NCCN Hepatobiliary Cancers Panel Members

* Al B. Benson, III, MD/Chair 
  Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Edgar Ben-Josef, MD §
University of Michigan
Comprehensive Cancer Center

Mark Bloomston, MD ¶
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

Jean F. Botha, MB, BCh ¶
UNMC Eppley Cancer Center at The Nebraska Medical Center

Bryan M. Clary, MD ¶
Duke Comprehensive Cancer Center

Steven A. Curley, MD ¶
The University of Texas M. D. Anderson Cancer Center

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

Rene Davila, MD ¶
St. Jude Children’s Research Hospital/University of Tennessee Cancer Institute

Craig C. Earle, MD, MSc ¶
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

William D. Ensminger, MD, PhD ¶
University of Michigan Comprehensive Cancer Center

Christopher Garrett, MD ¶
H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida

John F. Gibbs, MD ¶
Roswell Park Cancer Institute

Daniel Laheru, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Sean J. Mulvihill, MD ¶
Huntsman Cancer Institute at the University of Utah

James A. Posey, MD ¶
University of Alabama at Birmingham Comprehensive Cancer Center

* Riad Salem, MD, MBA §
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Elin R. Sigurdson, MD, PhD ¶
Fox Chase Cancer Center

Mika Sinanan, MD, PhD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Jean-Nicolas Vauthey, MD ¶
The University of Texas M. D. Anderson Cancer Center

Alan P. Venook, MD ¶
UCSF Helen Diller Family Comprehensive Cancer Center

Raymond S. W. Yeung, MD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Lawrence D. Wagman, MD ¶
City of Hope

† Medical Oncology
§ Radiotherapy/Radiation Oncology/Interventional Radiology
¶ Surgery/Surgical Oncology
▽ Internal Medicine
†§ Hematology/Hematology Oncology
* Writing Committee Member

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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.
Summary of the Guidelines Updates

Summary of the changes in the 2.2008 version of the Hepatobiliary Cancer guidelines from the 1.2008 version include:

- The addition of sorafenib as a treatment option for patients who are inoperable by performance status or comorbidity (local disease only) and who do not present with cancer-related symptoms (HCC-4).
- Footnote “l” revised to read “Caution: There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels” throughout the hepatocellular carcinoma guideline.

Summary of the changes in the 1.2008 version of the Hepatobiliary Cancer guidelines from the 2.2007 version include:

Hepatocellular Carcinoma:

- Footnote “e” regarding Child-Pugh score, now includes “and assessment of portal hypertension (eg, varices, splenomegaly, and thrombocytopenia).”

- Surgical Evaluation, Bottom branch: Included “...or hepatitis C antigen positive.”

- Footnote “i”: Removed the word “cadaveric” so that text now reads “Criteria for transplantation.” (Also for HCC-3)

- Footnote “k” that states, “For selected patients, a randomized clinical trial has demonstrated survival benefits” is new to the page.

- Treatment: The sorafenib recommendations now include Child-Pugh Class A or B, with corresponding footnote “l” that states, “There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels.” Previously, the guidelines only recommended sorafenib for Child-Pugh Class A patients. (Also for HCC-4)

Gallbladder Cancer:

- Top branch, second column: The phrase “Consider en bloc resection” was changed to “Consider extended cholecystectomy.”

- Postoperative Workup; Bottom branch: The recommendation “Strongly consider staging laparoscopy” was added.

- Resectable; Primary Treatment: Panel deleted the recommendation “± resection of port sites for laparoscopic operations.”

- Footnote “b” was amended with the following sentence: “Patients with nodal disease outside this area are unresectable.”

- Under Adjuvant Treatment: The panel changed “...chemotherapy/RT” to “...chemotherapy ± RT”

Intrahepatic Cholangiocarcinoma:

- Workup: After “Upper and lower endoscopy”, the panel deleted the phrase “as indicated”

- Primary Treatment, Unresectable: The panel deleted the recommendation “Ablative or embolization therapy” along with its corresponding footnote.

Extrahepatic Cholangiocarcinoma:

- Unresectable and metastatic pathways; Primary Treatment: The panel changed the recommendation to “Biliary drainage, if indicated”

- Surgical Procedures for Resectable Disease box: Proximal Third: The panel changed “± en bloc liver resection” to “+” en bloc liver resection.

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

**CLINICAL PRESENTATION**
- Rising alpha-fetoprotein (AFP)
  - Liver imaging studies\(^a,b\)

**WORKUP**
- Liver mass suspicious for hepatocellular carcinoma (HCC) or Histologically confirmed HCC
  - \(H&P\)
  - Hepatitis panel\(^d\)
    - Hepatitis B surface antigen
    - Hepatitis C antibodies
  - Bilirubin, transaminases, alkaline phosphatase, LDH, PT or INR, albumin, protein, BUN, creatinine
  - CBC, platelets
  - AFP
  - CT/MRI\(^b\)
  - Chest x-ray

**INITIAL FINDINGS OF TUMOR AND LIVER FUNCTION**
- Mass confirmed
- No mass\(^c\)
- Follow pathway for HCC, below
- Screen every 3 mo with AFP, liver imaging

