National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Hepatobiliary Cancers

Version 1.2018 — February 14, 2018

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NCCN Guidelines Version 1.2018 Panel Members
Hepatobiliary Cancers

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*Discussion section writing committee
ξ Bone marrow transplantation
ϕ Diagnostic radiology

NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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 indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2018 of the NCCN Guidelines for Hepatobiliary Cancers from Version 4.2017 include:

Hepatocellular Carcinoma

HCC-1

- **Patients a risk for HCC**
  - **5th sub-bullet was revised: "Stage 4 primary biliary ~~cirrhosis~~ *cholangitis*"**
  - **Footnote "f" was added: "Beuers U, Gershwin M, Gish R, et al. Changing Nomenclature for PBC: From 'Cirrhosis' to 'Cholangitis' Am J Gastroenterol 2015;110(11):1536–1538."**
- **Footnote "j" about alpha fetoprotein (AFP) was revised: "AFP is considered optional for ~~surveillance~~ *screening*. (See Principles of Imaging, HCC-A)."**
- **AFP Positive or US Nodule(s) ≥10 mm**
  - **"Abdominal multiphasic CT or MRI" statement was removed.**
  - **A footnote was removed: "Multiphase CT: Pre-contrast is suggested. Late hepatic arterial phase (AP), portal venous phase (PVP), and delayed phase (DP) are required." (Also for HCC-2)**
  - **A footnote was removed: "Multiphase MRI: Pre-contrast. Late hepatic AP, PVP, and DP are required." (Also for HCC-2)**

HCC-2

- **Additional Workup**
  - **A footnote linking to the Principles of Biopsy section was added to this statement: "Individualized workup, which may include additional imaging or biopsy, as informed by multidisciplinary discussion"**

HCC-4

- **Treatment**
  - **3rd bullet was revised: "~~External-beam radiation therapy (EBRT) (category 2B)~~ *Radiation therapy"* (Also for HCC-5 and HCC-6)**
  - **Footnote "bb" was revised: "Case series and single-arm studies *demonstrate* ~~suggest~~ safety and ~~possible~~ efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E)." (Also for HCC-5 and HCC-6)**
- **Surveillance**
  - **Footnote "cc" was revised: "Multiphasic abdominal*/pelvic* MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A)." (Also for HCC-5)**

HCC-5

- **Surveillance**
  - **Regorafenib (Child-Pugh Class A only) (Category 1)**
    - ◊ **Footnote"jj" was added: "Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Bruix J, Qin S, Merle P, et al. Lancet 2017;389:56-66." (Also for HCC-6)**

Continued

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HCC-A (1 of 3) Principles of Imaging

- **Imaging diagnosis of HCC**
  - 1st bullet, 5th sentence was revised: "Major imaging features of HCC include arterial phase hyperenhancement, venous *or delayed* phase washout appearance and capsule appearance, and threshold growth.
  - 2nd bullet, 2nd sentence was revised: "In these patients, the prevalence of HCC is sufficiently high ~~enough~~ that lesions meeting imaging criteria for HCC have close to a 100% probability of being HCC."
  - 4th bullet was added: "Quality of MRI is dependent on patient compliance."
- **Extrahepatic staging**
  - 1st bullet, was revised: "Frequent sites of extrahepatic metastases from HCC include lungs, ~~and~~ bone *and lymph nodes*. Adrenal and peritoneal metastases also may occur. For this reason, chest CT, complete imaging of abdomen and pelvis with contrast-enhanced CT or MRI, and selective use of bone scan when skeletal symptoms are present are recommended at initial diagnosis of HCC and for monitoring disease while on the transplant wait list *or during* or after treatment *for response assessment*. Chest CT may be performed with contrast if concurrently acquired with contrast-enhanced abdominal/pelvic CT. If MRI is performed, chest CT may be acquired without contrast."

HCC-A (2 of 3) Principles of Imaging

- **Imaging protocol for response assessment after treatment**
  - Statement was revised: "~~Multiphasic~~ CT of the chest and multiphasic CT or MRI of the abdomen *and pelvis* ~~CT or MRI~~ are the preferred modalities as they reliably assess intranodular arterial vascularity, a key feature of residual or recurrent tumor. Overall nodule size does not reliably indicate treatment response since a variety of factors may cause a successfully treated lesion to appear stable in size or even larger after treatment."

HCC-A (3 of 3) Principles of Imaging

- Reference "6" was added: "Fowler KJ, Potretzke TA, Hope TA, et al. LI-RADS M (LR-M): definite or probable malignancy, not specific for hepatocellular carcinoma. Abdom Radiol (NY) 2018; 43:149-157."

HCC-B Principles of Biopsy

- Initial biopsy
  - 3rd sub-bullet was revised: "*Confirmation of metastatic disease could change* clinical decision-making. ~~in metastatic disease should be considered~~"

HCC-E (1 of 3) Principles of Locoregional Therapy

- **Arterially Directed Therapies**
  - 4th bullet was revised: "Arterially directed therapies ~~are relatively contraindicated~~ *in highly selected* patients *have been shown to be safe in the presence of limited tumor invasion* ~~with main~~ of the portal vein. ~~thrombosis and Child-Pugh Class C~~."

HCC-E (2 of 3) Principles of Locoregional Therapy

- ~~External-beam~~ Radiation Therapy (~~EBRT~~) title was revised.
  - 2nd bullet was revised: "All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, intensity-modulated radiation therapy [IMRT], or stereotactic body radiation therapy [SBRT]). *Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity."*

Continued

HCC-E (2 of 3) Principles of Locoregional Therapy continued

- 5th bullet was added:"Dosing for SBRT is generally is 30-50 Gy in 3-5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated." (Also for GALL-C)
- 7th bullet was revised: "SBRT (1–5 fractions) is often used for patients with 1 to 3 tumors. SBRT could be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver and liver radiation tolerance can be *respected*."

Gallbladder Cancer

GALL-1

- A bullet was added under unresectable disease: "Microsatellite instability (MSI) testing" (Also for GALL-2)
- Primary treatment, unresectable disease
  - 3rd bullet was revised: "*EBRT with concurrent* fluoropyrimidine ~~chemoradiation~~" (Also for GALL-2, GALL-3, and GALL-4)
  - A bullet for "EBRT" option for unresectable disease was revised: "~~EBRT~~ *Radiation therapy*"(Also for GALL-2, GALL-3, and GALL-4)
  - A bullet: "Pembrolizumab (Only for MSI-H tumors)" for unresectable disease was added. (Also for GALL-2, GALL-3, and GALL-4)
  - A footnote was added: "There are limited clinical trial data to support pembrolizumab in this setting. Personalized, molecularly matched combination therapies for treatment-naïve, lethal malignancies: the I-PREDICT Study. Sicklick JK, Leyland-Jones B, Kato S, et al. J Clin Oncol 2017;35:2512." (also for GALL-2, GALL-3, GALL-4, INTRA-1, and EXTRA-1)
- Footnote "c" was revised: "If there is evidence of locoregionally advanced disease (big mass invading liver and/or nodal disease, *including cystic duct node positive)* consideration to neoadjuvant chemotherapy should be given, largely to rule out rapid progression and avoid futile surgery. *Neoadjuvant chemotherapy regimens include: 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."* (also for GALL-2, GALL-3, and GALL-4)

GALL-2

- Primary Treatment
  - Footnote "k" was removed and combined with footnote "c": "Neoadjuvant chemotherapy regimens include: 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."

GALL-3

- Biopsy for unresectable disease
  - A bullet for "MSI testing" was added.

GALL-4

- Jaundice for unresectable disease
  - A bullet for "MSI testing" was added.
- Metastatic disease
  - A bullet for "MSI testing" was added.

GALL-5

- Resected, positive margin (R1) or Resected gross residual disease (R2) or Positive regional nodes
  - Treatment statement was revised: "~~Consider~~ Fluoropyrimidine chemoradiation followed by additional fluoropyrimidine-based or gemcitabine-based chemotherapy or Fluoropyrimidine-based or gemcitabine-based chemotherapy+/- *fluoropyrimidine chemoradiation* ~~for positive regional lymph nodes~~ or Clinical trial"
    - ◊ Footnote "s" was added: "Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622.
  - Footnote "p" was revised: "*Management of patients* with R1 or R2 resections should be evaluated by a multidisciplinary team."
  - Footnote "r" was revised: "~~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. Oncologist 2008;13:415-423). *The phase 3 BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al: Adjuvant Capecitabine for Biliary Tract Cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4006."*

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GALL-A Principles of Imaging

- **Gallbladder Cancer**
  - 5th bullet was revised: "CT of the chest with or without contrast and *multiphasic* contrast-enhanced CT or MRI of the abdomen and pelvis are recommended for follow-up imaging."

GALL-C Principles of Radiation Therapy

- 1st bullet was added: "Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity."
- **Adjuvant *EBRT***
  - 1st bullet was revised: "Postoperative EBRT using conventional 3D conformal RT or IMRT is an option for resected extrahepatic cholangiocarcinoma and gallbladder cancer. Target volumes should cover the draining regional lymph nodes to 45 Gy at 1.8 Gy/fraction and ~~50.4–59.4 at 1.8 Gy at 1.8 gy/faction~~ *50–60 Gy in 1.8–2 Gy/*fraction to the tumor bed depending on margin positivity."
  - Reference "1" was added: "Mallick S, Benson R, and Haresh KP, et al. Adjuvant radiotherapy in the treatment of gallbladder carcinoma: What is the current evidence? Journal of the Egyptian National Cancer Institute. 2016; 28:1-6."
  - Reference "2" was added: "Kim Y, Amini N, Wilson A, et al. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: A multi-institutional analysis. Ann Surg Oncol. 2016; 23:2998-3008."
- **Unresectable**
  - 4th bullet was revised: "*Dosing for SBRT for biliary tract tumors is generally 30-50 Gy in 3-5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated.* For intrahepatic tumors, SBRT in 1-5 fractions is an acceptable option."

Intrahepatic Cholangiocarcinoma

INTRA-1

- Unresectable, Metastatic disease
  - A bullet was added for each: "Consider molecular testing, including MSI testing."
- Primary Treatment, Unresectable and Metastatic disease
  - Treatment options statement was revised: "*Consider* locoregional therapy ~~(category 2B)~~"
  - 1st sub-bullet under locoregional therapy was revised: "~~EBRT~~ *Radiation therapy*"
  - "Pembrolizumab (only for MSI-H tumors)" was added as a treatment option.
  - Footnote h was removed after clinical trial and added to locoregional therapy: "Intra-arterial chemotherapy (with or without systemic chemotherapy) may be used in a clinical trial or at experienced centers." (Also for INTRA-2)
- Primary Treatment, Metastatic disease
  - 2nd sub-bullet: "Arterially directed therapies" was added under locoregional therapy as a treatment option.

INTRA-2

- Treatment
  - Footnote "m" was revised to include: "*The phase 3 BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al: Adjuvant Capecitabine for Biliary Tract Cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4006."*
  - Microscopic margins (R1) or Positive regional nodes and Residual local disease (R2 resection)
    - ◊ Treatment option statement was revised: "Fluoropyrimidine-based or gemcitabine-based chemotherapy *+/- fluoropyrimidine chemoradiation*"
    - ◊ Footnote "n" was added: "Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622."

Continued

Extrahepatic Cholangiocarcinoma

EXTRA-1

- **Workup**
  - **Footnote "d" was added after "Consider serum IgG4 to rule out autoimmune cholangitis": "Patients with IgG-4–related cholangiopathy should be referred to an expert center."**
- **Unresectable and Metastatic disease**
  - **Sub-bullet under biopsy was added: "Consider molecular testing, including MSI testing"**
- **Resectable**
  - **4th bullet was added: "Multidisciplinary review"**
- **Primary Treatment**
  - **5th bullet for unresectable treatment was added: "Radiation therapy"**
  - **A bullet was added for unresectable and metastatic disease: "Pembrolizumab (only for MSI-H tumors)"**

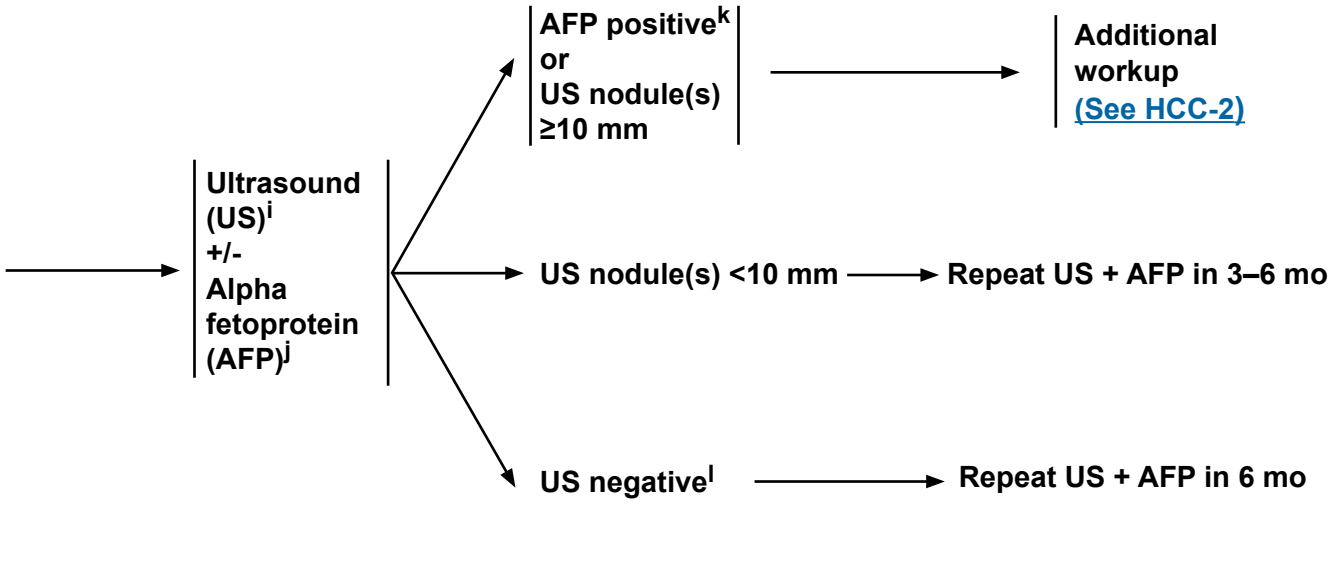
EXTRA-2

- **"Resected, positive margin (R1) or Resected gross residual disease (R2) or Positive regional nodes" statement was revised: "~~Consider~~ Fluoropyrimidine chemoradiation followed by additional fluoropyrimidine-based or gemcitabine-based chemotherapy or Fluoropyrimidine-based or gemcitabine-based chemotherapy *+/- fluoropyrimidine chemoradiation* ~~for positive regional lymph nodes~~ or Clinical trial"**
- **Footnote "n" was revised: "*Management of patients* with R1 or R2 resections should be evaluated by a multidisciplinary team."**
- **Footnote "p" was revised: "~~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. Oncologist 2008;13:415-423). *The phase 3 BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al: Adjuvant Capecitabine for Biliary Tract Cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4006."***
- **Footnote "q" was added: "Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622."**

ST-1 Staging Tables

- **Staging tables have been revised to reflect the 8th edition of the AJCC Cancer Staging System.**

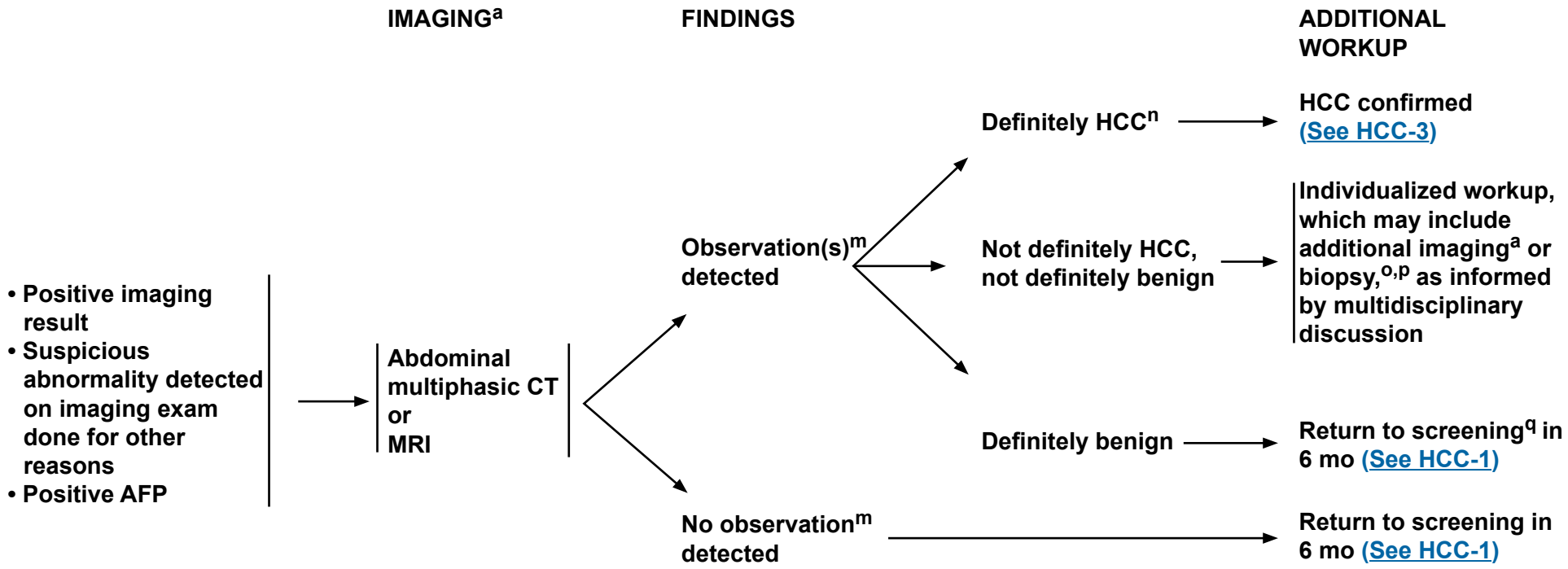
HEPATOCELLULAR CARCINOMA (HCC) SCREENING[a]



[a] See Principles of Imaging (HCC-A).
[b] Adapted with permission from Bruix J and Sherman M. Management of Hepatocellular Carcinoma: an Update. Hepatology 2011;53(3):1020-1022. doi: 10.1002/hep.24199.
[c] Patients with cirrhosis or chronic hepatitis B viral infection should be enrolled in an HCC screening program. (See Discussion).
[d] 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.
[e] White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systemic review. Clin Gastroenterol Hepatol 2012;10:1342-1359.
[f] Beuers U, Gershwin M, Gish R, et al. Changing Nomenclature for PBC: From 'Cirrhosis' to 'Cholangitis' Am J Gastroenterol 2015;110(11):1536–1538.
[g] Schiff ER, Sorrell MF, and Maddrey WC. Schiff's Diseases of the Liver. Philadelphia: Lippincott Williams & Wilkins (LWW); 2007.
[h] Additional risk factors include HBV carrier with family history of HCC, Asian males ≥40 y, Asian females ≥50 y, and African/North American Blacks with hepatitis B.
[i] Most clinical practice guidelines recommend ultrasound (US) for HCC screening. US exams should be done by qualified sonographers or physicians.
[j] AFP is considered optional for screening. (See Principles of Imaging, HCC-A).
[k] Positive AFP >100 ng/mL: (Waidely E, Al-Yuobi AR, Bashammakh AS, et al. Serum protein biomarkers relevant to hepatocellular carcinoma and their detection Analyst 2016;141:36-44), or if AFP increases by ≥7 ng/mL/month on at least 3 determinations (Arrieta O, Cacho B, Morales-Espinosa D, et al. The progressive elevation of alpha fetoprotein for the diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. BMC Cancer 2007;7:28). Positive AFP should prompt CT or MRI regardless of US results.
[l] US negative means no observation or only definitely benign observation(s).

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

DIAGNOSIS OF HCC[b]



[a]See Principles of Imaging (HCC-A).
[b]Adapted with permission from Bruix J and Sherman M. Management of Hepatocellular Carcinoma: an Update. Hepatology 2011;53(3):1020-1022. doi: 10.1002/hep.24199.
[m]An observation is an area identified at imaging that is distinctive from background liver. It may be a mass or a pseudo lesion.
[n]Criteria for observations that are definitely HCC have been proposed by LI-RADS, OPTN, and AASLD. These criteria apply only to patients at high risk for HCC. (See Principles of Imaging HCC-A).
[o]Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[p]See Principles of Biopsy (HCC-B).
[q]If no observations are detected at diagnostic imaging despite positive surveillance tests, then return to surveillance in 6 months if the most reasonable explanation is that surveillance tests were false positive. Consider imaging with an alternative method +/- AFP if there is reasonable suspicion that the diagnostic imaging test was false negative.

