and cisplatin. Results of a recent pooled analysis of 104 trials of patients with advanced biliary tract cancers showed that the subgroup of patients receiving a combination of gemcitabine and platinum-based agents had the greatest benefit. Additional support for gemcitabine as an anchor drug for the treatment of advanced biliary tract cancers comes from a retrospective review of 304 patients with advanced biliary tract cancer who received gemcitabine, a cisplatin-based regimen, or a fluoropyrimidine-based regimen. In that study, patients receiving a gemcitabine-based regimen were shown to have a lower risk of death.

Most importantly, the recently published randomized, controlled phase III ABC-02 study which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer demonstrated that the combination of gemcitabine and cisplatin improved overall survival and progression-free survival by 30% over gemcitabine alone. Median overall survival was 11.7 months and 8.1 months (hazard ratio=0.64; 95% CI, 0.52-0.80; P<0.001), and median progression-free survival was 8.0 months vs. 5.0 months (hazard ratio=0.63; 95% CI, 0.51-0.77; P<0.001), both in favor of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the 2 arms. Based on the results of this study, the combination of gemcitabine and cisplatin is considered to be the standard of care as first-line chemotherapy for patients with advanced or metastatic biliary tract cancers.

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; capcitabine with cisplatin or oxaliplatin; 5-FU with cisplatin or oxaliplatin; as well as single agent 5-FU, capcitabine, and gemcitabine. The combination of gemcitabine and 5-FU is not included due to the increased toxicity and decreased efficacy observed with this regimen when compared with results of studies of the gemcitabine and capcitabine regimen in the setting of advanced biliary tract cancer.
use of radiation therapy in biliary tract cancers are available and include specific citations to a number of relevant studies. In a retrospective analysis of 37 patients with inoperable extrahepatic cholangiocarcinoma who received chemoradiation, actuarial overall survival at 1 and 2 years was 59% and 22%, respectively, although effective local control was observed in the majority of patients during this time period (actuarial local control rates of 90% and 71% at 1- and 2-years, respectively). The most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers has been 5-FU, although capecitabine has been substituted for 5-FU in some studies. The panel recommends that concurrent chemoradiation should be limited to either 5-FU or capecitabine, and that such treatment should be restricted to patients without evidence of metastatic disease. Concurrent chemoradiation with gemcitabine is it not recommended due to the limited experience and toxicity associated with this treatment.

Summary

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

The safety and efficacy of sorafenib as front-line therapy for patients with advanced HCC and Child-Pugh A liver function was demonstrated in two randomized placebo-controlled studies. Sorafenib is recommended as a category 1 option for this group of patients and is included as a category 2A option for selected patients with Child-Pugh class B liver function. The results of the randomized phase III ABC-02 study demonstrated a survival advantage for the combination of gemcitabine and cisplatin over gemcitabine alone in patients with advanced or metastatic biliary tract cancers. Gemcitabine and cisplatin is included as a category 1 recommendation for this group of patients.

Locoregional therapies such as TACE and radioembolization with yttrium-90 microspheres play a key role in the management of HCC, especially in patients with early stage disease who are not candidates for surgery. Liver 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.

It is essential that all patients should be evaluated for treatment; careful patient selection for treatment and active multidisciplinary cooperation are essential. There are very few high-quality randomized clinical trials of patients with hepatobiliary cancers, and patient participation in prospective clinical trials is the preferred option for the treatment of patients with all stages of disease.
Figure 1: Classification of Cholangiocarcinoma

References


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


46. Sangiovanni A, Manini MA, Iavarone M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of


91. Vauthey J-N, Ribero D, Abdalla EK, et al. Outcomes of liver transplantation in 490 patients with hepatocellular carcinoma: validation...