**SURGICAL ASSESSMENT**
- Assess liver reserve\(^e\) and comorbidity
  - Additional imaging as required:
  - Chest CT
  - Bone scan
  - CT/MRI\(^b\)
  - Arterial CT
  - Ultrasound

**Metastatic**
- See Metastatic pathway (HCC-4)

**Nonmetastatic**
- Potentially resectable, operable liver mass (See HCC-2)
- Unresectable (See HCC-3)
- Inoperable by performance status or comorbidity, local disease only (See HCC-4)
- Metastatic disease (See HCC-4)

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\(^a\) If ultrasound negative, CT/MRI should be performed.
\(^b\) MRI/CT scan to define extent and number of primary lesions, vascular anatomy, involvement with tumor, and extrahepatic disease; triphasic helical CT or MRI to include early arterial phase enhancement.
\(^c\) Rule out germ cell tumor if clinically indicated. MRI or triple phase CT scan may be helpful.
\(^d\) An appropriate hepatitis panel should preferably include:
  - Hepatitis B surface antigen (HBsAg). HBe and anti-HBc (IgM) are included if HBsAg is positive
  - Hepatitis B surface antibody (for HBIG or vaccine evaluation only)
  - Hepatitis C virus antibodies. If low positive, recombinant immuno blot assay (RIBA) confirmation test is performed

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

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Hepatocellular Carcinoma

**CLINICAL PRESENTATION**

- Potentially resectable, operable liver mass (non-metastatic disease, liver confined)
  - AFP > 4,000 ng/mL, surface antigen positive
  - AFP > 400 ng/mL, surface antigen negative
  - AFP < 400 ng/mL, surface antigen negative or AFP < 4,000 ng/mL, hepatitis B surface antigen positive or hepatitis C antigen positive

**SURGICAL EVALUATION**

- Surgical evaluation
- Consider biopsy or Surgical evaluation
- Positive for HCC
- Nondiagnostic

**TREATMENT**

- Unresectable
  - Ablation
- Resectable:
  - Resection ± ablation or Transplant
  - Treatment (See HCC-3)
  - Ablation (category 2B)

**SURVEILLANCE**

- Treatment (See HCC-3)
- Imaging every 3-6 mo for 2 y, then annually
- AFP, if initially elevated, every 3 mo for 2 y, then every 6 mo

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1. Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
2. Ablation or embolization options: radiofrequency, alcohol, cryotherapy, microwave or embolization (chemoembolization, radioembolization, bland embolization).
3. Consider interferon or other antiviral therapy for selected low risk hepatitis C patients with completely resected tumors and good performance status.
4. Criteria for transplantation (UNOS criteria):
   - Patient is not a liver resection candidate
   - Patient has a tumor ≤ 5 cm in diameter or 2-3 tumors ≤ 3 cm each
   - No macrovascular involvement
   - No extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs, or bone
**CLINICAL PRESENTATION**

- **Unresectable or patient declines surgery**
  - Extensive
  - Cancer-related symptoms present
  - Cancer-related symptoms absent

**TREATMENT**

- Transplant candidate
  - Transplant
  - Options:
    - Sorafenib (Child-Pugh Class A or B)
    - Chemoembolization
    - Clinical trial
    - Ablation
    - Chemotherapy + RT in clinical trial
    - RT (conformal or stereotactic)
    - Radioembolization
    - Supportive care
    - Systemic or intra-arterial chemotherapy in clinical trial

**SURVEILLANCE**

- Imaging every 3-6 mo for 2 y, then annually
- AFP, if initially elevated, every 3 mo for 2 y, then every 6 mo

---

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---

**See Child-Pugh Score (HCC-A).**

**Ablation or embolization options:** radiofrequency, alcohol, cryotherapy, microwave or embolization (chemoembolization, radioembolization, bland embolization).

**Criteria for transplantation (UNOS criteria):**
- Patient is not a liver resection candidate
- Patient has a tumor ≤ 5 cm in diameter or 2-3 tumors ≤ 3 cm each
- No macrovascular involvement
- No extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs, or bone


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


**Contraindicated in cases of main portal thrombosis or Child-Pugh Class C.**
Hepatocellular Carcinoma

**TREATMENT**

Options:
- Sorafenib (Child-Pugh Class A or B)\(^e,j,k,l\)
- Clinical trial
- Ablation\(^g\)
- Chemoembolization\(^m\)
- RT (conformal or stereotactic)
- Radioembolization
- Supportive care

- Sorafenib (Child-Pugh Class A or B)\(^e,j,k,l\)
or
- Ablation
or
- Clinical trial

---

**Inoperable by performance status or comorbidity, local disease only**

- Cancer-related symptoms present
  - \(\text{AFP} > 4,000 \text{ ng/mL, surface antigen positive (Biopsy not required)}\)
  - \(\text{AFP} > 400 \text{ ng/mL, surface antigen negative (Biopsy not required)}\)

- Cancer-related symptoms absent
  - \(\text{AFP} < 400 \text{ ng/mL, surface antigen negative or } \text{AFP} < 4,000 \text{ ng/mL, hepatitis B surface antigen positive}\)

- Consider biopsy
- HCC confirmed

**Metastatic disease**

- \(\text{AFP} < 400 \text{ ng/mL, surface antigen negative or } \text{AFP} < 4,000 \text{ ng/mL, hepatitis B surface antigen positive}\)

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\(^e\)See Child-Pugh Score (HCC-A).