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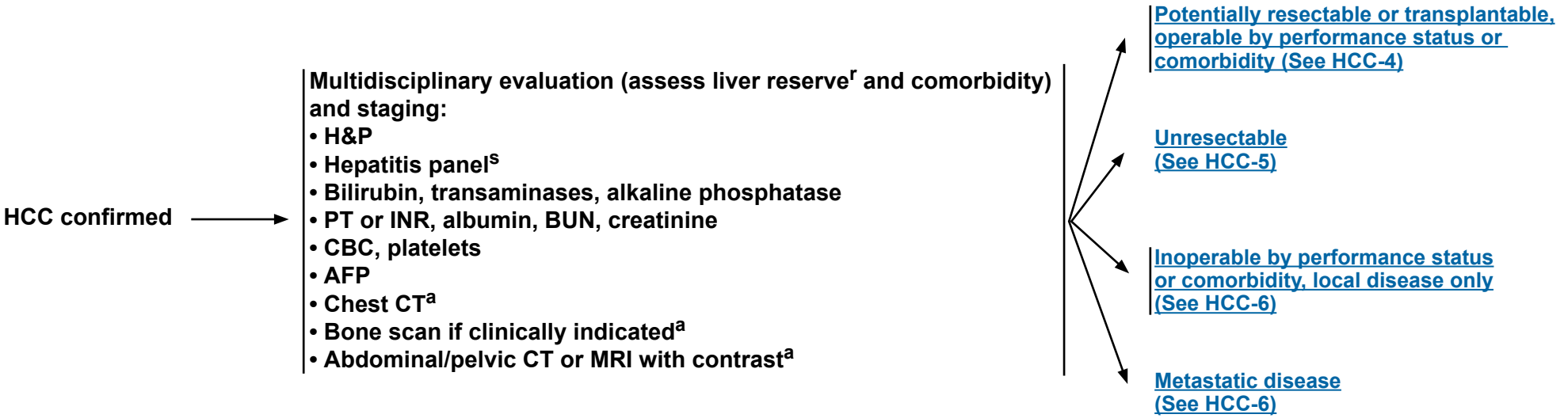
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

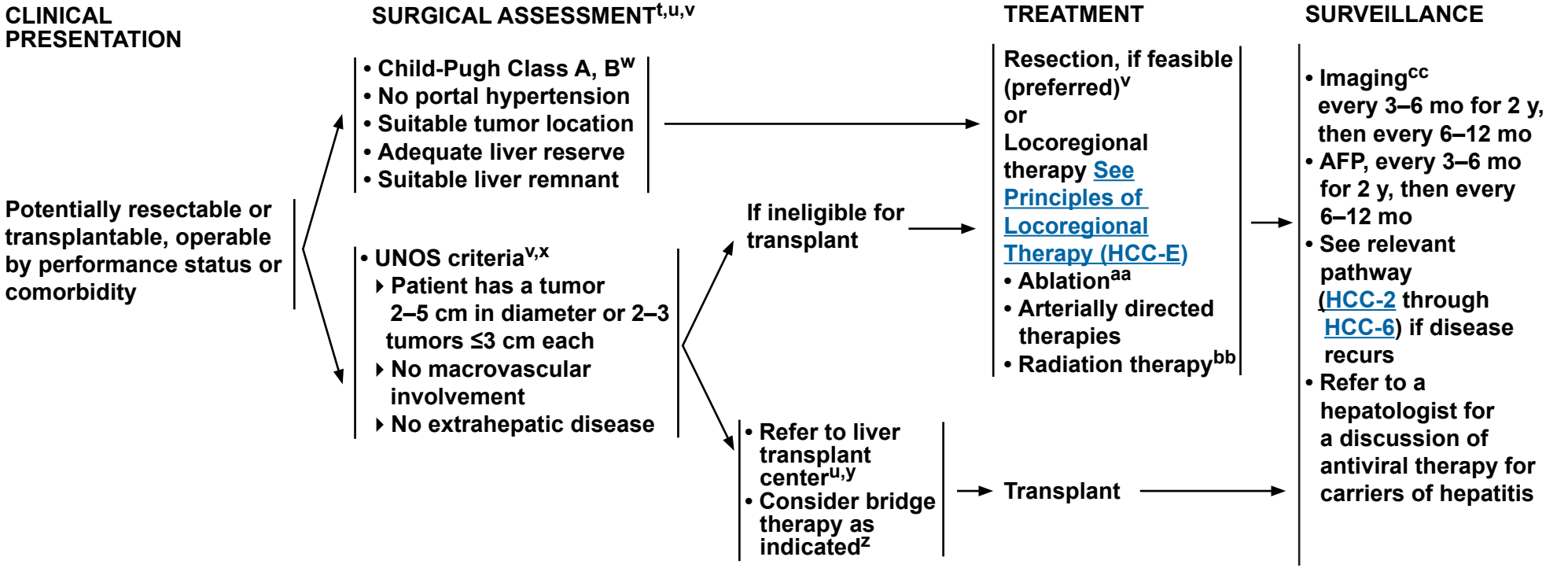
CLINICAL PRESENTATION

WORKUP



[a]See Principles of Imaging (HCC-A).
[r]See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[s]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.

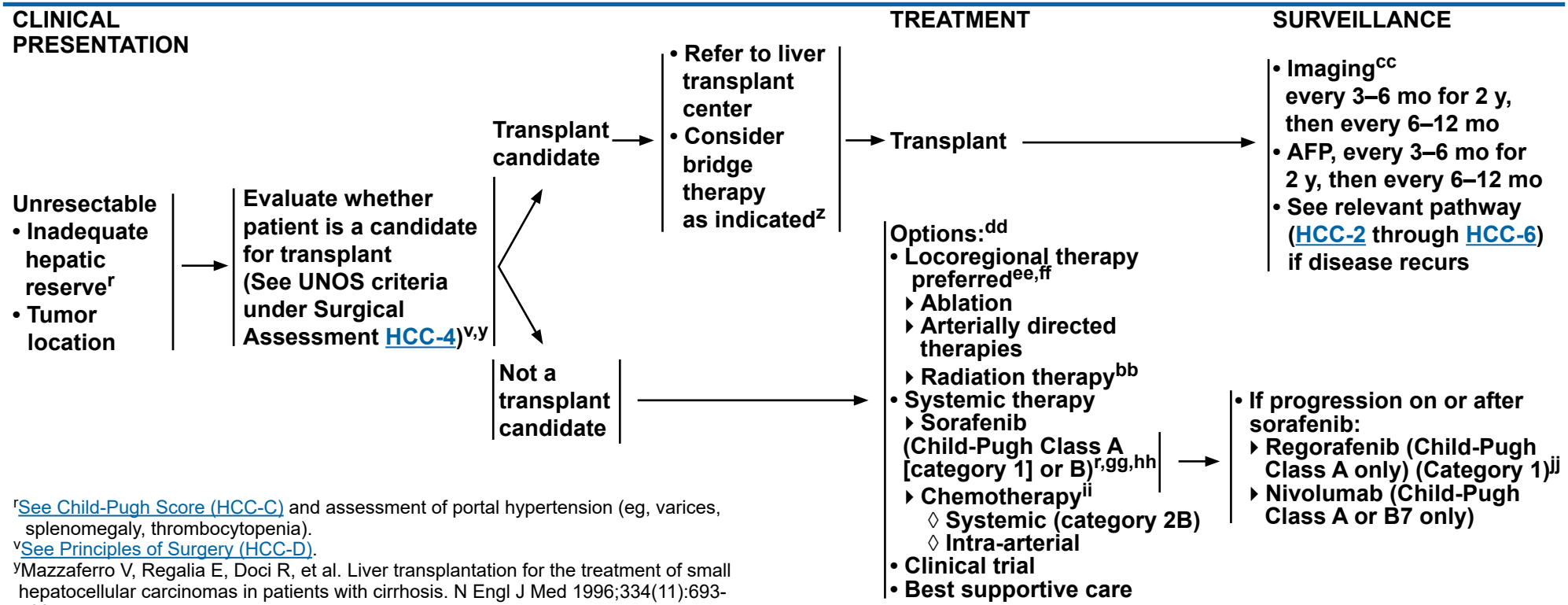
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[t]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.
[u]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.
[v]See Principles of Surgery (HCC-D).
[w]In highly selected Child-Pugh Class B patients with limited resection.
[x]Some patients beyond the Milan criteria can be considered for transplantation. Extended criteria/downstaging protocols are available at selected centers and through UNOS.
[y]Mazzaferro V, Regalia E, Doci, R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693-700.
[z]Many transplant centers consider bridge therapy for transplant candidates. (See Discussion).
[aa]In well-selected patients with small, properly located tumors ablation should be considered as definitive treatment in the context of a multidisciplinary review. (Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012;57(4):794-802 and Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg 2006, 243(3):321-328).
[bb]Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[cc]Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A).

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

For relapse, see initial Workup (HCC-3)



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

[v] See Principles of Surgery (HCC-D).

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

[z] Many transplant centers consider bridge therapy for transplant candidates. (See Discussion).

[bb] Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).

[cc] Multiphasic abdominal/pelvic MRI or multi-phase CT scans for liver assessment are recommended. Consider chest CT. See Principles of Imaging (HCC-A).

[dd] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.

[ee] See Principles of Locoregional Therapy (HCC-E).

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

[gg] For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia Pacific region with advanced hepatocellular carcinoma: a phase III randomized,double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).

[hh] Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction:CALGB 60301. J Clin Oncol 2009;27:1800-1805).The impact of sorafenib on patients potentially eligible for transplant is unknown.

[ii] There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.

[jj] Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Bruix J, Qin S, Merle P, et al. Lancet 2017;389:56-66.

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CLINICAL PRESENTATION

TREATMENT

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

Options:[dd]
- **Locoregional therapy preferred**[ee]
  - **Ablation**
  - **Arterially directed therapies**
  - **Radiation therapy**[bb]
- **Systemic therapy**
  - **Sorafenib (Child-Pugh Class A [category 1] or B)**[r,gg,hh] →
  - **Chemotherapy**[ii]
    - ◊ **Systemic (category 2B)**
    - ◊ **Intra-arterial**
- **Clinical trial**
- **Best supportive care**

Metastatic disease or Extensive liver tumor burden → **Consider biopsy to confirm metastatic disease**[p] →

Options:[dd]
- **Systemic therapy**
  - **Sorafenib (Child-Pugh Class A [category 1] or B)**[r,gg,hh] →
  - **Chemotherapy**[ii]
    - ◊ **Systemic (category 2B)**
    - ◊ **Intra-arterial**
- **Clinical trial**
- **Best supportive care**

→
- **If progression on or after sorafenib:**
  - **Regorafenib (Child-Pugh Class A only) (category 1)**[jj]
  - **Nivolumab (Child-Pugh Class A or B7 only)**

[p] See Principles of Biopsy (HCC-B).
[r] See Child-Pugh Score (HCC-C) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[bb] Case series and single-arm studies demonstrate safety and efficacy of radiation therapy in selected cases. See Principles of Locoregional Therapy (HCC-E).
[dd] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[ee] See Principles of Locoregional Therapy (HCC-E).
[gg] For selected patients, two randomized phase 3 clinical trials have demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008;359(4):378-390) and (Cheng A, Kang Y, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34).
[hh] Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. J Clin Onc 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.
[ii] There are limited data supporting the use of chemotherapy, and its use in the context of a clinical trial is preferred.
[jj] Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Bruix J, Qin S, Merle P, et al. Lancet 2017;389:56-66.

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PRINCIPLES OF IMAGING

Screening and Surveillance

- Screening and surveillance for HCC is considered cost effective in patients with cirrhosis of any cause and patients with chronic hepatitis B (CHB) even in the absence of cirrhosis.[1,2] The recommended screening and surveillance imaging method is US, and the recommended interval is every six months.[1,2] CT and MRI are more sensitive than US for HCC detection[3], but they are more costly and should be reserved for patients in whom US is inadequate (see below). Serum biomarkers such as AFP may incrementally improve the performance of imaging-based screening and surveillance, but their cost effectiveness has not been established;[1,2] their use as supplementary surveillance tests is optional.

Imaging Diagnosis of HCC

- After a positive screening or surveillance test or after lesions are detected incidentally on routine imaging studies done for other reasons, multiphasic abdominal CT or MRI studies with contrast are recommended to establish the diagnosis and stage the tumor burden in the liver. Optimal imaging technique depends on the modality and contrast agent, as summarized by LI-RADS.[4] To standardize interpretation, the AASLD,[1] EASL,[2] OPTN,[5] and LI-RADS[4,6] have proposed imaging criteria to diagnose HCC nodules ≥10 mm. Criteria have not been proposed for nodules smaller than 10 mm as these are difficult to definitively characterize at imaging. Major imaging features of HCC include arterial phase hyperenhancement, venous or delayed phase washout appearance and capsule appearance, and threshold growth.[4,6] LI-RADS also provides imaging criteria to diagnose major vascular invasion.[4] Having criteria for vascular invasion is necessary because the tumor in the vein may not have the same imaging features as parenchymal tumors.
- Importantly, imaging criteria for parenchymal nodules apply only to patients at high risk for developing HCC: namely, those with cirrhosis, CHB, or current or prior HCC. In these patients, the prevalence of HCC is sufficiently high that lesions meeting imaging criteria for HCC have close to a 100% probability of being HCC. The criteria do not apply to the general population or, except for CHB, to patients with chronic liver disease that has not progressed to cirrhosis. The criteria are designed to have high specificity for HCC; thus, lesions meeting these criteria can be assumed to represent HCC and may be treated as such without confirmatory biopsy. As a corollary, the criteria have modest sensitivity; thus, many HCCs do not satisfy the required criteria and failure to meet the criteria does not exclude HCC.[4]
- Lesions that do not meet the imaging criteria described above for HCC require individualized workup, which may include additional imaging or biopsy as informed by multidisciplinary discussion and are outlined in the treatment algorithms.
- Quality of MRI is dependent on patient compliance.

Extrahepatic Staging

- Frequent sites of extrahepatic metastases from HCC include lungs, bone, and lymph nodes. Adrenal and peritoneal metastases also may occur. For this reason, chest CT, complete imaging of abdomen and pelvis with contrast-enhanced CT or MRI, and selective use of bone scan when skeletal symptoms are present are recommended at initial diagnosis of HCC and for monitoring disease while on the transplant wait list or during or after treatment for response assessment. Chest CT may be performed with contrast if concurrently acquired with contrast-enhanced abdominal/pelvic CT. If MRI is performed, chest CT may be acquired without contrast.

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PRINCIPLES OF IMAGING

Imaging Diagnosis of ICC and H-ChC

Patients at risk for HCC due to cirrhosis, CHB, or other conditions are also at elevated risk for developing non-HCC primary hepatic malignancies such as intrahepatic cholangiocarcinoma (ICC) and hepatocholangiocarcinoma (H-ChC). ICCs and H-ChCs tend to have malignant imaging features, but the features are not sufficiently specific to permit noninvasive diagnosis.[6,7] Biopsy or definitive resection usually is necessary to make a diagnosis.

Imaging Protocol for Response Assessment After Treatment

CT of the chest and multiphasic CT or MRI of the abdomen and pelvis are the preferred modalities as they reliably assess intranodular arterial vascularity, a key feature of residual or recurrent tumor. Overall nodule size does not reliably indicate treatment response since a variety of factors may cause a successfully treated lesion to appear stable in size or even larger after treatment.

Role of CEUS

Contrast-enhanced US (CEUS) is considered a problem-solving tool for use at select centers with the relevant expertise for characterization of indeterminate nodules. It is not suitable for whole-liver assessment, surveillance, or cancer staging.[8]

Role of PET

PET/CT is not recommended for detection of HCC because of limited sensitivity. When an HCC is detected by CT or MRI and has increased metabolic activity on PET/CT, higher intralesional standardized uptake value (SUV) is a marker of biologic aggressiveness and might predict less optimal response to locoregional therapies.[9]

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PRINCIPLES OF IMAGING
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PRINCIPLES OF BIOPSY

Indicators for consideration of biopsy, which may include:

- **Initial biopsy**
  - **Lesion is highly suspicious for malignancy at multiphasic CT or MRI but does not meet imaging criteria[1] for HCC.**
  - **Lesion meets imaging criteria[1] for HCC but:**
    - ◊ **Patient is not considered at high risk for HCC development (ie, does not have cirrhosis, chronic hepatitis B, or current or prior HCC)**
    - ◊ **Patient has cardiac cirrhosis, congential hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia[2]**
    - ◊ **Patient has elevated CA 19-9 or CEA with suspicion of intrahepatic cholangiocarcinoma**
  - **Confirmation of metastatic disease could change clinical decision-making.**
  - **Histologic grading or molecular characterization is desired.**
  - **Surgical resection without biopsy should be considered with multi-disciplinary review.**

- **Repeat biopsy**
  - **Non-diagnostic biopsy**
  - **Prior biopsy discordant with imaging, biomarkers, or other factors**

[1]Imaging criteria for HCC have been proposed by LI-RADS, OPTN, and ASSLD. These criteria apply only to patients at high risk for HCC. See Principles of Imaging (HCC-A).
[2]These conditions are associated with formation of nonmalignant nodules that may resemble HCC at imaging.

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CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

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

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

[1]Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med 1966;274(9):473-481.
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Source: Pugh R, Murray-Lyon I, Dawson J, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J of Surg 1973;60(8):646-649.

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PRINCIPLES OF SURGERY

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

- **Hepatic resection is indicated as a potentially curative option in the following circumstances:**
  - **Adequate liver function (generally Child-Pugh Class A without portal hypertension, but small series show feasibility of limited resections in patients with mild portal hypertension)[1]**
  - **Solitary mass without major vascular invasion**
  - **Adequate future liver remnant (FLR) (at least 20% without cirrhosis and at least 30%–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**

- **For patients with chronic liver disease being considered for major resection, preoperative portal vein embolization should be considered.[2]**

- **Patients meeting the UNOS criteria ([single lesion ≤5 cm, or 2 or 3 lesions ≤3 cm] www.unos.org) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside of the UNOS guidelines and may be considered at some institutions for transplantation.[3] Furthermore, patients with tumor characteristics beyond Milan criteria that are downstaged to within criteria can also be considered for transplantation.[4]**

- **The Model for End-Stage Liver Disease (MELD) score is used by UNOS to assess the severity of liver disease and prioritize the allocation of the liver transplants.[3] MELD score can be determined using the MELD calculator: https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/. Additional MELD "exception points" may be granted to patients with HCC eligible for liver transplant.[5]**

- **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.**

[1]Santambrogio R, Kluger MD, Costa M, et al. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: Is clinical evidence of portal hypertension a contraindication? HPB (Oxford) 2013 Jan;15(1):78-84.
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PRINCIPLES OF LOCOREGIONAL THERAPY

All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are 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. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 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.[1,2,3]**
- **Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.[4-6]**
- **Sorafenib should not be used as adjuvant therapy post-ablation.[7]**

Arterially Directed Therapies:

- **All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.**
- **Arterially directed therapies include bland transarterial embolization (TAE),[5,6,8,9] chemoembolization (transarterial chemoembolization [TACE][10] and TACE with drug-eluting beads [DEB-TACE][6,11]), and radioembolization (RE) with yttrium-90 microspheres.[12,13]**
- **All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental treatment can be performed.[14] RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.[13]**
- **Arterially directed therapies in highly selected patients have been shown to be safe in the presence of limited tumor invasion of the portal vein.**
- **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 has not been associated with significant benefit in two randomized trials; other randomized phase III trials are ongoing to further investigate combination approaches.[15,16,17]**

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PRINCIPLES OF LOCOREGIONAL THERAPY

Radiation Therapy

- EBRT is a treatment option for patients with unresectable disease, or for those who are medically inoperable due to comorbidity.
- All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, intensity-modulated radiation therapy [IMRT], or stereotactic body radiation therapy [SBRT]). Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.
- Hypofractionation with photons[25] or protons[26,27] is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.
- SBRT is an advanced technique of hypofractionated EBRT with photons that delivers large ablative doses of radiation.
- Dosing for SBRT is generally is 30-50 Gy in 3-5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated.
- There is growing evidence for the usefulness of SBRT in the management of patients with HCC.[18,19] SBRT can be considered as an alternative to the ablation/embolization techniques mentioned above or when these therapies have failed or are contraindicated.
- SBRT (1–5 fractions) is often used for patients with 1 to 3 tumors. 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 extrahepatic disease or it should be minimal and addressed in a comprehensive management plan. The majority of data on radiation for HCC liver tumors arises from patients with Child-Pugh A liver disease; safety data are limited for patients with Child-Pugh B or poorer liver functon. Those with Child-Pugh B cirrhosis can be safely treated, but they may require dose modifications and strict dose constraint adherence.[20] The safety of liver radiation for HCC in patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for Child-Pugh C patients.[21,22]
- Proton beam therapy (PBT) may be appropriate in specific situations.[23,24]
- Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions, such as bone or brain.