\(^g\)Ablation or embolization options: radiofrequency, alcohol, cryotherapy, microwave or embolization (chemoembolization, radioembolization, bland embolization)

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


\(^m\)Contraindicated in cases of main portal thrombosis or Child-Pugh Class C.

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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>
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<tr>
<td>Prothrombin time prolonged (sec)</td>
<td>1-4</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
</tr>
<tr>
<td>• For primary biliary cirrhosis</td>
<td>1-4</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

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### Gallbladder Cancer

#### PRESENTATION

- **Incidental finding at surgery**
  - Intraoperative staging
  - Biopsy
  - Consider extended cholecystectomy

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

#### POSTOPERATIVE WORKUP

- CT/MRI, chest x-ray
- Observe

#### PRIMARY TREATMENT

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

- **Unresectable**
  - 5-FU-based chemotherapy/RT
  - or Supportive care

- **Hepatic resection + lymphadenectomy ± bile duct excision**
- **5-FU-based chemotherapy/RT**
- or Supportive care

---

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

- Depends on expertise of surgeon and/or resectability. If resectability not clear, close incision.
- Include porta hepatis, gastrohepatic ligament, retroduodenal. Patients with nodal disease outside this area are unresectable.
- There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

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Gallbladder Cancer

**PRESENTATION**
- Mass on imaging
- Jaundice
- Metastases

**WORKUP**
- CT/MRI
- Liver function tests
- Chest x-ray
- Surgical consultation
- Assessment of hepatic reserve
- Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography/MR cholangiography
- Biopsy

**PRIMARY TREATMENT**
- Resectable
  - Cholecystectomy + en bloc hepatic resection + lymphadenectomy ± bile duct excision
- Unresectable
  - 5-FU-based chemotherapy/RT
  - or Supportive care
  - Biopsy
  - Biliary decompression
  - Clinical trial
  - Gemcitabine and/or 5-FU-based regimen
  - 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.

GALL-2

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**GALL-3**

**Gallbladder Cancer**

**ADJUVANT TREATMENT**

- Consider 5-FU-based or gemcitabine chemotherapy ± RT\(^c\) (except T1, N0)

**SURVEILLANCE**

- Consider imaging every 6 mo for 2 y\(^9\)

For relapse, see Workup of the following initial Clinical Presentations:

- Mass on Imaging or Jaundice or Metastases
  (See GALL-2)

\(^c\) There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

\(^9\) 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.
Intrahepatic Cholangiocarcinoma

### Presentation

**Isolated intrahepatic mass**
- Biopsy
  - Adenocarcinoma
  - **(See NCCN Occult Primary Guidelines)**

### Workup

- **H&P**
- **CT/MRI**
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Upper and lower endoscopy
- Surgical consultation

### Primary Treatment

- **Resectable**
  - **± ablation**

- **Unresectable**
  - **Options:**
    - Supportive care
    - RT ± chemotherapy with 5-FU-based regimen or gemcitabine
    - Chemotherapy** with 5-FU-based regimen or gemcitabine

- **Metastatic**
  - **Options:**
    - Supportive care
    - Clinical trial
    - Chemotherapy** with 5-FU-based regimen or gemcitabine

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**a** Recommend delayed contrast-enhanced imaging.

**b** Consult with multidisciplinary team.

**c** There are limited clinical trial data to define a standard regimen. Participation in clinical trials is encouraged.
**Status post resection**

- **Microscopic margins or Residual local disease**<sup>b</sup> (R1, R2 resection)
  - Consider reresection or Ablation or RT ± chemotherapy with 5-FU-based regimen or gemcitabine

- **No residual local disease** (R0 resection)

**Consider imaging every 6 mo for 2 y**<sup>d</sup>

**For relapse, see initial Workup (INTRA-1)**

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

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

---

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Extrahepatic Cholangiocarcinoma

**PRESENTATION**
- Pain
- Jaundice
- Abnormal LFTs
- Obstruction or abnormality on ultrasound

**WORKUP**
- H&P
- CT/MRI
- Endoscopic retrograde cholangiopancreatography/ percutaneous transhepatic cholangiography/ MR cholangiography
- Consider vascular assessment
- Consider CEA
- Consider CA 19-9
- Liver function tests
- Surgical consultation
- Consider endoscopic ultrasound (EUS)

**PRIMARY TREATMENT**

**Resectable**
- Surgical exploration
- Consider laparoscopic staging

**Unresectable**
- Biliary drainage, if indicated
- Surgical bypass
- Stent

**Metastatic**
- Biliary drainage, if indicated
- Stent

**5-FU-based chemotherapy/RT**
- (brachytherapy or external beam)
- or
- Clinical trial
- or
- Supportive care
- or
- Chemotherapy with 5-FU-based regimen or gemcitabine

**Unresectable, see above**

**Resected**

**Supportive care**
- or
- Clinical trial
- or
- Chemotherapy with 5-FU-based regimen or gemcitabine

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

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**Extrahepatic Cholangiocarcinoma**

### Secondary or Adjuvant Treatment

| Resected, positive margin\(^e\) or Carcinoma in situ at margin or Positive regional nodes (R1, R2 resection) | Consider 5-FU–based chemotherapy/RT\(^d\) (brachytherapy or external beam) | Consider imaging every 6 mo for 2 y\(^f\) | For relapse, see initial Workup (EXTRA-1) |
| Resected, negative margin, Negative regional nodes (R0 resection) | Observe or 5-FU–based chemotherapy/RT |

\(^d\) There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

\(^e\) Multidisciplinary team review.