References on next page

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PRINCIPLES OF LOCOREGIONAL THERAPY

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NCCN Guidelines Version 1.2018
Gallbladder Cancer

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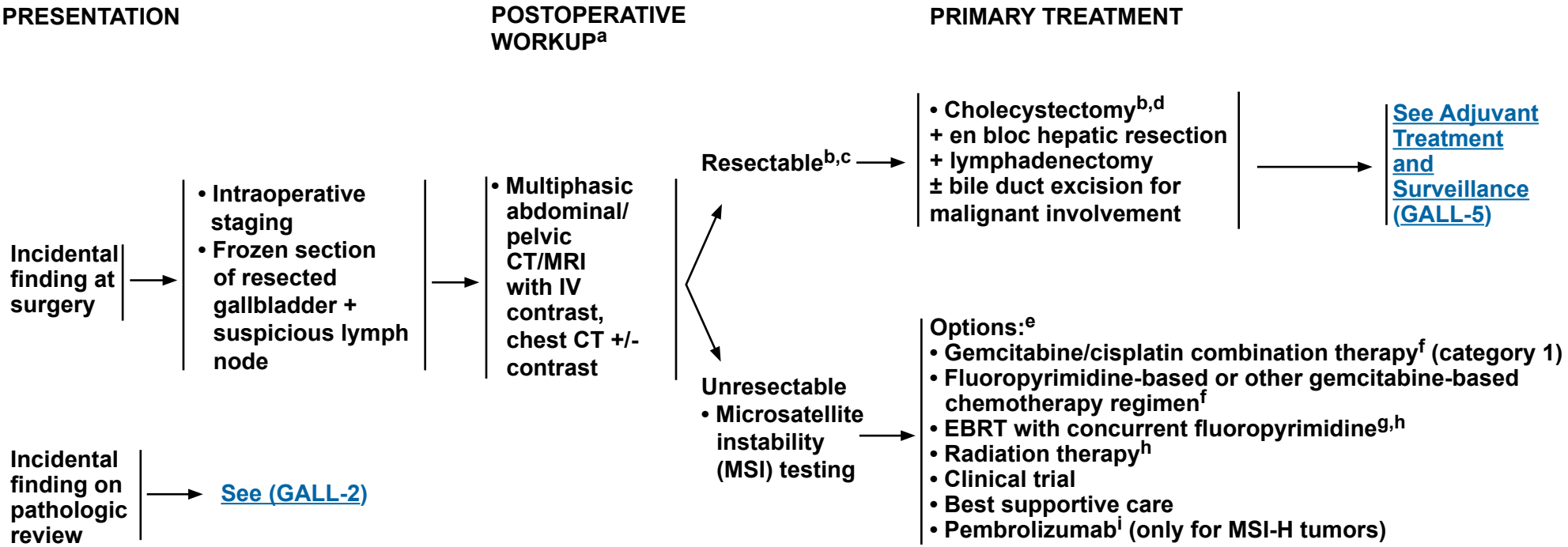
Discussion



[a] See Principles of Imaging (GALL-A).
[b] See Principles of Surgery and Pathology (GALL-B).
[c] If there is evidence of locoregionally advanced disease (big mass invading liver and/or nodal disease, including cystic duct node positive) consideration to neoadjuvant chemotherapy should be given, largely to rule out rapid progression and avoid futile surgery. Neoadjuvant chemotherapy regimens include: 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.
[d] Depends on expertise of surgeon and/or resectability. Consider referral to surgeon with hepatobiliary expertise and consider intraoperative photography. If resectability not clear, close incision.
[e] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[f] A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. Valle JW, Wasan HS, Palmer DD, et al. 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. Oncologist 2008;13:415-423).
[g] 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).
[h] See Principles of Radiation Therapy (GALL-C).
[i] There are limited clinical trial data to support pembrolizumab in this setting. Personalized, molecularly matched combination therapies for treatment-naïve, lethal malignancies: the I-PREDICT Study. Sicklick JK, Leyland-Jones B, Kato S, et al. J Clin Oncol 2017;35:2512.

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

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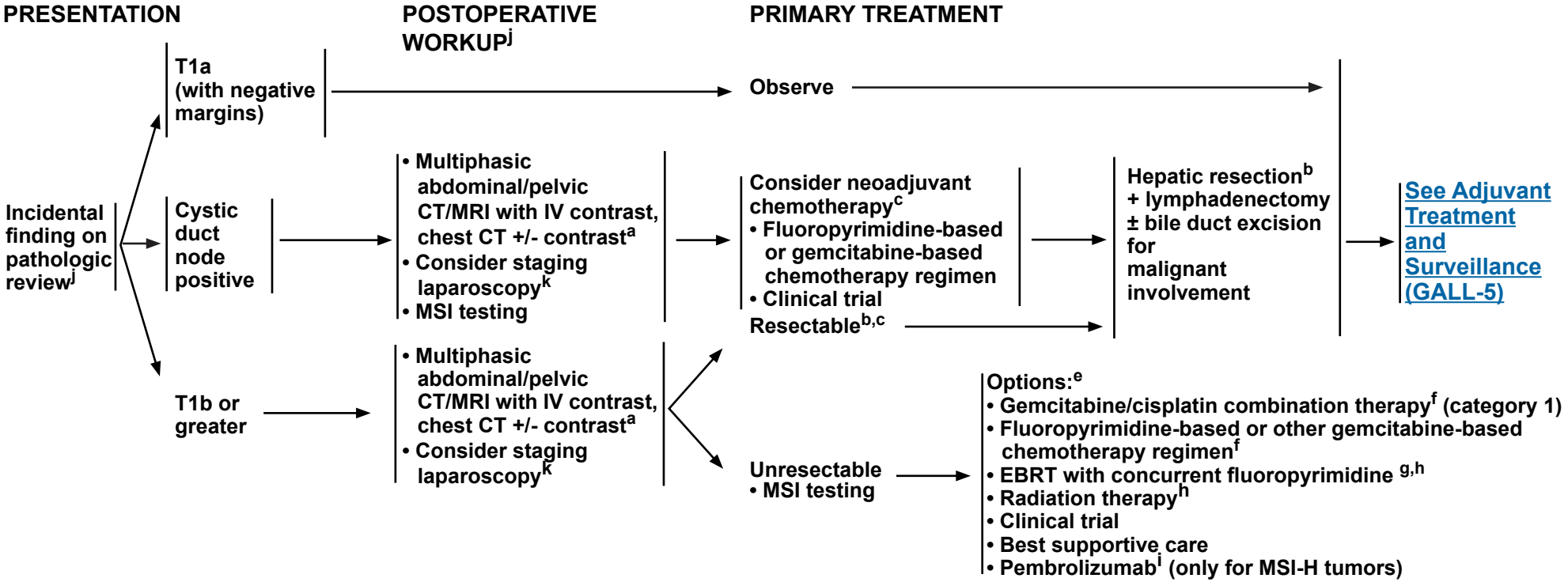

[a] See Principles of Imaging (GALL-A).
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[j] Consider multidisciplinary review.
[k] Butte JM, Gonen M, Allen PJ, et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. HPB (Oxford) 2011;13:463-472.

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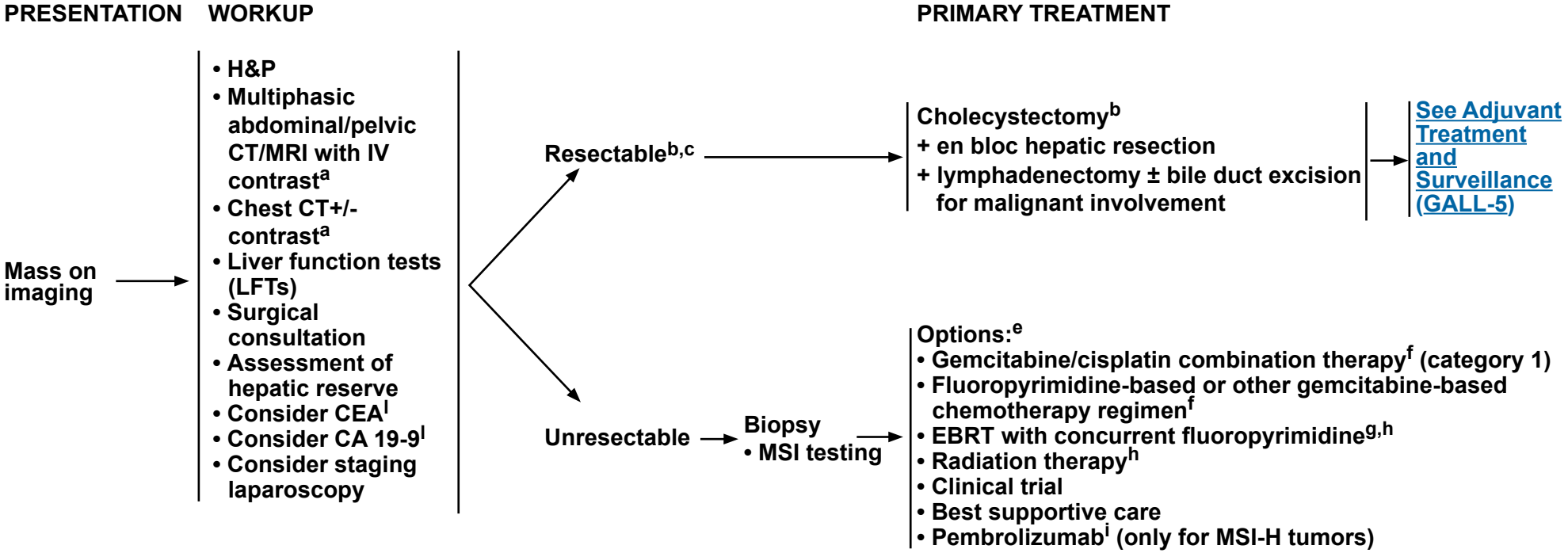
Other Clinical Presentations (See GALL-3) and (GALL-4)



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(See GALL-1), (GALL-2), and (GALL-4)

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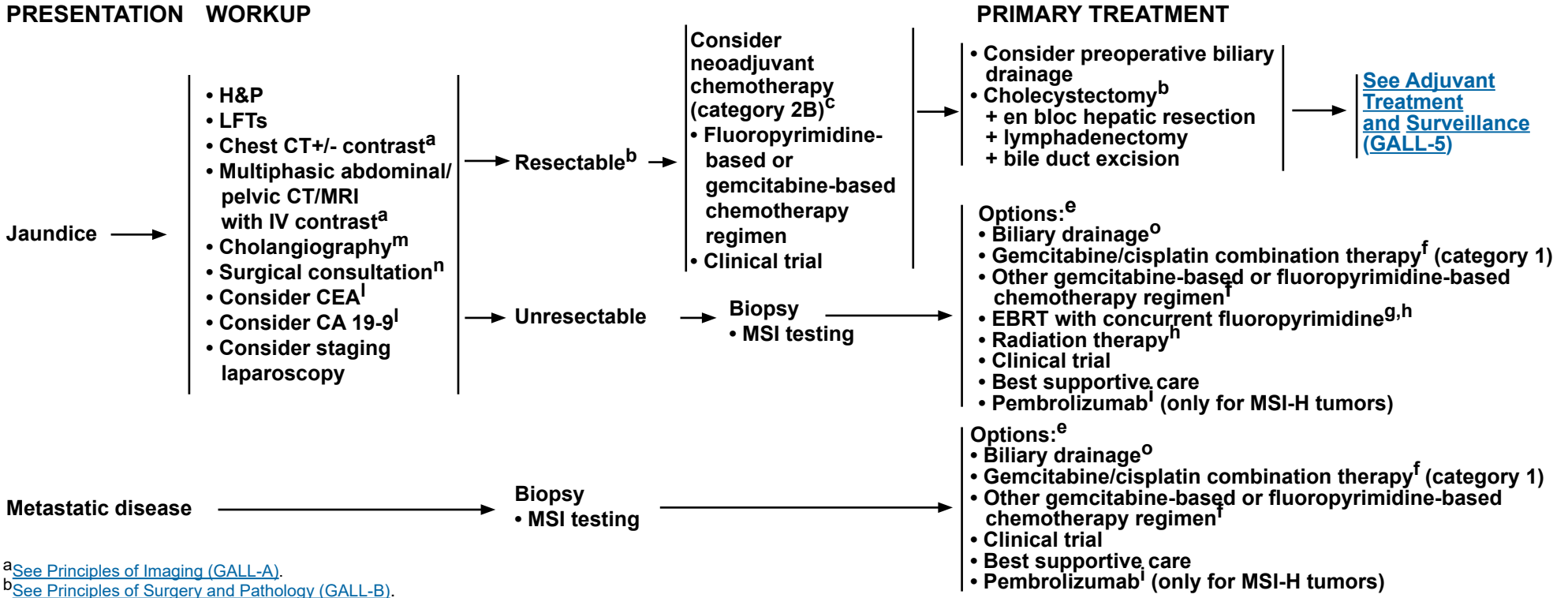

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[l] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[m] Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC) are used more for therapeutic intervention.
[n] Consult with a multidisciplinary team.
[o] Consider biliary drainage for patients with jaundice prior to instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.

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

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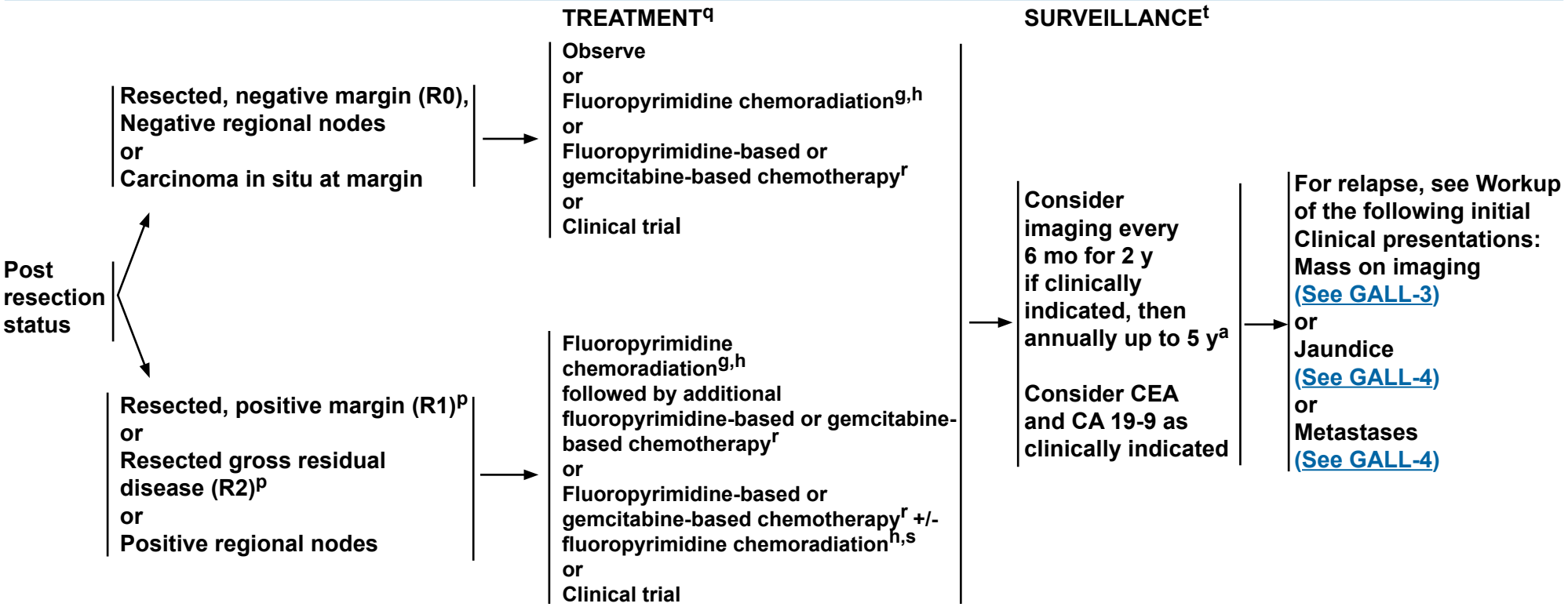

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[h] See Principles of Radiation Therapy (GALL-C).
[p] Management of patients with R1 or R2 resections should be evaluated by a multidisciplinary team.
[q] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancer (BTC), especially in patients with lymph node-positive disease (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940).
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[s] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622.
[t] There are no data to support surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

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PRINCIPLES OF IMAGING[1,2]

Gallbladder Cancer

- **Detection of early-stage gallbladder cancer remains difficult, and is commonly discovered incidentally at surgery or pathologic examination of the gallbladder.**
- **If gallbladder cancer is suspected preoperatively, multidetector multiphase CT of the abdomen (and pelvis) or contrast-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) of the abdomen (and pelvis) and chest CT with or without contrast should be performed. MRI is preferred for evaluating masses within the gallbladder and demonstrating bile duct involvement.**
- **Because lymphatic spread is common, careful attention should be made to evaluate nodal disease, specifically the porta hepatis and left gastric and aorto-caval basins.**
- **PET/CT has limited sensitivity but high specificity in the detection of regional lymph node metastases. PET/CT may be considered when there is an equivocal finding on CT/MRI. The routine use of PET/CT in the preoperative setting has not been established in prospective trials.**
- **CT of the chest with or without contrast and multiphasic contrast-enhanced CT or MRI of the abdomen and pelvis are recommended for follow-up imaging.**

[1]Srinivasa S, McEntee B, Koea JB. The role of PET scans in the management of cholangiocarcinoma and gallbladder cancer: a systematic review for surgeons. Int J Diagnostic Imaging 2015;2.
[2]Corvera CU, Blumgart LH, Akhurst T, et al. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. J Am Coll Surg 2008;206:57-65.

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PRINCIPLES OF SURGERY AND PATHOLOGY

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:

- **Consider pathologic re-review by a hepatobiliary pathology expert 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.[2,3]**
- **Port site resection has not been shown to be effective, as the presence of a port site implant is a surrogate marker of underlying disseminated disease and has not been shown to improve outcomes.[4]**

[1]Butte JM, Gonen M, Allen PJ et al. The role of laparoscopic staging in patients with incidental gallbladder cancer. HPB 2011;13:463-472.
[2]Fuks D, Regimbeau JM, Le Treut YP et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 2011;35:1887-1897.
[3]D'Angelica M, Dalal KM, Dematteo RP et al. Analysis of extent of resection for adenocarcinoma of gallbladder. Ann Surg Oncol 2009;16:806-816.
[4]Maker AV, Butte JM, Oxenberg J et al. Is port site resection necessary in the surgical management of gallbladder cancer. Ann Surg Oncol 2012;19:409-417.

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PRINCIPLES OF SURGERY AND PATHOLOGY

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 intraoperative 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.[5,6,7] 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.**

[5]Hawkins WG, DeMatteo RP, Jarnagin WR, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol 2004;11:310-315.
[6]Regimbeau JM, Fuks D, Bachellier P, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC -GBC-2009 study group. Eur J Surg Oncol 2011;37:505-512.
[7]Nishio H, Ebata T, Yokoyama Y, et al. Gallbladder cancer involving the extrahepatic bile duct is worthy of resection. Ann Surg 2011;253(5):953-960.

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PRINCIPLES OF RADIATION THERAPY

- **Image-guided radiotherapy is strongly recommended when using EBRT, IMRT, and SBRT to improve treatment accuracy and reduce treatment-related toxicity.**

Adjuvant EBRT[1,2]

- **Postoperative EBRT using conventional 3D conformal RT or IMRT is an option for resected extrahepatic cholangiocarcinoma and gallbladder cancer.**[3,4] **Target volumes should cover the draining regional lymph nodes to 45 Gy at 1.8 Gy/fraction and *50–60* Gy in 1.8–2 Gy/fraction to the tumor bed depending on margin positivity.**

Unresectable

- **All tumors irrespective of the location may be amenable to radiation therapy (3D conformal radiation therapy, IMRT, or SBRT).**
- **Conventionally fractionated radiotherapy with concurrent 5-fluorouracil–based chemotherapy to standard or high dose is acceptable for intrahepatic and extrahepatic tumors.**
- **Hypofractionation with photons**[5] **or protons**[6] **is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.**
- **Dosing for SBRT for biliary tract tumors is generally 30-50 Gy in 3-5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. Other hypofractionated schedules >5 fractions may also be used if clinically indicated. For intrahepatic tumors, SBRT in 1-5 fractions is an acceptable option.**[5]

[1]Mallick S, Benson R, and Haresh KP, et al. Adjuvant radiotherapy in the treatment of gallbladder carcinoma: What is the current evidence? Journal of the Egyptian National Cancer Institute. 2016; 28:1-6
[2]Kim Y, Amini N, Wilson A, et al. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: A multi-institutional analysis. Ann Surg Oncol. 2016; 23:2998-3008
[3]Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015 Aug 20;33(24):2617-22.
[4]Wang SJ, Lemieux A, Kalpathy-Cramer J, et al Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. J Clin Oncol 2011 Dec 10;29(35):4627-32.
[5]Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol 2016;34:219-226.
[6]Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2016;34(5):460-8.

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Intrahepatic Cholangiocarcinoma

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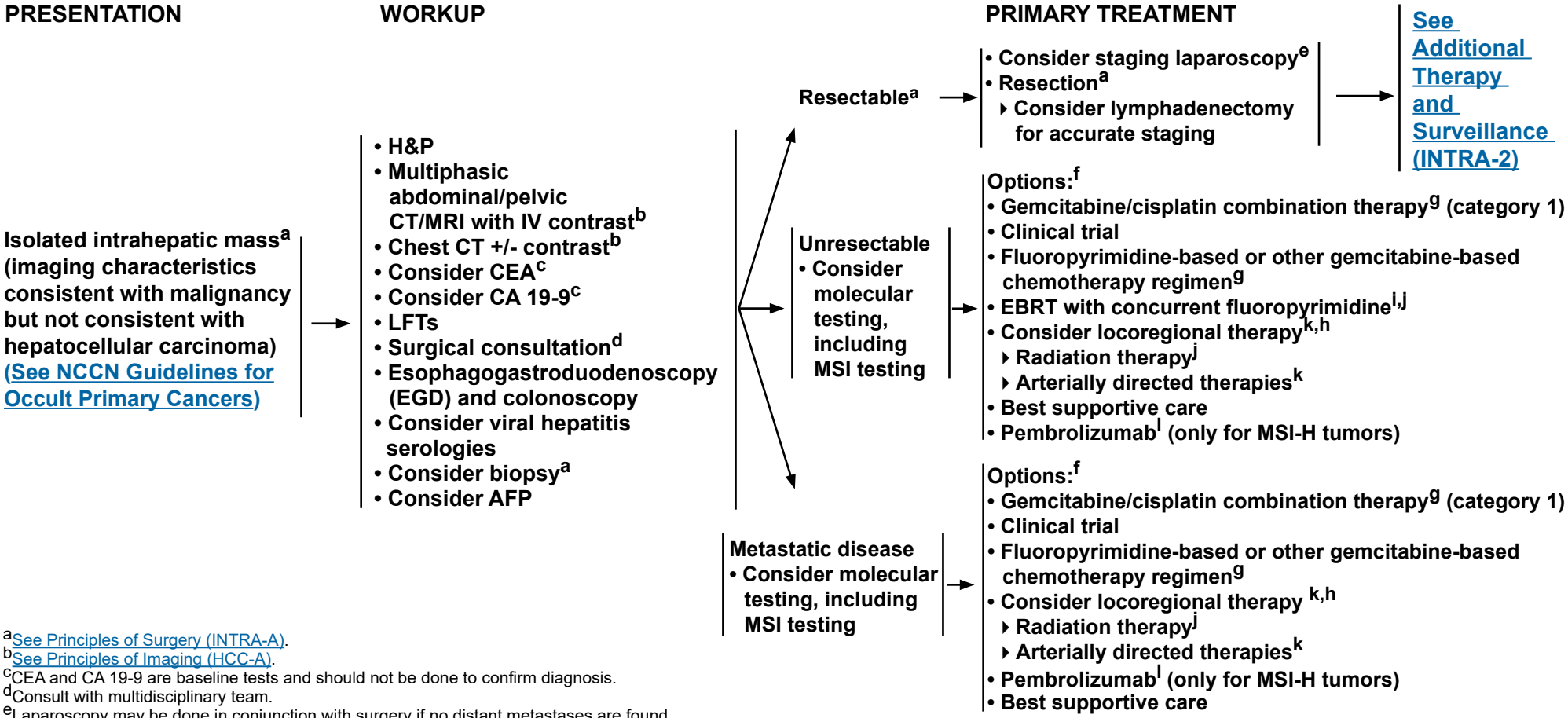

[a] See Principles of Surgery (INTRA-A).
[b] See Principles of Imaging (HCC-A).
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Consult with multidisciplinary team.
[e] Laparoscopy may be done in conjunction with surgery if no distant metastases are found.
[f] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[g] A phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic billiary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. 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. Oncologist 2008;13:415-423).
[h] Intra-arterial chemotherapy (with or without systemic chemotherapy) may be used in a clinical trial or at experienced centers.
[i] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954).
[j] See Principles of Radiation Therapy (GALL-C).
[k] Principles of Locoregional Therapy (HCC-E).
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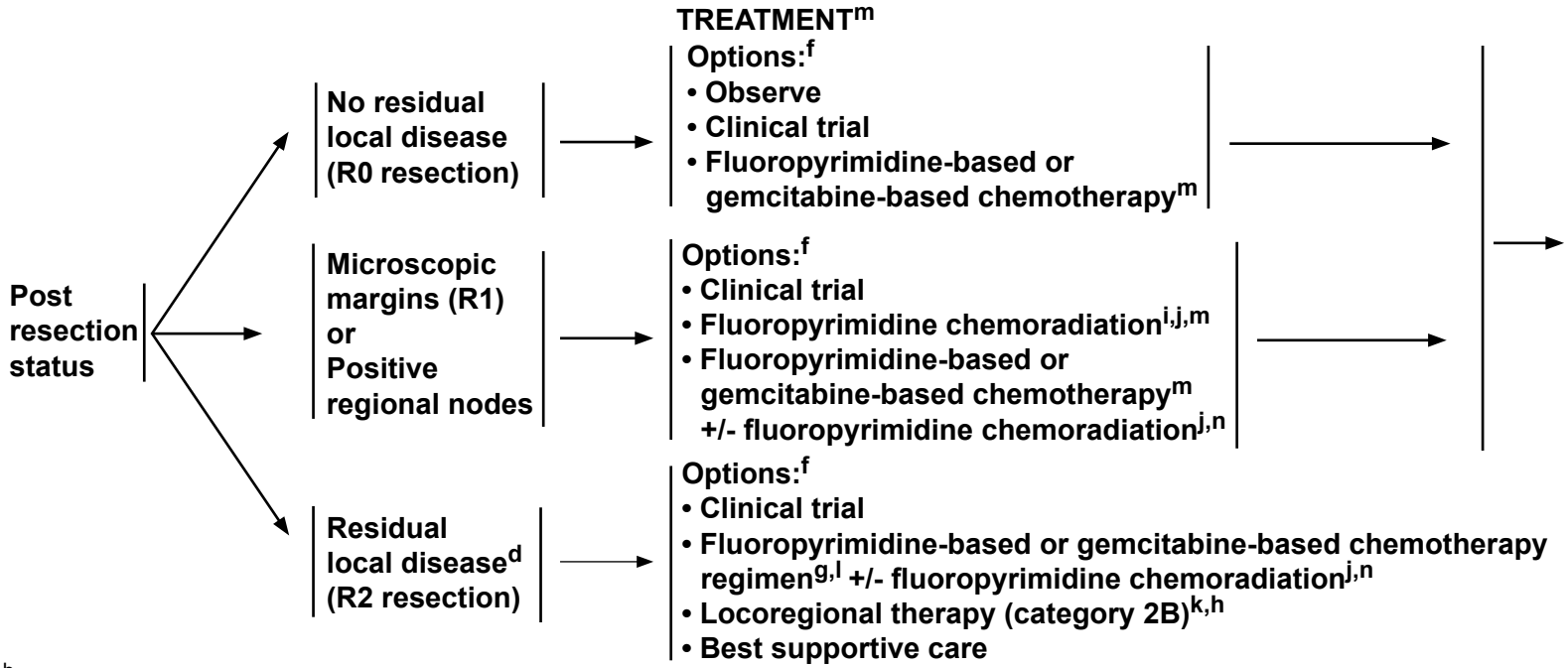

[b] See Principles of Imaging (HCC-A).
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[k] See Principles of Locoregional Therapy (HCC-E).
[m] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancers, especially in patients with lymph node-positive disease. (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940). However, this meta-analysis included only a few patients with intrahepatic cholangiocarcinoma. 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.Oncologist 2008;13:415-423). The phase 3 BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al: Adjuvant Capecitabine for Biliary Tract Cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4006.
[n] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622.
[o] 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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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SURGERY[1,2]

- **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 multifocal 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.**
- **Multifocal liver disease is generally representative of metastatic disease and is a contraindication to resection. In highly selected cases with limited multifocal 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.**

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

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Extrahepatic Cholangiocarcinoma

NCCN Guidelines Index
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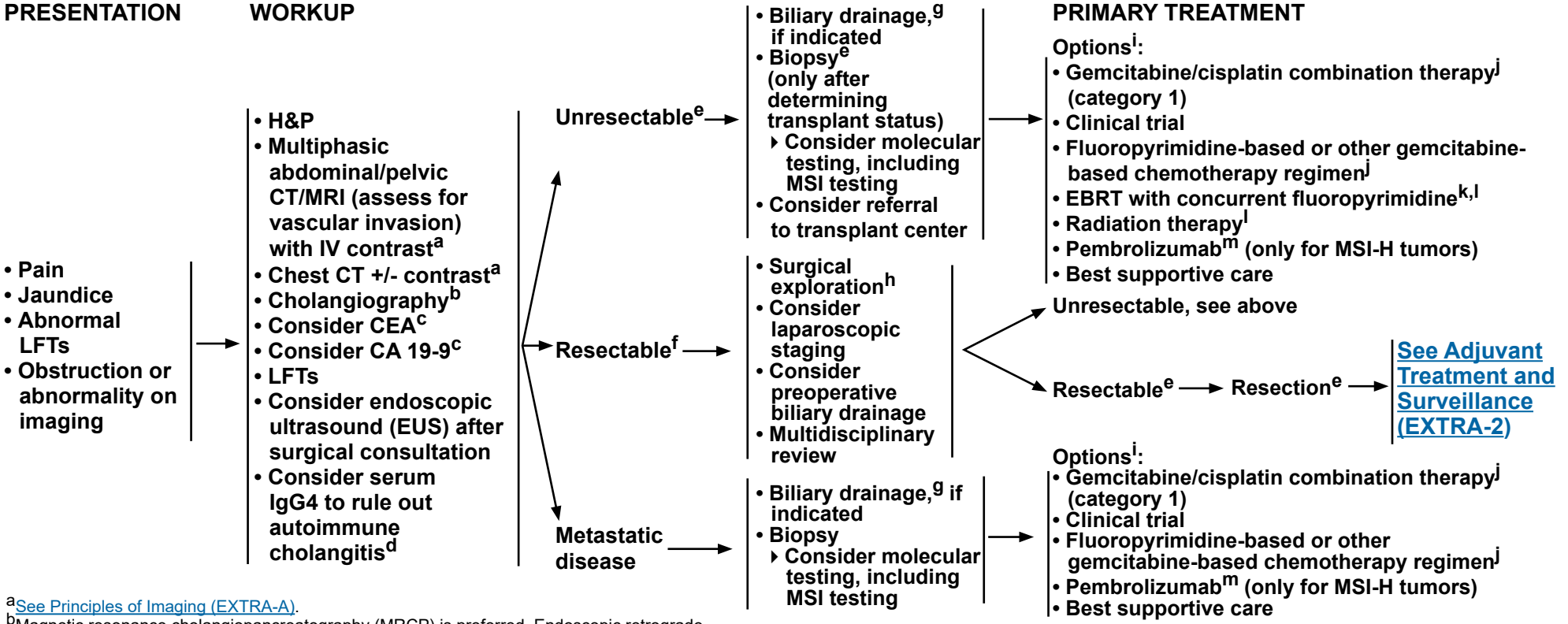
Discussion



[a] See Principles of Imaging (EXTRA-A).
[b] Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC) are used more for therapeutic intervention.
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Patients with IgG-4–related cholangiopathy should be referred to an expert center.
[e] Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.
[f] See Principles of Surgery (EXTRA-B).
[g] Consider biliary drainage for patients with jaundice prior to instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.
[h] Surgery may be performed when index of suspicion is high; biopsy is not required.
[i] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[j] 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. Oncologist 2008;13:415-423)
[k] 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)
[l] See Principles of Radiation Therapy (GALL-C).
[m] There are limited clinical trial data to support pembrolizumab in this setting. Personalized, molecularly matched combination therapies for treatment-naïve, lethal malignancies: the I-PREDICT Study. Sicklick JK, Leyland-Jones B, Kato S, et al. J Clin Oncol 2017;35:2512.

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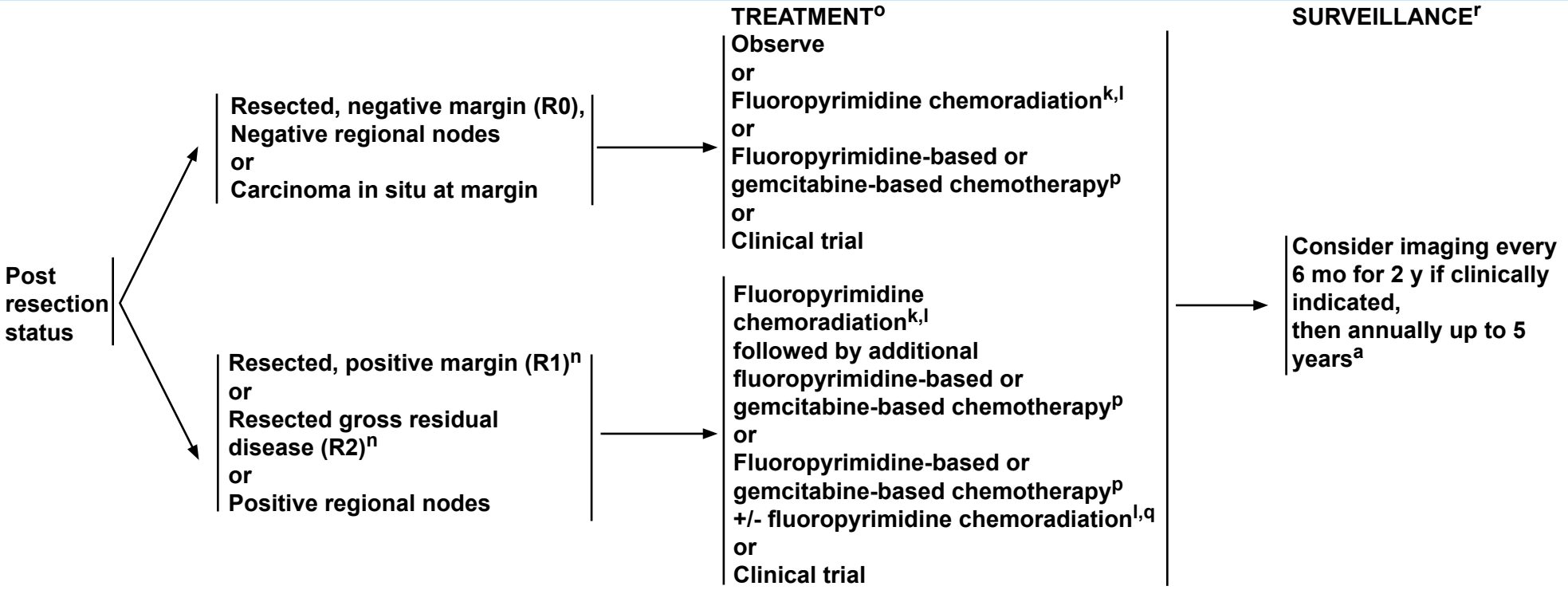

[a] See Principles of Imaging (EXTRA-A).
[k] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954)
[l] See Principles of Radiation Therapy (GALL-C).
[n] Management of patients with R1 or R2 resections should be evaluated by a multidisciplinary team.
[o] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with biliary tract cancers, especially in patients with lymph node-positive disease (Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940).
[p] 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. Oncologist 2008;13:415-423). The phase 3 BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, but the study is not yet published, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox R, Palmer DH, et al: Adjuvant Capecitabine for Biliary Tract Cancer. The BILCAP randomized study. ASCO Annual Meeting 2017. Abstract 4006.
[q] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33(24):2617-2622.
[r] There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

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PRINCIPLES OF IMAGING[1,2,3,4]

Extrahepatic Cholangiocarcinoma

- **Surgical management is based on the location and extent of the tumor.**
- **Preoperative imaging for accurate staging of extrahepatic cholangiocarcinoma should be done with multidetector multiphasic abdominal/pelvic CT or MRI. Contrast-enhanced MRI with MRCP is preferred for evaluating the extent of biliary tract involvement. Imaging with multiphasic CT or MRI with thin cuts, or multiphase CT or MRI of the liver and biliary tree should specifically address the anatomy of the biliary tree, hepatic arteries, and portal veins and their relationship to the tumor.**
- **Chest CT with or without contrast is recommended for staging.**
- **Imaging for staging ideally should be performed prior to biopsy or biliary drainage.**
- **EUS or endoscopic retrograde cholangiopancreatography (ERCP) may be helpful in the setting of bile duct dilation if no mass is seen on CT or MRI. EUS or ERCP can also be used to establish tissue diagnosis and provide access to relieve biliary obstruction.**
- **PET/CT has limited sensitivity but high specificity in the detection of distant or regional lymph node metastases. PET/CT may be considered when there is an equivocal finding on CT/MRI. PET/CT may be considered in patients being evaluated for resection to evaluate for the presence of distant extrahepatic disease.**
- **CT of the chest with or without contrast and CT or MRI of the abdomen and pelvis with contrast may be used for follow-up.**

[1]Srinivasa S, McEntee B, Koea JB. The role of PET scans in the management of cholangiocarcinoma and gallbladder cancer: a systematic review for surgeons. International Journal of Diagnostic Imaging 2015 Vol 2 No 1.
[2]Corvera CU, Blumgart LH, Akhurst T, et al 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. J Am Coll Surg 2008 Jan;206(1):57-65.
[3]Brandi G, Venturi M, Pantaleo MA, Ercolani G, GICO. Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. Dig Liver Dis 2016 Mar:48(3):231-41.
[4]Navaneethan U, Njei B, Venkatesh PG, Lourdusamy V, Sanaka MR. Endoscopic ultrasound in the diagnosis of cholangiocarcinoma as the etiology of biliary strictures: a systematic review and meta-analysis. Gastroenterol Rep (Oxf). 2015 Aug;3(3):209-15.

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PRINCIPLES OF SURGERY

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

Hilar Cholangiocarcinoma

- Detailed descriptions of imaging assessment of resectability are beyond the scope of this outline. The basic principle is that the tumor will need to be resected along with the involved biliary tree and the involved hemi-liver with a reasonable chance of a margin-negative resection. The contralateral liver requires intact arterial and portal inflow as well as biliary drainage.[1,2,3]
- Detailed descriptions of preoperative surgical planning are beyond the scope of this outline but require an assessment of the FLR. This requires an assessment of biliary drainage and volumetrics of the FLR. While not necessary in all cases, the use of preoperative biliary drainage of the FLR and contralateral portal vein embolization should be considered in cases of a small FLR.[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 is recommended if further resection can be carried out.

Distal Cholangiocarcinoma

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

References on next page

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

PRINCIPLES OF SURGERY
(References)

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

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Table 1
American Joint Committee on Cancer (AJCC)
TNM Staging for Hepatocellular Cancer (8th ed., 2017)

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a Solitary tumor ≤2 cm
T1b Solitary tumor >2 cm without vascular invasion
T2 Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3 Multiple tumors, at least one of which is >5 cm
T4 Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

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

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

Stage IA	T1a	N0	M0
IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Histologic Grade (G)
GX Grade cannot be accessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Fibrosis Score (F)
The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.
F0 Fibrosis score 0-4 (none to moderate fibrosis)
F1 Fibrosis score 5-6 (severe fibrosis or cirrhosis)

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Continued

Table 2
American Joint Committee on Cancer (AJCC)
TNM Staging for Gallbladder Carcinoma (8th ed., 2017)

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in *situ*
T1 Tumor invades lamina propria or muscular layer
T1a Tumor invades lamina propria
T1b Tumor invades muscle layer
T2 Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) Or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3 Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4 Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastases to one to three regional lymph nodes
N2 Metastases to four or more regional lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
IIB	T2b	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T1-3	N1	M0
Stage IVA	T4	N0-1	M0
IVB	Any T	N2	M0
	Any T	Any N	M1

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

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Continued

Table 3
American Joint Committee on Cancer (AJCC)
TNM Staging for Intrahepatic Bile Duct Tumors (8th ed., 2017)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* (intraductal tumor)
T1	Solitary tumor without vascular invasion, ≤5 cm or >5 cm
T1a	Solitary tumor ≤5 cm without vascular invasion
T1b	Solitary tumor >5 cm without vascular invasion
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis present

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

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

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Continued

Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging for Perihilar Bile Duct Tumors (8th ed., 2017)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals bilaterally with contralateral portal vein or hepatic artery involvement

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
IVB	Any T	Any N	M1

Histologic Grade (G)

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

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Continued

Table 5
American Joint Committee on Cancer (AJCC)
TNM Staging for Distal Bile Ducts Tumors (8th ed., 2017)

Primary Tumor (T)
TX Primary tumor cannot be assessed
Tis Carcinoma in situ/high-grade dysplasia
T1 Tumor invades the bile duct wall with a depth less than 5 mm
T2 Tumor invades the bile duct wall with a depth of 5–12 mm
T3 Tumor invades the bile duct wall with a depth greater than 12 mm
T4 Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in one to three regional lymph nodes
N2 Metastasis in four or more regional lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 8/15/17

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.