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

---

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### Staging

**Table 1**

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

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Stage Grouping</th>
</tr>
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<tbody>
<tr>
<td>TX</td>
<td>Stage I</td>
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<tr>
<td>T0</td>
<td>T1 N0 M0</td>
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<tr>
<td>T4</td>
<td>I1C Any T N1 M0</td>
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<tr>
<td>Any T</td>
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<table>
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<th>Regional Lymph Nodes (N)</th>
<th>Stage Grouping</th>
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<tbody>
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<td>N2</td>
<td>T3 N0 M0</td>
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<table>
<thead>
<tr>
<th>Distant Metastasis (M)</th>
<th>Stage Grouping</th>
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<td>M2</td>
<td>T3 N0 M0</td>
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<table>
<thead>
<tr>
<th>Histologic Grade (G)</th>
<th>Stage Grouping</th>
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</thead>
<tbody>
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<td>GX</td>
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</tr>
<tr>
<td>G3</td>
<td>T3 N0 M0</td>
</tr>
<tr>
<td>G4</td>
<td>I1B T4 N0 M0</td>
</tr>
<tr>
<td>G5</td>
<td>I1C Any T N1 M0</td>
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<table>
<thead>
<tr>
<th>Fibrosis Score (F)</th>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>Stage I</td>
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<td>T1 N0 M0</td>
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<tr>
<td>F2</td>
<td>T2 N0 M0</td>
</tr>
<tr>
<td>F3</td>
<td>T3 N0 M0</td>
</tr>
</tbody>
</table>

**Primary Tumor (T)**
- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **T1**: Solitary tumor without vascular invasion
- **T2**: Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
- **T3**: Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
- **T4**: Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

**Regional Lymph Nodes (N)**
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

**Distant Metastasis (M)**
- **MX**: Distant metastasis cannot be assessed
- **M0**: No distant metastasis
- **M1**: Distant metastasis

**Histologic Grade (G)**
- **GX**: Grade cannot be assessed
- **G1**: Well differentiated
- **G2**: Moderately differentiated
- **G3**: Poorly differentiated
- **G4**: Undifferentiated

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

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### Table 2

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

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Stage Grouping</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;X&lt;/sub&gt;</td>
<td>T&lt;sub&gt;is&lt;/sub&gt;</td>
</tr>
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<th>Regional Lymph Nodes (N)</th>
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### Staging, MS, References

#### Histologic Grade (G)
- G<sub>X</sub> Grade cannot be assessed
- G<sub>1</sub> Well differentiated
- G<sub>2</sub> Moderately differentiated
- G<sub>3</sub> Poorly differentiated
- G<sub>4</sub> 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, Sixth edition* (2002) published by Springer-Verlag New York. (For more information, visit [www.cancerstaging.net](http://www.cancerstaging.net).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.
Table 3
American Joint Committee on Cancer (AJCC) TNM Staging for Extrahepatic Bile Duct Tumors*

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<th>Primary Tumor (T)</th>
<th>Stage Grouping</th>
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<tr>
<td>M1</td>
<td>Distant metastasis</td>
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*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.
Hepatobiliary cancers are both common and highly lethal worldwide. Hepatocellular carcinoma is the most common of the hepatobiliary malignancies. However, in the United States, the incidence of hepatobiliary cancer is relatively low, with approximately 25,030 patients estimated to be diagnosed in 2005. The incidence of hepatocellular carcinoma is increasing probably because of the current epidemic of hepatitis C in the United States (1.8% of population). Along with summaries of the NCCN algorithm for the subtypes of hepatobiliary cancer, this manuscript includes a brief discussion of the epidemiology, pathology, etiology, staging, diagnosis, and treatment of each subtype as well as recommended readings. By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically useful and relevant information. The NCCN Hepatobiliary Cancers Panel is in favor of pathology synoptic reports from the College of American Pathologists (CAP). The CAP protocol information can be accessed at: http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

On January 1, 2004, the Commission on Cancer (COC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, pathologists should familiarize themselves with these documents. The CAP protocols comply with the COC requirements.

Hepatocellular Carcinoma

Epidemiology and Risk Factors

Hepatocellular carcinoma is the seventh most common cancer in the world and the most common cancer diagnosed in men, with a male-female ratio of 7:1 in high-incidence regions, such as China and Korea. The mean age at diagnosis worldwide is between 50 and 60 years.

The incidence of hepatocellular carcinoma has been increasing in the United States mainly because of the rising incidence of hepatitis
Currently, 3 to 4 million persons are infected with hepatitis C; it is estimated that 5% to 30% of these patients will develop chronic liver disease and of these, 30% will progress to cirrhosis. Once patients develop cirrhosis, the risk of hepatocellular carcinoma is 1% to 2% per year. Over the next 20 years, the number of patients with hepatitis C virus who progress to cirrhosis will double. Most patients who develop hepatocellular cancer in association with chronic hepatitis C virus infection have biopsy-proven cirrhosis or severe active hepatitis. The latency period between hepatitis B or C exposure and the development of hepatocellular cancer varies between 30 and 50 years. A recent report indicates that the pathogenetic mechanism of hepatocarcinogenesis may differ between hepatitis B-associated and hepatitis C--associated hepatocellular carcinoma. Chronic alcohol use by patients with hepatitis C may decrease the latency period between exposure and the development of cancer.