Table of Contents

Overview

Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma; HCC), gall bladder, and bile ducts (intrahepatic and extrahepatic cholangiocarcinoma). Gallbladder cancer and cholangiocarcinomas are collectively known as biliary tract cancers. In 2017, it was estimated that 40,710 people in the United States would be diagnosed with liver cancer and intrahepatic bile duct cancer and an additional 11,740 people would be diagnosed with gallbladder cancer or other biliary tract cancer. In 2017, it was estimated that there would be approximately 28,920 deaths from liver or intrahepatic bile duct cancer, and 3,830 deaths due to gallbladder cancer or other biliary tract cancer.[1]

The NCCN Guidelines for Hepatobiliary Cancers are the work of the members of the NCCN Hepatobiliary Cancers Guidelines Panel. The types of hepatobiliary cancers covered in these guidelines include: HCC, gallbladder cancer, and intrahepatic and extrahepatic cholangiocarcinoma. Guidelines for HCC are consistent with those offered by the European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer and the consensus statement from the 2009 Asian Oncology Summit.[2] However, some discrepancies exist regarding treatment and surveillance, largely due to geographical differences such as available resources. 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, participation in prospective clinical trials is the preferred option for treatment of patients with hepatobiliary cancers.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Hepatobiliary Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of hepatobiliary cancers published between August 26, 2015 and August 25, 2016, using the following search terms: (hepatocellular carcinoma) OR (liver cancer) OR (biliary tract cancer) OR (gallbladder cancer) OR (cholangiocarcinoma). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[3]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 130 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Hepatocellular Carcinoma

Risk Factors and Epidemiology

Incidence and mortality rates for cancer overall are declining, but both incidence and mortality rates for liver cancer are increasing.[4] An analysis of SEER data from 2003 to 2011 showed that Asians had the highest HCC incidence, relative to blacks, Hispanics, and whites.[5] However, forecast analyses predict that rates will remain highest in blacks and Hispanics over the next 15 years.[6] These analyses also predict increasing incidence rates in those born between 1950 and 1959, due to high rates of hepatitis C viral infection in this age group.

Risk factors for the development of HCC include viral infections caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV), particular comorbidities or conditions, and certain external sources.[7,8] 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.[9,10] A retrospective analysis of patients at liver transplantation centers in the United States found that nearly 50% and about 15% of patients were infected with the hepatitis C or B virus, respectively, with approximately 5% of patients having markers of both hepatitis B and hepatitis C infection.[11]

Seropositivity for hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) are associated with an increased risk for HCC in patients with chronic hepatitis B viral infection.[12,13] 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.[14-17]

Non-viral causes associated with an increased risk for HCC include cirrhosis from any cause (eg, alcoholic cirrhosis); inherited errors of metabolism (relatively rare), such as hereditary hemochromatosis, porphyria cutanea tarda, and alpha-1 antitrypsin deficiency; Wilson's disease; and stage IV primary biliary cirrhosis.[7,18] 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.[7,10,19] 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.[10,20]

Alcoholic cirrhosis is clearly a risk factor for HCC,[10] 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.[21,22]

Genetic hemochromatosis (GH) is a condition characterized by excess iron absorption due to the presence of mutations in the *HFE* gene. A study from the National Center for Health Statistics found that patients with a known diagnosis of hemochromatosis at death were 23 times more likely to have liver cancer than those without GH. The annual incidence rates of HCC associated with cirrhosis due to GH have been sufficiently high (about 3%–4%), and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend surveillance for this group of patients when cirrhosis is present.[10]

Metabolic disorders [ie, obesity, diabetes, impaired glucose metabolism, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD)] are associated with increased risk of HCC.[23] There is growing evidence for an association between the sequelae of NAFLD, such as non-alcoholic steatohepatitis (NASH, a spectrum of conditions characterized by histologic findings of hepatic steatosis with inflammation in individuals who consume little or no alcohol) in the setting of metabolic syndrome or diabetes mellitus and the

development of HCC.[24,25] Estimations of the prevalence of NASH in the United States are in the range of 3% to 5%, indicating that this sizable subpopulation is at risk for cirrhosis and development of HCC.[26] 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%.[27] Available epidemiologic evidence supports an association between NAFLD or NASH and an increased HCC risk predominantly in individuals with cirrhosis.[28] However, several studies suggest that HCC may be somewhat less likely to develop in the setting of NASH-associated cirrhosis compared with cirrhosis due to hepatitis C infection.[29,30]

In most cases, the risk factors for HCC are also risk factors for liver cirrhosis. It has been estimated that 60% to 80% of persons with HCC have underlying cirrhosis, possibly approaching 90% in the United States.[31] 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.[32] Importantly, certain populations chronically infected with HBV have been identified as being at increased risk for HCC in the absence of cirrhosis, especially when other risk factors are present,[10] and it has been estimated that 30% to 50% of patients with chronic hepatitis B viral infection who develop HCC do not have underlying cirrhosis.[19] Some risk factors for the development of HCC in HBV carriers without evidence of liver cirrhosis include active viral replication, high HBV DNA levels, and a family history of HCC.[10,33] Asian males ≥40 years, Asian females ≥50 years, and Black/African American men and women with hepatitis B are also at increased risk of HCC.[10] 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.[20,34] 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 risk for development of HCC.[7] However, HCC may also develop in patients with normal livers and no known risk factors.[35,36]

The incidence of HCC is increasing in the United States, particularly in the population infected with HCV. Approximately 4 million individuals in the United States are chronically infected with HCV,[37] and the annual incidence rate of HCC among patients with HCV-related cirrhosis has been estimated to be between 2% and 8%.[10] However, HCV often goes undetected. 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.[38,39] There is evidence that direct-acting antivirals (DAAs) improve sustained virologic response in patients with HCV,[40,41] which in turn may eventually decrease incidence of HCC.[42]

Approximately 1.5 million people in the United States are chronically infected with HBV.[43,44] 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,[45] although studies have shown wide variation in the annual incidence rate of HCC among individuals with chronic hepatitis B infection.[10] A meta-analysis including 68 studies with 27,854 patients with untreated HBV showed an annual HCC incidence of 0.88 per 100 person-years (95% CI, 0.76–0.99), with higher incidence per 100 person-years for patients with cirrhosis (3.16; 95% CI, 2.58–3.74).[46] An analysis of 634

patients with HBV showed that long-term antiviral therapy was associated with reduced risk of HCC in patients without cirrhosis (SIR, 0.40; 95% CI, 0.20–0.80).[47] HCV coinfection (3.73; 95% CI, 1.59–5.86), being older than age 50 (3.92; 95% CI, 2.72–5.11), and inflammatory activity (1.86; 95% CI, 1.30–2.42) were also associated with HCC incidence per 100 person-years in patients with HBV.

Fibrolamellar hepatocellular carcinoma (FLHC) is a variant of HCC that makes up a small number of all HCCs. Patients with FLHC tend to be younger and have a generally better prognosis than those with HCC,[48-50] though recurrences following resection are common.[49] FLHC also is rarely, if ever, associated with hepatitis, cirrhosis, or elevated alpha-fetoprotein (AFP) levels.[49,51] Though cross-sectional imaging results may be strongly suggestive of FLHC, histologic confirmation is needed.[52] A molecular target to identify FLHC, the DNAJB1-PRKACA chimera, has been found,[53] which accurately identifies FLHC in 79% to 100% of cases.[53-56] Surgical resection is the only curative option,[52] and patients who receive surgery have better survival outcomes than patients who receive chemotherapy, intra-arterial therapy, and transplantation.[57] Given its rarity, the panel does not provide treatment recommendations for FLHC in these guidelines.

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 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.”[10] The AASLD and EASL-EORTC recommends that ultrasound (US) screening in at-risk patients be done every 6 months.[10,58]

Support for enrolling individuals at high risk for HCC in a screening program comes from a large randomized controlled trial (RCT) of 18,816 men and women with hepatitis B infection or a history of chronic hepatitis in China. In this study, screening with serum AFP testing and US 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.[59]

HCC screening should not be restricted to older patients. In a prospective observational 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.[60] 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.

AFP and liver US are the most widely used methods of screening for HCC.[61] A review of serum protein biomarkers for early detection of HCC showed that an AFP cut-off value of 100 ng/mL was associated with high specificity (99%) but low sensitivity (31%).[62] In a screening study involving a large population of patients in China infected with the HBV or those with chronic hepatitis, the detection rate, false-positive rate, and positive predictive value were 84%, 2.9%, and 6.6% for US alone; 69%, 5.0%, and 3.3% for AFP alone; and 92%, 7.5%, and 3.0% for the combination of AFP and US.[63] These results demonstrate that US is a better imaging modality for HCC screening than AFP testing. Nevertheless, since US is highly operator dependent, the addition of AFP may increase the likelihood of detecting HCC in a screening

setting. However, AFP is frequently not elevated in patients with early-stage disease and its utility as a screening biomarker is limited.[64-66]

Citing the limited sensitivity and specificity of AFP as a screening tool, the AASLD does not recommend AFP testing in addition to US screening for populations at risk of developing HCC.[10] As noted previously, higher level evidence exists in support of US for HCC screening compared with that for AFP. Due to the low cost and ease of use, AFP may have utility for enhancing detection of HCC when used in combination with US in the screening setting for at-risk individuals. A progressive elevation rate of ≥7 ng/mL per month may be more useful as a diagnostic tool for HCC, relative to use of a fixed cutpoint such as 200 ng/mL.[67]

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 of cirrhosis (alcoholic cirrhosis, GH, NAFLD or NASH, stage IV primary biliary cirrhosis, alpha-1 antitrypsin deficiency) and hepatitis B carriers without cirrhosis. Other less common causes of cirrhosis include secondary biliary cirrhosis, Wilson's disease, sclerosing cholangitis, granulomatous disease, type IV glycogen storage disease, drug-induced liver disease, venous outflow obstruction, chronic right-sided heart failure, and tricuspid regurgitation.[68]

The panel recommends screening with US (every 6 months) and optional AFP testing for patients at risk for HCC. Additional imaging (abdominal multiphasic CT or MRI) is recommended in the setting of a rising serum AFP or following identification of a liver mass nodule 10 mm or greater on US, based on AASLD, OPTN (Organ Procurement and Transplantation Network), and LI-RADS (Liver Imaging Reporting and Data System) guidelines.[10,69,70] It is reasonable to screen patients with cross-sectional imaging (CT or MRI), and this is probably the most commonly employed, though not well-studied, method in the United States. Cost and availability may limit the widespread use of screening using cross-sectional imaging. Liver masses less than 10 mm are difficult to definitively characterize through imaging. If nodules of this size are found, then US and AFP testing should be repeated in 3 to 6 months.

Diagnosis

HCC is asymptomatic for much of its natural history. Nonspecific symptoms associated with HCC can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites.[25] Paraneoplastic syndromes, although rare, also can occur and include hypercholesterolemia, erythrocytosis, hypercalcemia, and hypoglycemia.[71]

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare hepatobiliary tumor type. Associated with a poor prognosis, resection is the only curative option.[72,73] Diagnosis of cHCC-CC through imaging is difficult since imaging characteristics consist of features of both HCC and cholangiocarcinoma.[72-74] Therefore, misdiagnosis may occur.[73,75] Further, though AFP levels may be elevated in patients with cHCC-CC, levels tend to not differ significantly from that of patients with HCC.[76] cHCC-CC may also be characterized by elevated serum CA 19-9, similar to intrahepatic cholangiocarcinoma.[74,77] If cHCC-CC is suspected, then thorough pathology review is recommended.

Imaging

HCC lesions are characterized by arterial hypervascularity, deriving most of their blood supply from the hepatic artery. This is unlike the

surrounding liver, which receives its blood supply from both the portal vein and hepatic artery.[78] Diagnostic HCC imaging involves the use of multiphasic liver protocol CT with IV contrast or multiphasic contrast-enhanced MRI.[10,79] 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.[10,69,80-83] LI-RADS also considers capsule appearance and threshold growth compared to previous imaging as part of diagnosis using CT or MRI imaging.[69]

Contrast-enhanced ultrasound (CEUS) is not commonly available in the United States. Though it may be used at centers of expertise as a problem-solving tool for characterization of indeterminate nodules, it is not recommended by the panel for whole-liver assessment, surveillance, or staging.[84] A meta-analysis including 22 studies with 1,721 patients with HCC showed that PET/CT may be useful for predicting prognosis (ie, overall survival [OS] and disease-free survival, *P*'s < .001),[85] but it is associated with low sensitivity for HCC detection.[86,87]

A meta-analysis including 241 studies showed that CT and MRI are more sensitive than US without contrast for detection of HCC, with MRI being more sensitive than CT.[88] Another meta-analysis including 40 studies and 1,135 patients with HCC also showed that MRI imaging is more sensitive than CT (*P* = .002) when assessing per-lesion.[89] A third meta-analysis that included only studies of patients with cirrhosis or chronic hepatitis (*N* = 30) also showed that US is less sensitive than CT and MRI (60%, 68%, and 81%, respectively) for diagnosis of HCC, though it is the most specific (97%, 93%, and 85%, respectively).[90] Contrast-enhanced MRI for detection of lesions up to 2 cm has acceptable sensitivity (78%) and excellent specificity (92%).[91] The use of gadoxetic acid disodium as a contrast agent is associated with good sensitivity (90%) and specificity (89%) for diagnosis of HCC.[92]

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 US demonstrated that the diagnosis of HCC can be established without biopsy confirmation if both imaging studies are conclusive.[82] However, as noted earlier, CEUS is not commonly utilized in the United States. Other investigators have suggested that a finding of classical arterial enhancement using a single imaging technique is sufficient to diagnose HCC in patients with cirrhosis and liver nodules between 1 and 2 cm detected during surveillance, thereby reducing the need for a biopsy.[93] In the updated AASLD guidelines, the algorithms for liver nodules between 1 and 2 cm have been changed to reflect these considerations.

Recommendations for imaging included in the NCCN Guidelines, if clinical suspicion for HCC is high (eg, following identification of a liver nodule on US or in the setting of a rising serum AFP level), are adapted from the updated guidelines developed by the AASLD.[10] The recommendations included in the NCCN Guidelines apply only to high-risk patients (ie, patients with cirrhosis, chronic HBV, or a history of previous HCC). For these patients, as well as patients with an incidental liver mass or nodule found on US or on another imaging exam, the guidelines recommend evaluation using multiphasic abdominal 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. If no mass is detected using multiphasic contrast-enhanced imaging, or if the observation is definitely benign, then the patients should return to a screening program (ie, US and AFP in 6 months). If there is suspicion that the diagnostic imaging test yielded a false

negative, then a different imaging method with or without AFP may be considered. If the observation is inconclusive (ie, not definitely HCC but not definitely benign), then multidisciplinary discussion and individualized workup may be pursued, including additional imaging or biopsy.

Biopsy

A diagnosis of HCC can be noninvasive in that biopsy confirmation may not be required. However, there are a few scenarios in which biopsy may be considered. First, biopsy may be considered when a lesion is suspicious for malignancy, but multiphasic CT or MRI results do not meet imaging criteria for HCC.[10,58,64,70,83] Second, biopsy may be done in patients who are not considered high risk for developing HCC (ie, patients who do not have cirrhosis, chronic HBV, or a previous history of HCC). Third, biopsy may be indicated in patients with conditions associated with formation of nonmalignant nodules that may be confused with HCC during imaging. These conditions include cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia.[94] Finally, biopsy may be considered in patients with elevated CA 19-9 or CEA, in order to rule out intrahepatic cholangiocarcinoma.[95,96] If transplant or resection is a consideration, patients should be referred to a transplant center or hepatic surgeon before biopsy since biopsy may not be necessary in certain patients with resectable malignant-appearing masses.

Both core needle biopsy and fine-needle aspiration biopsy (FNAB) have advantages and disadvantages in this setting. For example, FNAB may be associated with a lower complication rate when sampling deeply situated lesions or those located near major blood vessels. In addition, the ability to rapidly stain and examine cytologic samples can provide for immediate determinations of whether a sufficient sample has been obtained, as well as the possibility of an upfront tentative diagnosis.[97] However, FNAB is highly dependent on the skill of the cytopathologist,[98] and there are reports of high false-negative rates [82,99] as well as the possibility of false-positive findings with this procedure.[100] Although a core needle biopsy is a more invasive procedure, it has the advantage of providing pathologic information on both cytology and tissue architecture. Furthermore, additional histologic and immunohistochemical tests can be performed on the paraffin wax-embedded sample.[64,97,99] However, some evidence indicates that a core needle biopsy does not provide an accurate determination of tumor grade.[101]

Nevertheless, the use of biopsy to diagnose HCC is limited by a number of factors including sampling error, particularly when lesions are less than 1 cm.[10,31] 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. The guidelines emphasize that a growing mass with a negative biopsy does not rule out HCC. Continual monitoring with a multidisciplinary review including surgeons is recommended since resection may be indicated.

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 >400 ng/mL 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 >400 ng/mL and 46% of patients had normal serum AFP levels <20 ng/mL.[102] In patients with chronic liver disease, an elevated AFP could be more indicative of HCC than in non-infected patients.[103] Furthermore, AFP can also be elevated in intrahepatic

cholangiocarcinoma, some metastases from colon cancer, and germ cell tumors.[10,104] 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 growing liver mass has been shown to have a high positive predictive value for HCC in 2 retrospective analyses involving small numbers of patients.[105,106] However, the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institution.

The updated AASLD guidelines no longer recommend AFP testing as part of diagnostic evaluation.[10] 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,[107] which is in agreement with the updated AASLD guidelines recommendation.[10] 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. Further, assessment of AFP levels may be helpful in monitoring treatment response as appropriate (see *Surveillance* below).

Other serum biomarkers being studied in this setting include des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), and lens culinaris agglutinin-reactive AFP (AFP-L3), an isoform of AFP.[31,108,109] Although AFP was found to be more sensitive than DCP or AFP-L3 in detecting early-stage and very-early-stage HCC in a retrospective case control study, none of these biomarkers was considered optimal in this setting.[110] A 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.[65]

Initial Workup

The foundation of the initial workup of the patient diagnosed with HCC is a multidisciplinary evaluation involving investigations into the etiologic origin of liver disease, including a hepatitis panel for detection of hepatitis B and/or C viral infection (ie, HBsAg, hepatitis B surface antibody, hepatitis B core antibody [HBcAb], HBcAb IgM [recommended only in patients with acute viral hepatitis]), 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, HBcAb IgG (since an isolated HBcAb IgG may still indicate chronic HBV infection), and HCV antibodies. If viral load is positive, patients should be evaluated by a hepatologist for appropriate antiviral therapy.[19,111]

Common sites of HCC metastasis include the lung, abdominal lymph nodes, peritoneum, and bone.[112,113] Hence, routine chest CT is recommended since lung metastases are typically asymptomatic. Bone scan is recommended if suspicious bone pain is present or cross-sectional imaging raises the possibility of bone metastases. Multiphasic contrast-enhanced CT or MRI of the abdomen and pelvis is also used in the evaluation of the HCC tumor burden to detect the presence of metastatic disease, nodal disease, and vascular invasion; to assess whether evidence of portal hypertension is present; to provide an estimate of the size and location of HCC and the extent of chronic liver disease; and, in the case of patients being considered for resection, to

provide an estimate of the future liver remnant (FLR) in relation to the total liver volume.[81] Enlarged lymph nodes are commonly seen in patients with viral hepatitis, primary biliary cirrhosis, and other underlying liver disorders that predispose patients to HCC.[114] Detection of nodal disease by cross-sectional imaging can be challenging in patients with hepatitis.

Assessment of Liver Function

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), measurement of prothrombin time (PT) expressed as international normalized ratio (INR), albumin, and platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count and tests of kidney function (blood urea nitrogen [BUN] and creatinine), which are established prognostic markers in patients with liver disease.[115] Further assessment of hepatic functional reserve prior to hepatic resection in patients with cirrhosis may be performed with different tools.

The Child-Pugh classification has been traditionally used for the assessment of hepatic functional reserve in patients with cirrhosis.[116,117] The Child-Pugh score is an empirical score that incorporates laboratory measurements (ie, serum albumin, bilirubin, PT) as well as more subjective clinical assessments of encephalopathy and ascites. It provides a rough estimate of the liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis. Advantages of the Child-Pugh score include ease of performance (ie, can be done at the bedside) and the inclusion of clinical parameters.

An important additional assessment of liver function not included in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension (ie, esophagogastric varices, splenomegaly, abdominal collaterals, thrombocytopenia). Evidence of portal hypertension may also be evident on CT/MRI.[81] Measurement of hepatic venous pressure gradient is an evolving tool for the assessment of portal hypertension.[116-119] Esophagogastroduodenoscopy (EGD) may also be used to evaluate esophageal varices.

Model for End-Stage Liver Disease (MELD) is another system for the evaluation of hepatic reserve. MELD 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.[120,121] 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.[122] 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.[123]

Albumin and bilirubin are objectively measured, while ascites and encephalopathy, other scoring parameters used to calculate the Child-

Pugh score, are subjective. Therefore, another alternative to the Child-Pugh score is the Albumin-Bilirubin (ALBI) grade, a model proposed by Johnson et al that takes into account only serum bilirubin and albumin levels.[124] An analysis of almost 6,000 patients from Europe, the United States, Japan, and China showed that the ALBI grade, which stratifies patients into three risk categories, performs as well as the Child-Pugh score.[124] Further, patients scored as Child-Pugh grade A were categorized into either ALBI grade 1 or 2.

Indocyanine green (ICG) clearance test is extensively used in Asia for the assessment of liver function prior to hepatic resection in patients with cirrhosis.[125] In patients with HCC associated with cirrhosis, an ICG retention rate of 14% at 15 minutes (after intravenous injection of the dye) has been used as a cut-off for the selection of patients for hepatic resection.[126] The Japanese evidence-based clinical guidelines for HCC recommend the ICG retention rate at 15 minutes (ICGR-15) after intravenous injection for the assessment of liver function prior to surgery.[127] However, this test is not widely used in Western countries.

Pathology and Staging

Pathology

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

Staging

Clinical staging systems for the cancer patient can provide a more accurate prognostic assessment before and after a particular treatment intervention, and they may be used to guide treatment decision-making. Therefore, staging can have a critical impact on treatment outcome by facilitating appropriate patient selection for specific therapeutic interventions, and by providing risk stratification information following treatment. The key factors affecting prognosis in patients with HCC are the clinical stage, aggressiveness and growth rate of the tumor, the general health of the patient, the liver function of the patient, and the treatments administered.[79] A number of staging systems for patients with HCC have been devised.[128,129] Each of the staging systems includes variables that evaluate one or more of the factors listed above. For example, the Child-Pugh[130] and MELD scores[120] can be considered to be staging systems that evaluate aspects of liver function only.

The AJCC staging system provides information on the pathologic characteristics of resected specimens only,[131] whereas the Okuda system incorporates aspects of liver function and tumor characteristics.[132] The French classification (GRETCH) system incorporates the Karnofsky performance score as well as measurements of liver function and serum AFP.[133] Several staging systems include all parameters from other staging systems as well as additional parameters. For example, the Chinese University Prognostic Index (CUPI) system[134] and the Japanese Integrated Staging (JIS)[135] scores incorporate the TNM staging system and the Cancer of the Liver Italian Program (CLIP),[136] Barcelona Clinic Liver Cancer (BCLC),[137] SLiDe (stage, liver damage, des-gamma-carboxy prothrombin),[138] and JIS systems include the Child-Pugh score (with modified versions of CLIP and JIS substituting the MELD score for the Child-Pugh score).[139-141] In addition, the BCLC system also incorporates the Okuda system, as well as other tumor characteristics, measurements of liver function, and patient performance status.[142]

Although some of these systems have been found to be applicable for all stages of HCC (eg, BCLC),[31,142,143] limitations of all of these systems have been identified. For example, the AJCC staging system has limited usefulness since most patients with HCC do not undergo surgery. A number of studies have shown that particular staging systems perform well for specific patient populations likely related to differing etiologies. Furthermore, staging systems may be used to direct treatment and/or to predict survival outcomes following a particular type of therapeutic intervention. For example, the AJCC staging system has been shown to accurately predict survival for patients who underwent orthotopic liver transplantation.[144] The CLIP, CUPI, and GRETCH staging systems have been shown to perform well in predicting survival in patients with advanced disease.[145]

The CLIP system has been specifically identified as being useful for staging patients who underwent transarterial chemoembolization (TACE) and those treated in a palliative setting.[146,147] 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.[148] 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.[129] Furthermore, the BCLC staging system was shown to be very useful for predicting outcome in patients following liver transplantation or radiofrequency ablation (RFA).[149,150] In a multicenter cohort study of 1328 patients with HCC eligible for liver transplantation, survival benefit for liver transplantation was seen in patients with advanced liver cirrhosis and in those with intermediate tumors (BCLC stage D and stages B–C, respectively), regardless of the number and size of the lesions, provided there was no macroscopic vascular invasion and extrahepatic disease.

A 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, that was developed has been shown to perform well in predicting postoperative outcome for patients undergoing liver resection for HCC.[151] In addition, another study showed tumor size greater than 2 cm, multifocal tumors, and vascular invasion to be independent predictors of poor survival in patients with early HCC following liver resection or liver transplantation.[152] This staging system has been retrospectively validated in a population of patients with early HCC.[153]

Due to the unique characteristics of HCC that vary with the geographic region, many of the existing staging systems are specific to the region that they are developed in and there is no universal staging system that could be used across all institutions in different countries. Although a particular staging system (with the exception of the Child-Pugh score and TNM system) is not currently used in these guidelines, following an initial workup patients are stratified into one of the following 4 categories:

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

Treatment Options

All patients with HCC should be carefully evaluated for the many available treatment options. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, it is possible that the different etiologies of HCC and their effects on the host liver may impact treatment response and outcome. The treatment of patients with HCC often necessitates multidisciplinary care with the involvement of hepatologists, cross-sectional radiologists, interventional radiologists, transplant surgeons, pathologists, medical oncologists, and surgical oncologists, thereby requiring careful coordination of care.[31]

Surgery

Partial hepatectomy is a potentially curative therapy for patients with a solitary tumor of any size with no evidence of gross vascular invasion.[154] Partial hepatectomy for well-selected patients with HCC can now be performed with low operative morbidity and mortality (in the range of 5% or less).[155,156] Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC,[156-158] and some studies suggest that for selected patients with preserved liver function and early-stage HCC, liver resection is associated with a 5-year survival rate of about 70%.[158,159,160] However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.[142,157]

Since liver resection for patients with HCC includes surgical removal of functional liver parenchyma in the setting of underlying liver disease, careful patient selection, based on patient characteristics as well as characteristics of the liver and the tumor(s), is essential. Assessments of patient performance status must be considered; the presence of comorbidity has been shown to be an independent predictor of perioperative mortality.[161] Likewise, estimates of overall liver function and the size and function of the putative FLR, as well as technical considerations related to tumor and liver anatomy, must be taken into account before a patient is determined to have potentially resectable disease.

Resection is recommended only in the setting of preserved liver function. The Child-Pugh score provides an estimate of liver function, although it has been suggested that it is more useful as a tool to rule out patients for liver resection (ie, serving as a means to identify patients with substantially decompensated liver disease).[162] An evaluation of the presence of significant portal hypertension is also an important part of the surgical assessment. A meta-analysis including 11 studies showed that clinically significant portal hypertension is associated with increased 3- and 5-year mortality (pooled odds ratio [OR], 2.09; 95% CI, 1.52–2.88 for 3-year mortality; pooled OR, 2.07; 95% CI, 1.51–2.84 for 5-year mortality), as well as postoperative clinical decompensation (pooled OR, 3.04; 95% CI, 2.02–4.59).[163] 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. Further, limited resection may be feasible in cases where portal hypertension is mild. A prospective observational study of 223 cirrhotic patients with HCC showed that, though portal hypertension was significantly associated with liver morbidity following resection, it was only associated with worse survival when there was biochemical evidence of liver decompensation. A multivariate analysis showed that albumin, but not portal hypertension, was significantly associated with survival following resection.[164]

With respect to tumor characteristics and estimates of the FLR following resection, preoperative imaging is essential for surgical planning.[81] 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 hepatic veins/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.[155,165] However, in one study no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors 10 cm or greater.[155] Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence.[155,166,167] The role of liver resection for patients with limited and resectable multifocal disease and/or signs of major vascular invasion is controversial,[154,166,168] although results of a retrospective analysis showed a 5-year OS rate of 81% for selected patients with a single tumor 5 cm or less, or 3 or fewer tumors 3 cm or less undergoing liver resection.[169]

Another critical preoperative assessment includes evaluation of the postoperative FLR volume 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.[170] The panel recommends that this ratio be at least 25% in patients without cirrhosis and at least 30% to 40% in patients with chronic liver disease and a Child-Pugh A score.[171] For patients with an estimated FLR/total liver volume ratio below recommended values who are otherwise suitable candidates for liver resection, preoperative portal vein embolization (PVE) should be considered. PVE is a safe and effective procedure for redirecting blood flow toward the portion of the liver that will remain following surgery. Hypertrophy is induced in these segments of the liver while the embolized portion of the liver undergoes atrophy.[172]

In a recent analysis, Roayaie et al categorized 8,656 patients with HCC from Asia, Europe, and North America into one of four groups: 1) met standard criteria for resection and underwent resection (n = 718); 2) met standard criteria for resection but did not undergo resection (n = 144); 3) did not meet standard criteria for resection but underwent resection (n = 1,624); and 4) did not meet standard criteria for resection and did not undergo resection (n = 6,170).[173] For patients who met criteria for resection (including those who did not actually undergo resection), receiving a treatment other than resection was associated with an increased risk of mortality (hazard ratio [HR], 2.07; 95% CI, 1.35–3.17; $P < .001$). For patients who did not meet criteria for resection (including those who underwent resection), resection was associated with lower mortality, relative to embolization (HR, 1.43; 95% CI, 1.27–1.61; $P < .001$) and other treatments (eg, yttrium-90 radioembolization, external beam radiation, systemic therapy) (HR, 1.78; 95% CI, 1.36–2.34, $P < .001$). However, mortality rates for resection in these patients were worse than those for ablation (HR, 0.85; 95% CI, 0.74–0.98, $P = .022$) and transplantation (HR, 0.20; 95% CI, 0.14–0.27, $P < .001$). The study investigators suggest that criteria for resection could potentially be expanded, since patients who are not considered candidates for resection based on current criteria may still benefit.

Postoperative Adjuvant Therapy

The phase III STORM trial examined sorafenib, an antiangiogenic agent approved for treating unresectable HCC, for use in the adjuvant

setting for patients who underwent hepatic resection or ablation with curative intent. This international trial accrued 1114 patients, 62% of whom were Asian.[174] Patients were randomized to receive sorafenib (800 mg daily) or placebo until progression or for a maximum duration of 4 years. Treatment-emergent adverse events were high in both study groups, and sorafenib was not tolerable at the intended study dose (median dose achieved was 578 mg daily). No significant between-group differences were observed in OS, recurrence-free survival, and time to recurrence (TTR). The panel does not recommend sorafenib as adjuvant therapy.

Historically, postoperative prognosis for patients with HBV-related HCC has been poor. In a two-stage longitudinal study that enrolled 780 patients with HBV infection and HCC, viral load above 10,000 copies per milliliter was correlated with poor outcomes.[175] Adjuvant antiviral therapy in a postoperative setting may improve outcomes. In a randomized trial including 163 patients, antiviral therapy with lamivudine, adefovir, dipivoxil, or entecavir significantly decreased HCC recurrence (HR, 0.48; 95% CI, 0.32–0.70) and HCC-related death (HR, 0.26; 95% CI, 0.14–0.50), and improved liver function at 6 months after surgery (P = .001).[175] In another RCT including 200 patients who received R0 resection for HBV-related HCC, adefovir improved recurrence-free survival (P = .026) and OS (P = .001), relative to those who did not receive adefovir.[176] The relative risk (RR) of mortality with adefovir after resection was 0.42 (95% CI, 0.27–0.65; P < .001), and results indicated that antiviral therapy may protect against late tumor recurrence (HR, 0.35; 95% CI, 0.18–0.69; P = .002).

With the recent availability of newer potent antiviral therapies for chronic hepatitis C viral infection, similar trials need to be conducted. Two recent meta-analyses showed that antiviral therapy for HBV or HCV after curative HCC treatment may improve outcomes such as survival.[177,178] There is some concern that the rising use of DAAs might increase HCC recurrence or progression following treatment.[179-181] This is an area of controversy, and well-designed trials are needed to determine the mechanism through which HCC incidence increases.[179,180] The panel recommends that providers discuss the potential use of antiviral therapy with a hepatologist to individualize postoperative therapy.

Immunotherapy, or using the immune system to treat cancer, is beginning to be investigated as adjuvant HCC treatment. A systematic review of adjuvant treatment options for HCC including 14 studies (2 immunotherapy studies with 277 patients) showed that immunotherapy may prevent recurrence in resected HCC.[182] In a recent Korean phase III randomized trial, the efficacy and safety of activated cytokine-induced killer cells was examined as adjuvant immunotherapy for HCC.[183] Patients (N = 230) who received the adjuvant immunotherapy had greater recurrence-free survival relative to patients in the control group (HR, 0.63; 95% CI, 0.43–0.94; P = .01). Data are currently too preliminary for the panel to provide specific recommendations regarding immunotherapy treatment in an adjuvant setting.

Liver Transplantation

Liver transplantation is an attractive, potentially curative therapeutic option for patients with early HCC. It removes both detectable and undetectable tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small FLR. In a landmark study published in 1996, Mazzaferro et al proposed the Milan criteria (single tumors ≤5 cm in diameter or no more than three nodules ≤3 cm in diameter in patients with multiple tumors) for patients with unresectable HCC and cirrhosis.[184] The 4-year OS and relapse-free survival (RFS) rates were 85% and 92%, respectively, when liver transplantation was restricted to a subgroup of patients meeting the

Milan selection criteria. These results have been supported by studies in which patient selection for liver transplantation was based on these criteria.[185] These selection criteria were adopted by UNOS, because they identify a subgroup of patients with HCC whose liver transplantation results are similar to those who underwent liver transplantation for end-stage cirrhosis without HCC.

The UNOS criteria (radiologic evidence of a single tumor 2–5 cm in diameter, or 2 to 3 tumors 3 cm or less in diameter, and no evidence of macrovascular involvement or extrahepatic disease) specify that patients eligible for liver transplantation should not be candidates for liver resection. Therefore, liver transplantation has been generally considered to be the initial treatment of choice for patients with early-stage HCC and moderate-to-severe cirrhosis (ie, patients with Child-Pugh class B and C scores), with partial hepatectomy generally accepted as the best option for the first-line treatment of patients with early-stage HCC and Child-Pugh class A scores when tumor location is amenable to resection. Retrospective studies have reported similar survival rates for hepatic resection and liver transplantation in patients with early-stage HCC.[158,186-189] However, there are no prospective randomized studies that have compared the effectiveness of liver resection and liver transplantation for this group of patients.

Resection or liver transplantation can be considered for patients with Child-Pugh Class A liver function who meet UNOS criteria (www.unos.org/) and are resectable. Controversy exists over which initial strategy is preferable to treat such patients. The guidelines recommend that these patients be evaluated by a multidisciplinary team when deciding an optimal treatment approach.

The MELD score as a measure of liver function is also used as a measure of pre-transplant mortality.[120] MELD score was adopted by UNOS in 2002 to provide an estimate of risk of death within 3 months for patients on the waiting list for cadaveric liver transplant. MELD score is also used by UNOS to assess the severity of liver disease and prioritize the allocation of the liver transplants. According to the current UNOS policy, patients with T2 tumors (defined by UNOS as a single nodule between 2 and 5 cm or 2 or 3 nodules all <3 cm) receive an additional 22 priority MELD points (also called a “MELD-exception”).[122] In a retrospective analysis of data provided by UNOS of 15,906 patients undergoing first-time liver transplantation during 1997 to 2002 and 19,404 patients undergoing the procedure during 2002 to 2007, 4.6% of liver transplant recipients had HCC compared with 26% in 2002 to 2007, with most patients in the latter group receiving an “HCC MELD exception.”[190] In 2002 to 2007, patients with an “HCC MELD-exception” had similar survival to patients without HCC. Important predictors of poor posttransplantation survival for patients with HCC were a MELD score of ≥20 and serum AFP level of ≥455 ng/mL,[190] although the reliability of the MELD score as a measure of posttransplantation mortality is controversial. Survival was also significantly lower for the subgroup of patients with HCC tumors between 3 and 5 cm.

Expansion of the Milan/UNOS criteria to provide patients who have marginally larger HCC tumors with liver transplant eligibility is an active area of debate.[142,185,191,192] 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 larger than 4.5 cm (and cumulative tumor size <8 cm) as liver transplant candidates has been proposed by Yao et al at the University of California at San Francisco (UCSF).[193,194] 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%–93%).[191-193,195-197] 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.[185,191,195] Some support for the former objection comes from a large retrospective analysis of the UNOS database showing significantly lower survival for the subgroup of patients with tumors between 3 and 5 cm compared with those who had smaller tumors.[190]

There is a risk of tumor recurrence following liver transplantation. A group from France argued that the Milan criteria may be overly restrictive and thus developed a predictive model of HCC recurrence that combines AFP value with tumor size and number.[198] Analyses from samples of patients from France and Italy who underwent liver transplantation showed that this AFP model predicted an increase in 5-year risk of recurrence and decreased survival.[198,199] The panel does not provide specific recommendations regarding whether or not AFP should be considered a transplant criterion, and this may depend on local practice.

Bridge Therapy

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list.[200] It is considered for patients who meet the transplant criteria. A number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list.[201,202] These studies included RFA,[203-206] transarterial embolization (TAE),[207,208] chemoembolization,[205,209] TACE,[205,210,211] TACE with drug-eluting beads (DEB-TACE),[212] transarterial radioembolization (TARE) with yttrium-90 microspheres,[213] conformal radiation therapy (RT),[214] and sorafenib[215] as “bridge” therapies. In a more recent retrospective analysis of 130 patients with HCC (who met the Milan criteria) treated with TACE or DEB-TACE prior to liver transplant, DEB-TACE was associated with a trend towards higher response rates (necrosis ≥90%; 44.7% vs. 32.0%, *P* = .2834) and higher 3-year RFS rates after liver transplant (87.4% vs. 61.5%, *P* = .0493) compared to TACE.[212]

However, the small size and retrospective methodology of these studies, as well as the heterogeneous nature of the study populations, and the absence of RCTs evaluating the utility of bridge therapy for reducing the liver transplantation waiting list drop-out rate, limit the conclusions that can be drawn.[216,217] Nevertheless, the use of bridge therapy in this setting is increasing, and it is administered at most NCCN Member Institutions.

Downstaging Therapy

Downstaging therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) who are beyond the accepted transplant criteria.[200,218,219] A systematic review including 13 studies with 950 patients showed that downstaging decreased tumor burden to within Milan criteria (pooled success rate of 0.48; 95% CI, 0.39–0.58), with recurrence rates after transplantation at 16% (95% CI, 0.11–0.23).[220] Prospective studies have demonstrated that downstaging (prior to transplant) with percutaneous ethanol injection (PEI),[221] RFA,[221,222] TACE,[221-225] TARE with yttrium-90 microspheres,[224] and transarterial chemoinfusion[226] improves outcomes such as DFS and recurrence 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.[227-229] Further validation is needed to define the endpoints for successful downstaging prior to transplant.[219]

The guidelines recommend that patients meeting the UNOS criteria be considered for transplantation using either cadaveric or living donation. Patients with tumor characteristics that are marginally outside of the UNOS guidelines may be considered for transplantation at select institutions. For patients with initial tumor characteristics beyond the Milan criteria who have undergone successful downstaging therapy (ie, tumor currently meeting Milan criteria), transplantation can also be considered.

Locoregional Therapies

Locoregional therapies are directed toward inducing selective tumor necrosis, and are broadly classified into ablation and arterially directed therapies. Tumor necrosis induced by locoregional therapy is typically estimated by the extent to which contrast uptake on dynamic CT/MRI is diminished at a specified time following the treatment when compared with pretreatment imaging findings. The absence of contrast uptake within the treated tumor is believed to be an indication of tumor necrosis. A number of factors are involved in measuring the effectiveness of locoregional therapies, and the criteria for evaluating tumor response are evolving.[79,230-233] AFP response after locoregional therapy has also been reported to be a reliable predictor of tumor response, time to progression (TTP), progression-free survival (PFS), and OS.[234]

Ablation

In an ablative procedure, tumor necrosis can be induced either by chemical ablation (PEI or acetic acid injection), thermal ablation (RFA or microwave ablation [MWA]), or cryoablation. Any ablative procedure can be performed by laparoscopic, percutaneous, or open approaches. RFA and PEI are two commonly used ablation therapies.

The safety and efficacy of RFA and PEI in the treatment of Child-Pugh class A patients with early-stage HCC tumors (either a single tumor ≤5 cm or multiple tumors [up to 3 tumors] each ≤3 cm) has been compared in a number of RCTs.[235-242] Both RFA and PEI were associated with relatively low complication rates. RFA was shown to be superior to PEI with respect to complete response (CR) rate (65.7% vs. 36.2%, respectively; $P = .0005$)[240] and local recurrence rate (3-year local recurrence rates were 14% and 34%, respectively; $P = .012$).[238] Local tumor progression rates were also significantly lower for RFA than PEI (4-year local tumor progression rates were 1.7% and 11%, respectively; $P = .003$).[239]

In addition, in two studies patients in the RFA arm were shown to require fewer treatment sessions.[236,239] However, the OS benefit for RFA over PEI was demonstrated only in 3 randomized studies performed in Asia,[237-239] whereas 3 European randomized studies failed to show a significant difference in the OS between the two treatment arms.[236,240,241] In an Italian randomized trial of 143 patients with HCC, the 5-year survival rates were 68% and 70%, respectively, for PEI and RFA groups; the corresponding RFS rates were 12.8% and 11.7%, respectively.[241] Nevertheless, independent meta-analyses of randomized trials that have compared RFA and PEI have concluded that RFA is superior to PEI with respect to OS and tumor response in patients with early-stage HCC, particularly for tumors larger than 2 cm.[243-245] Results of some long-term studies show survival rates of over 50% at 5 years for patients with early HCC treated with RFA.[246-249]

The reported OS and recurrence rates vary widely across the studies for patients treated with RFA, which is most likely due to differences in the size and number of tumors and, perhaps more importantly, tumor biology and the extent of underlying liver function in the patient

populations studied. In multivariate analysis, Child-Pugh class, tumor size, and tumor number were independent predictors of survival.[247-249]

RFA and PEI have also been compared with resection in few randomized studies. In the only randomized study that compared PEI with resection in 76 patients without cirrhosis, with one or two tumors 3 cm or smaller, PEI was equally as effective as resection.[250] On the other hand, studies that have compared RFA and resection have failed to provide conclusive evidence (reviewed by Weis et al[242]). RFA and liver resection in the treatment of patients with HCC tumors have been evaluated in randomized prospective studies.[251-254] The results of one randomized trial showed a significant survival benefit for resection over RFA in 235 patients with small HCC conforming to the Milan criteria (single tumors ≤5 cm or multiple tumors with no more than 3 tumor nodules ≤3 cm).[252] The 5-year OS rates were 54.8% and 75.6%, respectively, for the RFA group and resection. The corresponding RFS rates for the 2 groups were 28.7% and 51.3%, respectively. However, more patients in the resection group were lost to follow-up than the RFA group. Conversely, other randomized studies demonstrated that percutaneous locally ablative therapy and RFA are as effective as resection for patients with small tumors.[251,253,254] These studies failed to show statistically significant differences in OS and DFS between the two treatment groups. In addition, in one of the studies, tumor location was an independent risk factor associated with survival.[253] These studies, however, were limited by the small number of patients (180 patients and 168 patients, respectively) and the lack of a non-inferiority design. Nevertheless, results from these studies support ablation as an alternative to resection in patients with small, properly located tumors.