Geographic variations exist for hepatitis; this fact suggests differences in the severity of cirrhosis and the development of hepatocellular cancer. Hepatocellular cancer incidence also varies geographically, secondary to exposure to carcinogens, including aflatoxin B1, which is an important natural chemical product of the Aspergillus fungus found in various grains.

**Diagnosis and Initial Workup**

Hepatocellular cancer typically produces nonspecific symptoms such as jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Paraneoplastic syndromes also occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.

The level of alpha-fetoprotein (AFP) is elevated in approximately 60% to 90% of patients with hepatocellular cancer and varies by geographic distribution. The highest percentage of AFP-secreting tumors is found in Asia. Proposed surveillance for the early detection of hepatocellular carcinoma among high-risk populations includes liver ultrasonography every 3 to 6 months and evaluation of alkaline phosphatase, albumin, and AFP. It is not yet clear if early detection of hepatocellular cancer with routine screening improves the percentage of patients detected with disease at a potentially curative stage, but high-risk chronic hepatitis C virus--infected patients should be considered for ongoing recurrent screening until these issues have been resolved.

For patients with a rising AFP level but with negative liver imaging studies, screening should continue every 3 months. For patients with a suspicious mass, the evaluation should include a history and physical examination, complete blood count (CBC) and platelets, hepatitis screening, liver chemistries, prothrombin, albumin, protein, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), and chest radiograph. Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed to better define the extent and number of primary lesions, vascular anatomy, vessel involvement, involvement with tumor, and extrahepatic disease. Helical CT or MRI should include early arterial phase enhancement.

The level of des-gamma-carboxy prothrombin protein induced by vitamin K absence (PIVKA-II) is also increased in many patients with hepatocellular carcinoma. However, as is true with AFP, PIVKA-II may be elevated in patients with chronic hepatitis. Initial findings of tumor and liver function, such as the Child-Pugh score and whether there is evidence of metastatic disease, are important management issues. A recent study found that preoperative serum C-reactive protein (CRP) levels can predict early recurrence and poor
prognosis in patients with hepatocellular cancer who undergo resection. Of patients in the CRP-positive group, 75% had recurrence 1 year after surgery.16

Pathology and Staging
As described by Eggel's classification, hepatocellular carcinoma includes nodular, massive, and diffuse types. Histologic examination reveals trabecular, pseudoglandular or acinar, compact, scirrhous, clear cell, and fibrolamellar types. The fibrolamellar variant is associated with a better prognosis, is not associated with cirrhosis, and may be resectable more often.

The sixth edition of the AJCC (American Joint Committee on Cancer) Cancer Staging Manual presents a new simplified classification for hepatocellular cancer (see Table 1), which is identical to the UICC (the Union Internationale Contre le Cancer) staging system.17 Based on a recent international multicenter study,18 the new AJCC/UICC staging accounts for the presence or absence of severe fibrosis/cirrhosis because of its significant value on prognosis. It is useful in predicting prognosis after resection.

Other scoring systems based on clinical and radiographic factors are more applicable to predicting prognosis of patients with unresectable disease. These include the CLIP (Cancer of the Liver Italian Program), the Okuda, and the BLCL (Barcelona Clinic Liver Cancer) scoring systems.19 The CLIP score has been prospectively validated and is currently the most commonly used staging system for unresectable hepatocellular carcinoma associated with liver disease.20

Management
Surgical Assessment and Evaluation. Surgery, including transplantation, remains the only curative modality for hepatocellular cancer.21-24 Presurgical assessment may require additional imaging to rule out metastatic disease and to better assess the extent of intrahepatic disease. Determination of liver reserve and comorbid conditions are essential in the assessment of potential surgical candidates.

Biopsy can be considered for patients with potentially resectable, operable disease who have (1) an AFP of less than 400 ng/mL and are negative for hepatitis B surface antigen, or (2) for those who have an AFP of less than 4000 ng/mL and are positive for hepatitis B surface antigen. Alternatively, surgical evaluation is an appropriate strategy, which includes a discussion of surgical treatment with the patient and determination of whether the patient is amenable to surgery. As mentioned, the presence of hepatitis can increase AFP in the absence of hepatocellular cancer. For selected low-risk patients with hepatitis C who have completely resected tumors and good performance status, interferon-based therapy or antiviral therapy may be considered.