RFA has been compared to resection in some meta-analyses. The results of one meta-analysis that included 2,535 patients (1,233 treated with resection and 1,302 treated with RFA) revealed that resection is associated with a significantly improved survival and higher rate of complications than ablation for patients with early-stage HCC, although there was no significant difference in local recurrence rates between the 2 treatment groups.[255] A more recent meta-analysis including 23 studies (mainly retrospective studies) with 15,482 patients with HCC showed that 1-, 3- and 5-year survival and recurrence-free survival rates were greater for resection than RFA, and 2- and 3-year recurrence rates were greater for RFA than resection.[256] Morbidity, but not mortality, from complications was greater for resection than for RFA. One meta-analysis comparing RFA to reresection in recurrent HCC (including 6 retrospective comparative studies) showed that 3- and 5-year DFS rates were greater for reresection, relative to RFA (OR, 2.25; 95% CI, 1.37–3.68; P = .001; OR, 3.70; 95% CI, 1.98–6.93; P < .001, respectively).[257] Despite an increase in morbidity due to complications, resection may be associated with greater survival and less recurrence, relative to RFA.

Subgroup analyses from some of retrospective studies suggest that tumor size is a critical factor in determining the effectiveness of RFA or resection.[203,204,258-260] In a series of 126 patients with cirrhosis or chronic hepatitis, although RFA was safe and effective for the treatment of both medium (between 3.1 and 5.0 cm) and large (between 5.1 and 9.5 cm) tumors, smaller and medium and/or noninfiltrating tumors were treated successfully significantly more often than large and/or infiltrating tumors.[258] Mazzaferro et al also reported similar findings in a prospective study of 50 consecutive patients with liver cirrhosis undergoing RFA while awaiting liver transplantation (the rate of overall complete tumor necrosis was 55% [63% for tumors ≤3 cm and 29% for tumors ≥3 cm]).[204] In a retrospective analysis, Vivarelli et al reported that OS and DFS were significantly higher with surgery compared to percutaneous RFA. The advantage of surgery was more evident for

Child-Pugh class A patients with single tumors of more than 3 cm in diameter, and the results were similar in 2 groups for Child-Pugh class B patients.[259] In another retrospective analysis of 40 Child-Pugh class A or B patients with HCC treated with percutaneous ablative procedures, the overall rate of complete necrosis was 53%, which increased to 62% when considering only the subset of tumors less than 3 cm treated with RFA.[203] In a propensity case-matched study that compared liver resection and percutaneous ablative therapies in 478 patients with Child-Pugh A cirrhosis, survival was not different between resection and ablation for tumors that met the Milan criteria; however, resection was associated with significantly improved long-term survival for patients with single HCC tumors larger than 5 cm or multiple tumors (up to 3 tumors) larger than 3 cm.[260] Median survival for the resection group was 80 months and 83 months, respectively, compared to 21.5 months and 19 months, respectively, for patients treated with ablative procedures.

Some investigators consider RFA as the first-line treatment in highly selected patients with HCC tumors that are 2 cm or less in diameter in an accessible location and away from major vascular and biliary structures.[261,262] In one study, RFA as the initial treatment in 218 patients with a single HCC lesion 2.0 cm or less induced complete necrosis in 98% of patients (214 of 218 patients).[261] After a median follow-up of 31 months, the sustained CR rate was 97% (212 of 218 patients). In a retrospective comparative study, Peng et al reported that percutaneous RFA was better than resection in terms of OS and RFS, especially for patients with central HCC tumors less than 2 cm.[262] The 5-year OS rates in patients with central HCC tumors were 80% for RFA compared to 62% for resection (P = .02). The corresponding RFS rates were 67% and 40%, respectively (P = .033).

MWA is emerging as an alternative to RFA for the treatment of patients with small or unresectable HCC.[263-267] So far, only 2 randomized trials have compared MWA with resection and RFA.[263,267] In the RCT that compared RFA with percutaneous microwave coagulation, no significant differences were observed between these two procedures in terms of therapeutic effects, complication rates, and the rates of residual foci of untreated disease.[263] In a randomized study that evaluated the efficacy of MWA and resection in the treatment of HCC conforming to Milan criteria, MWA was associated with lower DFS rates than resection with no differences in OS rates.[267]

Although inconclusive, available evidence suggests that the choice of ablative therapy for patients with early-stage HCC should be based on tumor size and location, as well as underlying liver function. Ablative therapies are most effective for tumors less than 3 cm that are in an appropriate location away from other organs and major vessels/bile ducts.

Arterially Directed Therapies

Arterially directed therapy involves the selective catheter-based infusion of particles targeted to the arterial branch of the hepatic artery feeding the portion of the liver in which the tumor is located.[268] Arterially directed therapy is made possible by the dual blood supply to the liver; whereas the majority of the blood supply to normal liver tissue comes from the portal vein, blood flow to liver tumors is mainly from the hepatic artery.[78] Furthermore, HCC tumors are hypervascular resulting from increased blood flow to tumor relative to normal liver tissue. Arterially directed therapies that are currently in use include transarterial bland embolization (TAE), TACE, DEB-TACE, and TARE with yttrium-90 microspheres.

The principle of TAE is to reduce or eliminate blood flow to the tumor, resulting in tumor ischemia followed by tumor necrosis. Gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres have been used to block arterial flow. TAE has been shown to be an effective treatment option for patients with unresectable HCC.[269-272] In a multicenter retrospective study of 476 patients with unresectable HCC, TAE was associated with prolonged survival compared to supportive care (P = .0002). The 1-, 2-, and 5-year survival rates were 60.2%, 39.3%, and 11.5%, respectively, for patients who underwent TAE. The corresponding survival rates were 37.3%, 17.6%, and 2%, respectively, for patients who underwent supportive care.[270] In a multivariate analysis, tumor size <5 cm and earlier CLIP stage were independent factors associated with a better survival. In another retrospective analysis of 322 patients undergoing TAE for the treatment of unresectable HCC in which a standardized technique (including small particles to cause terminal vessel blockade) was used, 1-, 2-, and 3-year OS rates of 66%, 46%, and 33%, respectively, were observed. The corresponding survival rates were 84%, 66%, and 51%, respectively, when only the subgroup of patients without extrahepatic spread or portal vein involvement was considered.[271] In multivariate analysis, tumor size 5 cm or larger, 5 or more tumors, and extrahepatic disease were identified as predictors of poor prognosis following TAE.

TACE is distinguished from TAE in that the goal of TACE is to deliver a highly concentrated dose of chemotherapy to tumor cells, prolong the contact time between the chemotherapeutic agents and the cancer cells, and minimize systemic toxicity of chemotherapy.[273] The results of two randomized clinical trials have shown a survival benefit for TACE compared with supportive care in patients with unresectable HCC.[274,275] In one study that randomized patients with unresectable HCC to TACE or best supportive care, the actuarial survival was significantly better in the TACE group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3%; P = .002).[274] Although death from liver failure was more frequent in patients who received TACE, the liver functions of the survivors were not significantly different between the two groups. In the other randomized study, which compared TAE or TACE with supportive care for patients with unresectable HCC, the 1- and 2-year survival rates were 82%; 63%, 75%, and 50%; and 63% and 27% for patients in the TACE, TAE, and supportive care arms, respectively.[275] The majority of the patients in the study had liver function classified as Child-Pugh class A, a performance status of 0, and a main tumor nodule size of about 5 cm. For the group of evaluable patients receiving TACE or TAE, partial and CR rates sustained for at least 6 months were observed in 35% (14/40) and 43% (16/37), respectively. However, this study was terminated early due to an obvious benefit associated with TACE. Although this study demonstrated that TACE was significantly more effective than supportive care (P = .009), there were insufficient patients in the TAE group to make any statement regarding its effectiveness compared to either TACE or supportive care.

A retrospective analysis of patients with advanced HCC undergoing embolization in the past 10 years revealed that TACE (with doxorubicin plus mitomycin C) is significantly associated with prolonged PFS and TTP but not OS, as compared to TAE.[276] In a multivariable analysis, the type of embolization and CLIP score were significant predictors of PFS and TTP, whereas CLIP score and AFP were independent predictors of OS.

Many of the clinical studies evaluating the effectiveness of TAE and/or TACE in the treatment of patients with HCC are confounded by use of a wide range of treatment strategies, including type of embolic particles, type of chemotherapy and type of emulsifying agent (for studies

involving TACE), and number of treatment sessions. The relative effectiveness of TACE over TAE has not been established in randomized trials. In a recent randomized trial, the effectiveness of TAE was compared to that of doxorubicin-based TACE in 101 patients with HCC.[277] Study investigators did not find statistically significant differences in response, PFS, and OS between the two groups.

Complications common to TAE and TACE include non-target embolization, liver failure, pancreatitis, and cholecystitis. Additional complications following TACE include acute portal vein thrombosis (PVT) and bone marrow suppression and pancreatitis (very rare), although the reported frequencies of serious adverse events vary across studies.[61,278] Reported rates of treatment-related mortality for TAE and TACE are usually well under 5%.[61,271,275,278] A transient postembolization syndrome involving fever, abdominal pain, and intestinal ileus is relatively common in patients undergoing these procedures.[61,278] There is evidence showing PVT and liver function categorized as Child-Pugh class C to be significant predictors of poor prognosis in patients treated with TACE.[279] However, TACE has been shown to be safe and feasible in patients with HCC and PVT,[280] and results of a meta-analysis (5 prospective studies with 600 patients) showed that TACE may improve survival in these patients, compared to patients who received control treatments.[281] Therefore, the panel considers main PVT to be only a relative contraindication for TACE. TACE is not recommended in those with liver function characterized as Child-Pugh class C (absolute contraindication). Because TAE can increase the risk of liver failure, hepatic necrosis, and liver abscess formation in patients with biliary obstruction, the panel recommends that a total bilirubin level greater than 3 mg/mL should be considered as a relative contraindication for TACE or TAE unless segmental injections can be performed. Furthermore, patients with previous biliary enteric bypass have an increased risk of intrahepatic abscess following TACE and should be considered for prolonged antibiotic coverage at the time of the procedure.[282,283]

TACE causes increased hypoxia leading to an up-regulation of vascular endothelial growth factor receptor (VEGFR) and insulin-like growth factor receptor 2 (IGFR-2).[284] Increased plasma levels of VEGFR and IGFR-2 have been associated with the development of metastasis after TACE.[285,286] These findings have led to the evaluation of TACE in combination with sorafenib in patients with residual or recurrent tumor not amenable to additional locoregional therapies.[287-294]

DEB-TACE has also been evaluated in patients with unresectable HCC.[295-302] In a randomized study (PRECISION V) of 212 patients with localized, unresectable HCC with Child-Pugh class A or B cirrhosis and without nodal involvement, TACE with doxorubicin-eluting embolic beads (DEB) induced statistically non-significant higher rates of CR, objective response, and disease control compared with conventional TACE with doxorubicin (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively).[297] Overall, DEB-TACE was not superior to conventional TACE with doxorubicin (P = .11) in this study. However, DEB-TACE was associated with a significant increase in objective response (P = .038) compared to conventional TACE in patients with Child-Pugh class B, ECOG performance status 1, bilobar disease, and recurrent disease. DEB-TACE was also associated with improved tolerability with a significant reduction in serious liver toxicity and a significantly lower rate of doxorubicin-related side effects, compared to conventional TACE.[297] In another small prospective randomized study (n = 83), Malagari et al also showed that DEB-TACE resulted in higher response rates, lower recurrences, and longer TTP compared to TAE in patients with intermediate-state HCC; however, this study also did not show any OS benefit for DEB-TACE.[298] A randomized study comparing DEB-TACE to

conventional TACE in 177 patients with intermediate stage, unresectable, persistent, or recurrent HCC revealed no significant efficacy or safety differences between the two approaches; however, DEB-TACE was associated with less post-procedural abdominal pain.[302] Conversely, Dhanasekaran et al reported a survival advantage for DEB-TACE over conventional TACE in a prospective randomized study of 71 patients with unresectable HCC.[299] However, these results are from underpowered studies and need to be confirmed in large prospective studies.

Results from non-randomized phase II studies and a retrospective analysis suggest that concurrent administration of sorafenib with TACE or DEB-TACE may be a treatment option for patients with unresectable HCC.[288-294,303] In a phase III randomized trial, however, sorafenib when given following treatment with TACE did not significantly prolong TTP or OS in patients with unresectable HCC that responded to TACE.[294]

TARE is a method that involves internal delivery of high-dose beta radiation to the tumor-associated capillary bed, thereby sparing the normal liver tissue.[268,304] TARE is accomplished through the catheter-based administration of microspheres (glass or resin microspheres) embedded with yttrium-90, an emitter of beta radiation. There is a growing body of literature to suggest that radioembolization might be an effective treatment option for patients with liver-limited, unresectable disease,[305-310] though additional randomized clinical trials are needed to determine the harms and benefits of TARE with yttrium-90 microspheres in patients with unresectable HCC.[311] Although radioembolization with yttrium-90 microspheres, like TAE and TACE, involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia.[305]

Reported complications of TARE include cholecystitis/bilirubin toxicity, gastrointestinal ulceration, radiation-induced liver disease, and abscess formation.[305,307,312] A partial response (PR) rate of 42.2% was observed in a phase II study of 108 patients with unresectable HCC with and without PVT treated with TARE and followed for up to 6 months.[305] Grade 3/4 adverse events were more common in patients with main PVT. However, patients with branch PVT experienced a similar frequency of adverse events related to elevated bilirubin levels as patients without PVT. Results from a single-center, prospective longitudinal cohort study of 291 patients with HCC treated with TARE showed a significant difference in median survival times based on liver function level (17.2 months for Child-Pugh class A patients and 7.7 months for Child-Pugh class B patients; $P = .002$).[307] Median survival for Child-Pugh class B patients and those with PVT was 5.6 months.

A multicenter study analyzed radiation segmentectomy, a selective TARE approach that limits radioembolization to 2 or fewer hepatic segments. This technique was evaluated in 102 patients with solitary unresectable HCC not amenable to RFA treatment due to tumor proximity to critical structures. The procedure resulted in CR, PR, and stable disease (SD) in 47%, 39%, and 12% of patients, respectively.[310]

In comparative effective analyses, patients with HCC treated with TACE or TARE with yttrium-90 microspheres had similar survival times.[313-315] However, TARE resulted in a longer TTP and less toxicity than TACE.[314] These findings need to be confirmed in randomized controlled studies.

External Beam Radiation Therapy

External beam radiation therapy (EBRT) allows focal administration of high-dose radiation to liver tumors while sparing surrounding liver tissue, thereby limiting the risk of radiation-induced liver damage in

patients with unresectable or inoperable HCC.[316,317] Advances in EBRT, such as intensity-modulated radiation therapy (IMRT), have allowed for enhanced delivery of higher radiation doses to the tumor while sparing surrounding critical tissue. Stereotactic body radiation therapy (SBRT) is an advanced technique of EBRT that delivers large ablative doses of radiation. There is growing evidence (primarily from non-RCTs) supporting the usefulness of SBRT for patients with unresectable, locally advanced, or recurrent HCC.[318-322]

In a phase II trial of 50 patients with inoperable HCC treated with SBRT after incomplete TACE, SBRT induced CRs and PRs in 38.3% of patients within 6 months of completing SBRT.[321] The 2-year local control rate, OS, and PFS rates were 94.6%, 68.7%, and 33.8%, respectively. In another study that evaluated the long-term efficacy of SBRT for patients with primarily small HCC ineligible for local therapy or surgery (42 patients), SBRT induced an overall CR rate of 33%, with 1- and 3-year OS rates of 92.9% and 58.6%, respectively.[318] In patients with recurrent HCC treated with SBRT, tumor size, recurrent stage, and Child-Pugh were identified as independent prognostic factors for OS in multivariate analysis.[320] In a report from Princess Margaret Cancer Centre on 102 patients treated with SBRT for locally advanced HCC in sequential phase I and phase II trials, Bujold et al reported a 1-year local control rate of 87% and a median survival of 17 months. The majority of these patients were at high risk with relatively advanced-stage tumors (55% of patients had tumor vascular thrombosis, and 61% of patients had multiple lesions with a median sum of largest diameter of almost 10 cm and a median diameter of 7.2 cm for the largest lesion).[322] A retrospective analysis comparing RFA and SBRT in 224 patients with inoperable, nonmetastatic HCC showed that SBRT may be a preferred option for tumors 2 cm or larger.[323]

SBRT has also been shown to be an effective bridging therapy for patients with HCC and cirrhosis awaiting liver transplant.[324-326]

All tumors, irrespective of their location, may be amenable to SBRT, IMRT, or 3D conformal RT. SBRT is often used for patients with 1 to 3 tumors with minimal or no extrahepatic disease. There is no strict size limit, so SBRT may be used for larger lesions if there is sufficient uninvolved liver and liver radiation dose constraints can be respected. The majority of safety and efficacy data on the use of SBRT are available for patients with HCC and Child-Pugh A liver function; limited safety data are available for the use of SBRT in patients with Child-Pugh B or poorer liver function.[319,322,327-329] Those with Child-Pugh B cirrhosis can safely be treated, but they may require dose modifications and strict dose constraint adherence. The safety of SBRT for patients with Child-Pugh C cirrhosis has not been established, as there are not likely to be clinical trials available for this group of patients with a very poor prognosis.

In 2014, ASTRO (American Society for Radiation Oncology) released a model policy supporting the use of proton beam therapy (PBT) in some oncology populations.[330] In a recent phase II study, 94.8% of patients with unresectable HCC who received high-dose hypofractionated PBT demonstrated >80% local control after two years, as defined by RECIST criteria.[331] In a recent meta-analysis including 70 studies, charged particle therapy (mostly including PBT) was compared to SBRT and conventional radiotherapy.[332] OS (RR, 25.9; 95% CI, 1.64–408.5; $P = .02$), PFS (RR, 1.86; 95% CI, 1.08–3.22; $P = .013$), and locoregional control (RR, 4.30; 95% CI, 2.09–8.84; $P < .001$) through five years were greater for charged particle therapy than for conventional radiotherapy. There were no significant differences between charged particle therapy and SBRT for these outcomes. Analyses from a prospective RCT including 69 patients with HCC

showed that PBT tended to be associated with improved 2-year local control (*P* = .06), better progression-free survival (*P* = .06), and fewer hospitalization days following treatment (*P* < .001), relative to patients who received TACE.[333] The panel advises that PBT may be considered and appropriate in select settings for treating HCC. Several ongoing studies are continuing to investigate the impact of hypofractionated PBT on hepatocellular carcinoma outcomes (eg, NCT02395523, NCT02632864), including randomized trials comparing PBT to RFA (NCT02640924) and PBT to TACE (NCT00857805).

Combinations of Locoregional Therapies

Results from retrospective analyses suggest that the combination of TACE with RFA is more effective (both in terms of tumor response and OS) than TACE or RFA alone or resection in patients with single or multiple tumors fulfilling the UNOS or Milan criteria[169,334] or in patients with single tumors up to 7 cm.[335,336] The principle behind the combination of RFA and embolization is that the focused heat delivery of RFA may be enhanced by vessel occlusion through embolization since blood circulation inside the tumor may interfere with the transfer of heat to the tumor.