The treatment of choice for noncirrhotic patients is surgical resection whenever possible.25 Resection of liver tumors in the cirrhotic patient is more controversial.26 The best indication for resection is in cirrhotic patients with small peripheral lesions and preserved liver function (Child-Pugh class A). Treatment paradigms have been developed that include Child-Pugh classification, fibrosis score, and the determination of the future liver remnant (ie, the amount of the remaining viable liver after resection) to determine the safety of resectability. If deemed unsafe for resection, small hepatocellular carcinoma tumors are treated with ablation or liver transplantation.1

The Child-Pugh classification may be inaccurate in truly assessing the risk of postresection liver failure in cirrhotic patients with
hepatocellular carcinoma. The hepatic venous pressure gradient (HVPG) may be a useful measurement of potential hepatic decompensation in patients with cirrhosis after resection of hepatocellular cancer. Several other tests (including galactose elimination, aminopyrine clearance, and lidocaine metabolite [MEGX] clearance) can be combined with the HVPG and with CT volumetry to calculate the percentage of liver that will be resected as well as the liver remnant (which is termed functional liver reserve).

A recent multicenter study compared the clinicopathologic characteristics and outcomes in patients with hepatocellular carcinoma who were treated with surgical resection in the United States, France, and Japan. Despite the significant difference among the three patient populations in the median tumor size and underlying liver damage (such as hepatitis C serology and severe fibrosis/cirrhosis in the adjacent liver), the post-resection 5-year survival of patients was not statistically different among the United States, France, and Japan (31% versus 31% versus 41%, respectively; P = .3). A recent survey in Japan found that operative mortality was 0.9% and the 5-year survival rate after surgery was 52%. However, future studies using uniform criteria on histopathologic differences are needed to allow better comparison of results.

Portal vein embolization (PVE) has been used to induce hypertrophy of the anticipated liver remnant after a major hepatic resection. PVE is safe (< 5% complication rate), causes little peripoortal reaction and fibrosis that would be problematic during a hepatic resection, and produces durable portal vein occlusion. In cirrhotic patients or patients with chronic liver disease, PVE decreases the incidence of postoperative complications, length of total hospital stay, and incidence of liver dysfunction. The selective use of PVE may enable safe and potentially curative hepatic resection, including extended hepatectomy when necessary, in a subset of patients with cirrhosis and hepatocellular cancer who would have otherwise been marginal candidates for resection based on their chronic liver disease.

In liver transplantation recipients, 5-year survival has been reported to be as high as 75%, which exceeds survival after resection or ablation. The United Network for Organ Sharing (UNOS) criteria for liver transplant include patients who are not candidates for resection who have (1) a single tumor that is 5 cm or less in diameter, or who have 2 to 3 tumors, each 3 cm or less in diameter; (2) no macrovascular invasion; and (3) no extrahepatic spread to surrounding lymph nodes, lungs, abdominal organs, or bone. Liver transplantation is an option for the cirrhotic patient with hepatocellular carcinoma who will not tolerate liver resection and fulfills current UNOS criteria. Recent reports have suggested that patients with tumor size up to 6.5 cm may result in comparable outcomes after transplantation. The model for end-stage liver disease (MELD) allocation system was designed to give priority status for the sickest patients to receive livers and does not appear to compromise survival.

The single uniform negative prognostic finding for transplantation is histopathologic evidence of vascular invasion. There are conflicting data regarding the role of ablative or resection therapy as a bridge to transplantation, although percutaneous radiofrequency ablation appears useful. The major limit to transplantation is the lack of donor organs. Living donor liver transplantation is being performed with greater frequency in the United States with results similar to those individuals undergoing cadaveric donor transplantation.
Patients With Unresectable and Inoperable Disease or Those Who Decline Surgery. Alternative therapies for patients with unresectable disease or those who decline surgery include clinical trial, ablative therapy (e.g., radiofrequency, alcohol, cryotherapy, microwave), chemoembolization, chemotherapy plus radiation in a clinical trial, conformal radiation, radiotherapeutic microspheres, supportive care, and systemic or intra-arterial chemotherapy in a clinical trial.\(^{41-56}\)

Patients with inoperable disease are those who should not undergo surgery because of performance status, comorbidity, or extent of liver disease. Options for patients with cancer-related symptoms include clinical trial, ablative therapy (e.g., radiofrequency alcohol, cryotherapy, microwave), chemoembolization (contraindicated in cases of main portal thrombosis or Child-Pugh class C score), conformal or stereotactic radiation, radiotherapeutic microspheres, and supportive care. Chemoembolization, ablation, and conformal or stereotactic radiotherapy have produced local control in some patients. All of these modalities have limitations, such as the size and number of lesions, potential toxicities, and a questionable effect on long-term survival. For patients without cancer-related symptoms, options include participation in a clinical trial or ablation of small-volume disease. Patients with metastatic disease may be offered supportive care or therapy as part of a clinical trial. Unfortunately, there is no proven advantage of single-agent or combination chemotherapy in these patients.

Surveillance

Follow-up consists of imaging studies every 3 to 6 months for 2 years, then annually; AFP levels, if initially elevated, can be measured every 3 months for 2 years, then every 6 months. If the patient's disease progresses, the initial workup guidelines should be consulted again.

Gallbladder Cancer

Epidemiology and Risk Factors

Gallbladder cancer is the most common of the biliary tract malignancies, accounting for approximately 5000 newly diagnosed cases in the United States.\(^2\) Gallbladder carcinoma is diagnosed most frequently in individuals between ages 70 and 75 years and shows a 3:1 predilection for women over men.\(^{57-60}\) Worldwide, the highest prevalence of gallbladder cancer is seen in Israel, Mexico, Chile, Japan, and among Native American women, particularly those living in New Mexico.\(^4\)

The greatest risk factor for the development of gallbladder cancer is the presence of gallstones, in particular those associated with chronic cholecystitis. Other risks include the presence of a calcified gallbladder (porcelain gallbladder), gallbladder polyps, typhoid carriers, and carcinogens (e.g., azotoluene, nitrosamines).\(^{61}\)

Diagnosis and Initial Workup

Unfortunately, most gallbladder cancers are diagnosed at advanced stages when the tumor is unresectable. Patients often present with nonspecific symptoms, such as abdominal pain, weight loss, anorexia, nausea, acute cholecystitis, and jaundice. Up to 20\% of cancers are diagnosed incidentally at the time of gallbladder surgery. No specific laboratory or marker tests are available to assist in making the diagnosis.

A suspicious mass detected on ultrasound should warrant further evaluation, including CT or MRI, liver function tests, chest radiograph, and staging laparoscopy. Laparoscopy can be done in conjunction with surgery if no distant metastasis is found. If a polypoid mass is seen on ultrasound, the cholecystectomy should be performed by a surgeon who is prepared to do a cancer
operation. For patients presenting with jaundice, additional workup should include endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or magnetic resonance (MR) cholangiography.

**Pathology and Staging**
Most gallbladder cancers are adenocarcinomas. Histologic subtypes include papillary, nodular, and tubular variations. The best prognosis is seen in individuals with well-differentiated cancers and associated metaplasia discovered incidentally. In addition, papillary tumors are often less invasive.

The AJCC has developed staging criteria for gallbladder cancer (see Table 2). Although other staging classifications have been used, no single staging system encompasses all of the components of gallbladder cancer, including pathology.

**Management**

**Surgical Assessment and Evaluation.** As is true for all hepatobiliary cancers, surgery remains the only curative modality for gallbladder cancer. The algorithm distinguishes between patients (1) in whom cancer is found incidentally at surgery or on pathologic review; and (2) those who exhibit a mass on ultrasound, present with jaundice, or present with metastases. Within these groups (except for metastases), the algorithm differentiates between those with resectable disease and those with unresectable disease.

Patients who present with an incidental finding of cancer at surgery and are deemed resectable may be treated with cholecystectomy, en bloc hepatic resection, and lymphadenectomy with or without bile duct excision. This approach may improve overall survival. A similar approach is appropriate for patients who present with a mass on ultrasound or with jaundice, surgery is recommended if the mass is deemed resectable after more extensive evaluation. For patients with mass on imaging, this evaluation includes CT or MRI, liver function tests, chest radiograph, surgical consultation, and assessment of hepatic reserve. For patients with jaundice, this evaluation includes CT or MRI, liver function tests, chest radiograph, surgical consultation, and endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography/MR cholangiography.

Among patients in whom gallbladder cancer is diagnosed as an incidental finding on pathologic review, those with T1a lesions may be observed if the margins were negative (which assumes the gallbladder was removed intact); if the gallbladder was not removed intact, then patients should be considered for surgery. For patients with T1b or greater lesions, surgery is recommended for resectable lesions, after CT/MRI and chest x-ray confirm the absence of metastatic disease. If resectable, patients should receive hepatic resection and lymphadenectomy with or without bile duct excision. In addition, for those who undergo laparoscopic operations, resection of port sites should be considered because of the risk of local recurrence at these sites.

Adjuvant 5-fluorouracil (5-FU)--based chemotherapy and radiation is recommended as postoperative therapy for resectable patients, except those with T1, N0 disease. A small trial showed the 5-year survival rate was improved (64% versus 33%) in completely resected patients (21) receiving concurrent 5-FU plus external-beam radiation. Unfortunately, because there are relatively few patients with gallbladder cancer, only one randomized phase III trial of adjuvant therapy has been conducted. This trial assessed postoperative adjuvant chemotherapy using mitomycin/5-FU; the
5-year overall survival rate was increased with adjuvant chemotherapy (26% versus 14%, \(P = .03\)) in patients with gallbladder carcinoma.\(^{63,64}\)

**Patients With Unresectable Tumor and Without Obvious Metastatic Disease.** Patients with unresectable tumor, without obvious metastatic disease, and without jaundice may benefit from a regimen of 5-FU-based chemotherapy and radiation similar to the regimen used adjuvantly. However, overall survival of such patients remains poor. Because there is no definitive treatment with proven survival benefit, supportive care or enrollment in a clinical trial are appropriate options for patients with unresectable disease. A recent small study (8 patients) showed that oral capecitabine was effective for unresectable gallbladder carcinoma; 2 patients had a complete response and 50% of patients responded. The median survival time was 9.9 months.\(^{65}\)

For jaundiced patients whose disease is unresectable after preoperative evaluation, a biopsy should be performed to confirm the diagnosis. In such patients, biliary decompression would be an appropriate palliative procedure and should be done before instituting chemotherapy (gemcitabine and/or 5-FU-based regimen). Participation in a clinical trial or supportive care is also appropriate. Biliary decompression followed by chemotherapy can result in improved quality of life.\(^{64}\)

**Surveillance**

Follow-up consists of imaging studies every 6 months for 2 years. If the patient's disease progresses, the initial workup guidelines should be consulted again.

**Cholangiocarcinomas**

**Epidemiology and Risk Factors**

Although cholangiocarcinomas are diagnosed throughout the biliary tree, they are usually classified as intrahepatic or extrahepatic.\(^{58,61,66-69}\)

Intrahepatic cholangiocarcinomas have been called “peripheral carcinomas,” because they arise from intrahepatic small-duct radicals. Extrahepatic cholangiocarcinomas encompass hilar carcinomas (including Klatskin's tumors) and may occur anywhere within the major hepatic ducts, in the region of the junction of the right and left hepatic ducts, and in the common hepatic and the common bile ducts (including the intrapancreatic portion of the common bile duct).

Extrahepatic cholangiocarcinomas are the most common type. Overall, most individuals with extrahepatic cholangiocarcinoma are diagnosed between ages 60 and 70 years. Incidence is equal in men and women. The worldwide distribution of cases is similar to gallbladder cancer, with the greatest incidence occurring in Israel, Japan, and among Native Americans.

Although the exact etiology of cholangiocarcinoma in the United States is often unknown, there are well-established risk factors for the development of the disease. These risk factors include hepatolithiasis (with or without infection or stasis), ulcerative colitis, sclerosing cholangitis, choledochal cysts, chemical carcinogens (eg, nitrosamines), and liver fluke infections.\(^{51}\)

**Diagnosis and Initial Workup**

Most patients with cholangiocarcinoma present with jaundice. Symptoms may be nonspecific and may include weight loss, anorexia, abdominal pain, and fever. Most patients are initially evaluated with a
complete history and physical examination, liver function studies, and CT scan or MRI. For intrahepatic cholangiocarcinomas, upper and lower endoscopy is also recommended as indicated. The evaluation for extrahepatic cholangiocarcinomas should include a delayed-contrast CT scan, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or MR cholangiography. For vascular assessment, an angiogram may also be needed; endoscopic ultrasound should be considered.

Early surgical consultation with a multidisciplinary team as part of the workup is recommended for assessment of resectability in both types of cholangiocarcinomas. Both carcinoembryonic assay (CEA) and CA 19-9 levels may be elevated in patients with cholangiocarcinomas. Other than an elevation in bilirubin, there are no specific laboratory parameters to assist in the diagnosis.

Pathology and Staging
Most cholangiocarcinomas are adenocarcinomas. Histologic subtypes include papillary, nodular, and sclerosing variants. An improved prognosis is associated with the papillary histology.

The AJCC has developed staging criteria for cholangiocarcinomas (see Table 1 and Table 3) comparable to the UICC staging system. Other staging systems, which include the extent of invasion into blood vessels and other organs have been used, particularly in Japan. The Bismuth-Corlette classification describes the extent of biliary ductal involvement by the tumor. Jarnagin and colleagues have developed a useful preoperative staging system for hilar cholangiocarcinoma that predicts respectability, likelihood of metastatic disease, and survival.

Management
Because the management of intrahepatic and extrahepatic cholangiocarcinomas differs, separate algorithms have been created for the two types and are summarized in the next section.

**Intrahepatic Cholangiocarcinoma.** Patients who have undergone a resection (R0) of their tumor with or without ablation with negative margins may be followed up with observation, because there is no definitive adjuvant regimen to improve their overall survival. Adjuvant chemotherapy can be administered if appropriate clinical trials are available.

For individuals whose disease is resectable but who have microscopic positive margins after resection (R1 or R2), it is essential for a multidisciplinary team to review the available options on a case-by-case basis. These options might include (1) consider additional resection; (2) ablative therapy; or (3) combined radiation with or without chemotherapy using either 5-FU--based regimen or gemcitabine. As previously mentioned, no randomized clinical trials have provided definitive data to define a standard regimen. Additional chemotherapy should be considered only in the context of a clinical trial.

For patients with unresectable disease, the options include (1) supportive care; (2) ablative therapy with cryotherapy, radiofrequency, or microwave; (3) radiation with or without chemotherapy using either 5-FU--based regimen or gemcitabine; or (4) chemotherapy with either 5-FU--based regimen or gemcitabine.

For patients with metastatic disease, options include (1) supportive care; (2) clinical trials; or (3) chemotherapy with either 5-FU--based regimen or gemcitabine.

**Extrahepatic Cholangiocarcinoma.** The surgical procedures for resectable extrahepatic cholangiocarcinoma are outlined in the algorithm. Patients with disease of the proximal third of the duct...
Those with metastatic disease should undergo biliary drainage by stent placement. Further options include clinical trial, best supportive care, or chemotherapy with either 5-FU--based regimen or gemcitabine, depending on performance status.\textsuperscript{77} Given the lack of clinical trial data, there is no standard regimen for these patients, although new therapies appear encouraging.\textsuperscript{78,79}

**Surveillance**

Follow-up consists of imaging scans every 6 months for 2 years. If the patient's disease progresses, the initial workup information can be consulted again.

**Disclosures for the NCCN Hepatobiliary Cancers Guidelines Panel**

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Adolor, Amgen, Bristol-Myers Squibb, Eli Lilly, Genentech, Genzyme, Imclone, MDS Nordion, NexCura, Novartis, Pfizer, Roche, Sanofi-Aventis, Tyco, and US Surgical. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.
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Hepatobiliary Cancers


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