However, randomized trials that have compared the combination of ablation and embolization with ablation or embolization alone have shown conflicting results. Combination therapy with TACE and PEI resulted in superior survival compared to TACE or PEI alone in the treatment of patients with small HCC tumors, especially for patients with HCC tumors measuring less than 2 cm.[337,338] In a more recent randomized study, Peng et al reported that the combination of TACE and RFA was superior to RFA alone in terms of OS and RFS for patients with tumors less than 7 cm, although this study had several limitations (small sample size and the study did not include TACE alone as one of the treatment arms, thus making it difficult to assess the relative effectiveness of TACE alone compared to the combination of TACE and RFA).[339] In one prospective randomized study, Shibata et al reported that the combination of RFA and TACE was equally as effective as RFA alone for the treatment of patients with small (≤3 cm) tumors.[340] Conversely, results from other randomized trials indicate that the survival benefit associated with the combination approach is limited only to patients with tumors that are between 3 cm and 5 cm.[341,342] In the randomized prospective trial that evaluated sequential TACE and RFA versus RFA alone in 139 patients with recurrent HCC ≤5 cm, the sequential TACE and RFA approach was better than the RFA in terms of OS and RFS only for patients with tumors between 3.1 and 5.0 cm (*P* = .002 and *P* < .001) but not for those with tumors 3 cm or smaller (*P* = .478 and *P* = .204).[342]

The results of a meta-analysis of 10 randomized clinical trials comparing the outcomes of TACE plus percutaneous ablation with those of TACE or ablation alone suggest that while there is a significant OS benefit for the combination of TACE and PEI compared to TACE alone for patients with large HCC tumors, there was no survival benefit for the combination of TACE and RFA in the treatment of small lesions as compared with that of RFA alone.[343]

Therefore, available evidence suggests that the combination of TACE with RFA or PEI may be effective, especially for patients with larger lesions that do not respond to either procedure alone. A recent meta-analysis including 25 studies with 2,577 patients with unresectable HCC showed that TACE combined with RT (eg, 3D conformal RT, SBRT) was associated with a complete tumor response (OR, 2.73; 95% CI, 1.95–3.81) and survival through 5 years (OR, 3.98; 95% CI, 1.89–8.50), compared with TACE delivered alone.[344] However, this combination was also associated with increased gastroduodenal ulcers

(OR, 12.80; 95% CI, 1.57–104.33), levels of ALT (OR, 2.46; 95% CI, 1.30–4.65), and total bilirubin (OR, 2.16; 95% CI, 1.05–4.45).

NCCN Recommendations for Locoregional Therapies

The relative effectiveness of locoregional therapies compared to resection or liver transplantation in the treatment of patients with HCC has not been established. The consensus of the panel is that liver resection or transplantation, if feasible, is preferred for patients who meet surgical or transplant selection criteria since these are established potentially curative therapies. Locoregional therapy (eg, ablation, arterially-directed therapies, EBRT) is the preferred treatment approach for patients who are not amenable to surgery or liver transplantation. Systemic therapy with sorafenib can also be considered.

All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. Tumors should be in a location accessible for laparoscopic, percutaneous, or open approaches. Lesions in certain portions of the liver may not be accessible for ablation. Similarly, ablative treatment of tumors located on the liver capsule may cause tumor rupture with track seeding. Tumor seeding along the needle track has been reported in less than 1% of patients with HCC treated with RFA.[345-347] Lesions with subcapsular location and poor differentiation seem to be at higher risk for this complication.[345] During an ablation procedure, major vessels in close proximity to the tumor can absorb large amounts of heat (known as the “heat sink effect”), which can decrease the effectiveness and significantly increase local recurrence rates. The panel emphasizes that caution should be exercised when ablating lesions near major bile ducts, and other intra-abdominal organs such as the colon, stomach, diaphragm, heart, and gallbladder to decrease complications.

The consensus of the panel is that ablation alone may be a curative treatment for tumors ≤3 cm. In well-selected patients with small, properly located tumors ablation should be considered as definitive treatment in the context of a multidisciplinary review.[251,253] Tumors between 3 and 5 cm may be treated with a combination of ablation and arterially directed therapies to prolong survival, as long as the tumor location is favorable to ablation.[341,342,348] The panel recommends that patients with unresectable or inoperable lesions larger than 5 cm should be considered for treatment using arterially directed therapies or systemic therapy.

All HCC tumors, irrespective of location in the liver, may be amenable to arterially directed therapies, provided that the arterial blood supply to the tumor may be isolated.[271,275,305,335] An evaluation of the arterial anatomy of the liver, patient’s performance status, and liver function is necessary prior to the initiation of arterially directed therapy. In addition, more individualized patient selection that is specific to the particular arterially directed therapy being considered is necessary to avoid significant treatment-related toxicity. General patient selection criteria for arterially directed therapies include unresectable or inoperable tumors not amenable to ablation therapy only, and the absence of large volume extrahepatic disease. Minimal extrahepatic disease is considered a “relative” contraindication for arterially directed therapies.

All arterially directed therapies are relatively contraindicated in patients with bilirubin greater than 3 mg/dL unless segmental treatment can be performed. TARE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin greater than 2 mg/dL.[307] Arterially directed therapies are relatively contraindicated in patients with main PVT and are contraindicated in Child-Pugh Class C patients. The angiographic endpoint of embolization may be chosen by the treating physician.

Sorafenib following arterially directed therapies may be appropriate in patients with adequate liver function once bilirubin returns to baseline, if there is evidence of residual or recurrent tumor not amenable to additional locoregional therapies.[289-291] Ongoing phase III randomized studies are evaluating the combination of sorafenib with TACE or DEB-TACE in patients with unresectable HCC (NCT01906216, NCT01829035). The findings of these studies will clarify whether sorafenib when used in combination with arterially directed therapies improves outcomes**.**

The panel recommends that SBRT can be considered as an alternative to ablation and/or embolization techniques or when these therapies have failed or are contraindicated (in patients with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation and those with local disease but who are not considered candidates for surgery due to performance status or comorbidity). Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions in bone or brain.[349] The panel encourages prospective clinical trials evaluating the role of SBRT in patients with unresectable, locally advanced, or recurrent HCC.

Systemic Therapy

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

Clinical studies evaluating the use of cytotoxic chemotherapy in the treatment of patients with advanced HCC have typically reported low response rates, and evidence for a favorable impact of chemotherapy on OS in patients with HCC is lacking.[350-352]

Sorafenib

Sorafenib, an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis, has been evaluated in two randomized, placebo-controlled, phase III trials for the treatment of patients with advanced or metastatic HCC.[352,353]

In one of these phase III trials (SHARP trial), 602 patients with advanced HCC were randomly assigned to sorafenib or best supportive care. In this study, advanced HCC was defined as patients not eligible for or those who had disease progression after surgical or locoregional therapies.[352] 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 class A) and good performance status (>90% of patients had ECOG performance status of 0 or 1). Disease etiology for the enrolled patients was varied with hepatitis C, alcohol, and hepatitis B determined to be the cause of HCC in 29%, 26%, and 19% of patients, respectively. Median OS was significantly longer in the sorafenib arm (10.7 months in the sorafenib arm vs. 7.9 months in the placebo group; HR, 0.69; 95% CI, 0.55–0.87; $P < .001$). Sorafenib was well-tolerated in both randomized clinical trials. Adverse sorafenib-related events in the SHARP trial included diarrhea, weight loss, and hand-foot skin reaction.[352]

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).[353] Although inclusion/exclusion criteria and the percentage of patients with Child-Pugh A liver function (97%) were

similar in the Asia-Pacific and SHARP studies, there were significant differences in patient and disease characteristics between the two studies. Only Asian patients were enrolled in the Asia-Pacific study and these patients were more likely to be younger, to have HBV-related disease, to have symptomatic disease, and to have a higher number of tumor sites than patients in the SHARP study. The HR for the sorafenib arm compared with the placebo arm (HR, 0.68; CI, 0.50–0.93; *P* = .014) was nearly identical to that reported for the SHARP study, although median OS was lower in both treatment and placebo groups in the Asia-Pacific study (6.5 months vs. 4.2 months).

Results of the subgroup analyses from the Asia-Pacific study and the SHARP study suggest that sorafenib may be an effective treatment in patients with advanced HCC irrespective of the baseline ECOG performance status (0–2), tumor burden (presence or absence of macroscopic vascular invasion and/or extrahepatic spread), presence or absence of either lung or lymph node metastasis, tumor stage, prior therapy, and disease etiology (alcohol-related or HCV-related HCC).[354,355] Sorafenib is also an effective treatment irrespective of serum concentrations of ALT/AST/AFP and total bilirubin levels; the hepatic function is not appreciably affected.[355,356] Ultimately, however, the survival difference between the treatment conditions and the placebo groups in the SHARP trial[354] and the Asia-Pacific study[353] were small (2.8 months in the SHARP trial and 2.3 months in the Asia-Pacific study) and not clinically meaningful.

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).[357] 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.[358] A subgroup analysis of data from this study showed lower median OS for patients in the Child-Pugh class B group compared with those in the Child-Pugh class A group (3.2 months vs. 9.5 months).[359] Other investigators have also reported lower median OS for Child-Pugh class B patients.[360-364] In a large retrospective study of 148 patients with advanced HCC treated with sorafenib, the median OS for Child-Pugh class B patients was 5.5 months compared to 11.3 months for Child-Pugh class A patients.[360] Among Child-Pugh class B patients, the baseline AST level was a significant predictor of OS. The median OS was 6.5 months for patients with AST levels <100 U/L compared to 2.1 months for those with AST levels ≥100 U/L. In the GIDEON trial, the safety profile of sorafenib was generally similar for Child-Pugh class B and Child-Pugh class A patients. However, the median OS was shorter in the Child-Pugh class B patients, reflecting the poorer prognosis and natural history of liver disease in this patient population.[363] In the final analysis of the trial, in the intent-to-treat population (3,213 patients), the median OS was 13.6 months for the Child-Pugh class A patients compared to 5.2 months for the Child-Pugh class B patients.[365] The TTP was, however, similar for the 2 groups (4.7 months and 4.4 months, respectively). The median OS was shorter in patients with a higher Child-Pugh B score.

In a phase II study that evaluated the efficacy and tolerability of sorafenib in the treatment of Asian patients with advanced HBV-related HCC (36 patients with Child-Pugh A cirrhosis, 13 patients with Child-Pugh B cirrhosis, and 2 patients with Child-Pugh C cirrhosis), there were no significant differences in OS (5.5 months vs. 5 months), grade 3 or 4 hematologic toxicities (17% vs. 33%; *P* = .18), and nonhematologic toxicities (47% for Child-Pugh class A and Child-Pugh class B or C; *P* = .97) between Child-Pugh class A and Child-Pugh class B or C patients.[366] However, the grade 3 or 4 liver toxicity, (although not statistically different) was 73% for Child-Pugh class B or

C patients compared to 56% for the Child-Pugh class A patients.[366] Chiu et al also reported similar findings in a retrospective study that explored the tolerability and survival in patients with underlying liver cirrhosis (108 patients with Child-Pugh class A and 64 patients with Child-Pugh class B) treated with sorafenib.[364] However, in this study, although the median OS was similar in patients with Child-Pugh class A and Child-Pugh class B with a score of 7 (6.1 months and 5.4 months, respectively), the median OS was significantly lower for those with Child-Pugh class B with a score of 8 or 9 (2.7 months).

While more mature results from ongoing studies are needed to recommend sorafenib for Child-Pugh B or C patients, available evidence so far suggests that the Child-Pugh status is a strong predictor of OS for patients with unresectable HCC treated with sorafenib and it should be used with caution in Child-Pugh class B patients. A meta-analysis including three phase III RCTs in which sorafenib was the control arm (3,256 patients with advanced HCC) showed that, when taking into account HBV and HCV status, OS was significantly improved only in patients who were both HBV negative and HCV positive (log HR, -0.26; 95% CI, -0.46 to -0.04).[367]

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.[359] 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.[368] Finally, it is important to mention that validated criteria to evaluate tumor response (such as RECIST[230] or EASL criteria[142]) to sorafenib are needed since true objective volumetric responses are rare.[357]

Sorafenib combined with erlotinib for patients with advanced HCC was recently assessed in a phase III RCT (N = 720).[369] Results showed that this combination did not significantly improve survival, relative to sorafenib delivered with a placebo. Further, disease control rate was significantly lower for patients who received the sorafenib/erlotinib combination, relative to those in the comparison group (P = .021). Treatment duration was shorter for those receiving the sorafenib/erlotinib combination (86 vs. 123 days).

In a recent phase III trial, linifanib, a VEGF and PDFG receptor inhibitor, was compared to sorafenib in patients with advanced HCC (N = 1,035).[370] Patients who were randomized to receive linifanib had a greater objective response rate (P = .018), but also a greater rate of serious adverse events (P < .001) and adverse events leading to dose reduction and drug discontinuation (P < .001), compared to patients randomized to receive sorafenib. Overall, survival did not significantly differ between the two drugs.

Second-line Therapy Following Sorafenib

The randomized, double-blind, placebo-controlled, international phase III RESORCE trial assessed the efficacy and safety of regorafenib in 573 patients with HCC and Child-Pugh A liver function who progressed on sorafenib.[371] Compared to the placebo (median survival of 7.8 months), regorafenib (median survival of 10.6 months) improved OS (HR, 0.63; 95% CI, 0.50–0.79; P < .001), PFS (HR, 0.46; 95% CI, 0.37–0.56; P < .001), TTP (HR, 0.44; 95% CI, 0.36–0.55; P < .001), objective response (11% vs. 4%; P = .005), and disease control (65% vs. 36%; P < .001). Adverse events were universal among patients randomized to receive regorafenib (n = 374), with the most frequent grade 3 or 4

treatment-related events being hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and diarrhea (3%). Seven deaths that occurred were considered by the investigators to have been related to treatment with regorafenib. Based on the results of this trial, the FDA approved use of regorafenib in 2017 for patients with HCC who progressed on or after sorafenib, and the panel recommends regorafenib as a category 1 option for this setting in patients with Child-Pugh A liver function.

In a recent phase III RCT, the effects of the VEGF receptor inhibitor ramucirumab were assessed as second-line therapy following sorafenib in patients with advanced HCC (*N* = 565).[372] Though this regimen did not improve OS, median PFS (HR, 0.63; 95% CI, 0.52–0.75; *P* < .001) and time to tumor progression (HR, 0.59; 95% CI, 0.49–0.72; *P* < .001) were improved, relative to the placebo group. Data from a phase II trial has demonstrated potential activity of axitinib and tolerability for patients with intermediate/advanced Child Pugh class A disease as a second-line therapy.[373]

Other Agents and Emerging Therapies

Other therapeutic agents have been assessed in patients with advanced HCC. Nivolumab, an anti-PD-1 antibody, was assessed in a phase I/II nonrandomized multi-institution trial including 48 patients with advanced HCC in a dose-escalation phase and 214 patients in a dose-expansion phase.[374] In patients treated with nivolumab 3 mg/kg, the objective response rate was 20% for patients in the dose-expansion phase and 15% for patients in the dose-escalation phase. The disease control rates were 64% and 58% for patients in these phases, respectively. Nine-month OS for patients in the dose-expansion phase was 74%. In the dose-escalation phase, 25% of patients had grade 3 or 4 treatment-related adverse events.

FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) was compared to doxorubicin in a phase III trial including 371 Asian patients with advanced HCC.[375] The primary OS endpoint was not met, but PFS was greater for FOLFOX4, relative to doxorubicin (HR, 0.62; 95% CI, 0.49–0.79; *P* < .001).

Bevacizumab, another VEGF receptor inhibitor, has shown modest clinical activity (single agent or in combination with erlotinib or chemotherapy) in phase II studies in patients with advanced HCC.[376-380] Randomized trials are required to determine the role of bevacizumab in the management of patients with advanced HCC. At the present time, the consensus of the panel is that there are no mature data to support the use of bevacizumab in the treatment of patients with HCC.

The effects of metuximab administered after RFA were assessed in a single-center RCT (*N* = 127).[381] The median time to tumor recurrence was greater in those randomized to receive metuximab following RFA, relative to those randomized to only receive RFA (HR, 0.60; 95% CI, 0.38–0.96; *P* = .03).

Additionally, trials are ongoing to evaluate experimental systemic therapies for emerging molecular targets in hepatobiliary cancers. For patients with advanced disease, providers may wish to consider molecular profiling to determine eligibility for clinical trials of new molecular targeted agents (ie, for agents targeting mutated versions of *IDH1, IDH2, FGF, and KRAS*, among others).[382,383]

Management of Resectable Disease

Results of an RCT (*N* = 200) showed that partial hepatectomy was associated with better overall and recurrence-free survival, relative to combination TACE and RFA.[384] The consensus of the panel is that initial treatment with either partial hepatectomy or transplantation

should be considered for patients with liver function characterized by a Child-Pugh class A score, lack of portal hypertension, and 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.[385,386] The presence of extrahepatic metastasis is considered to be a contraindication for resection. Hepatic resection is controversial in patients with limited 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. Patients with tumor characteristics that are marginally outside of the UNOS guidelines may be considered for transplantation at select institutions. Additionally, transplantation can be considered for patients who have undergone successful downstaging therapy (ie, tumor currently meeting Milan criteria). If transplant is not feasible, the panel recommends hepatic resection for this group of patients.

Management of Advanced Disease

Liver transplantation is indicated for patients who meet the UNOS criteria. Based on clinical experience with non-transplant candidates, the panel considers locoregional therapy to be the preferred approach for treating patients with unresectable disease, or for those who are medically inoperable due to comorbidity. However, sorafenib has produced a small but statistically significant survival benefit in large, randomized clinical trials. 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 (liver-confined) 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. These recommendations are consistent with those offered by the European Association for the Study of the Liver/European Organization for Research and Treatment of Cancer and the consensus statement from the 2009 Asian Oncology Summit.[2]

Nevertheless, the panel considers the data on safety and dosing of sorafenib to be inadequate in patients with liver function characterized as Child-Pugh class B, and recommends extreme caution when considering use of sorafenib in patients with elevated bilirubin levels. The panel recommends that best supportive care measures be administered to patients with unresectable disease, metastatic disease, or extensive tumor burden. Biopsy should be considered to confirm metastatic disease prior to initiation of treatment.

Alternative treatment options for patients with advanced disease include chemotherapy [systemic (category 2B) or intra-arterial].There are limited data supporting the use of cytotoxic chemotherapy for patients with unresectable disease,[350,351] and it should be used

preferably in the context of a clinical trial. Patients with advanced disease who have progressed on or after sorafenib and have Child-Pugh Class A liver function may receive regorafenib (category 1).

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 ongoing surveillance — specifically, multiphasic high-quality cross-sectional imaging of the chest, abdomen, and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months. Multiphasic cross-sectional imaging (ie, CT or MRI) is the preferred method for surveillance following treatment because of its reliability in assessing arterial vascularity,[58] which is associated with increased risk of HCC recurrence following treatment.[387,388] AFP levels are associated with poor prognosis following treatment[193,389,390] and should be measured every 3 months for 2 years, then every 6 to 12 months. Re-evaluation according to the initial workup should be considered in the event of disease recurrence.

Biliary Tract Cancers

Gallbladder Cancer

Gallbladder cancer is the most common of all the biliary tract cancers. A vast majority of gallbladder cancers are adenocarcinomas.[391] Incidence steadily increases with age, women are more likely to be diagnosed with gallbladder cancer than men, and incidence and mortality rates in the United States are highest among American Indian and Alaska Native men and women.[392] Globally, there are pockets of increased incidence in Korea, Japan, some areas of Eastern Europe and South America, Spain, and in women in India, Pakistan, and Ecuador.[393,394] Analyses from SEER data from 1973 to 2009 showed that, out of total cases diagnosed, the proportion of cases that are diagnosed as distant disease (vs. regional and localized disease) is increasing over time.[395] Gallbladder cancer is characterized by local and vascular invasion, extensive regional lymph node metastasis, and distant metastases. Gallbladder cancer is also associated with shorter median survival duration, a much shorter TTR, and shorter survival duration after recurrence than hilar cholangiocarcinoma.[396]

Risk Factors

Cholelithiasis with the presence of chronic inflammation is the most prevalent risk factor for gallbladder cancer, and the risk increases with stone size.[397,398] Calcification of the gallbladder (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been regarded as a risk factor for gallbladder cancer, with estimates of cancer in up to 22% of gallbladders with calcification.[397] More recent reports, however, suggest that the risk of developing gallbladder cancer in patients with gallbladder calcification is lower than anticipated, with gallbladder cancer being present in 7% to 15% of these patients.[399-401] Other risk factors include anomalous pancreaticobiliary duct junctions, gallbladder polyps (solitary and symptomatic polyps greater than 1 cm), chronic typhoid infection, primary sclerosing cholangitis, and inflammatory bowel disease.[398,402-404] Adenomyomatosis of the gallbladder is also a potential, albeit somewhat controversial, risk factor. Prophylactic cholecystectomy may be beneficial for patients who are at high risk of developing gallbladder cancer;[397] this procedure is performed in certain parts of the world with high disease incidence, although definitive data suggesting a benefit are lacking. Patients with a history of chronic cholecystitis or pancreaticobiliary maljunction have a greater prevalence of gallbladder cancers that are microsatellite instability-high,[405] and HER2/neu overexpression has been found in 13% of gallbladder cancer cases.[406]

Staging and Prognosis

In the AJCC staging system, gallbladder cancer is classified into 4 stages based on the depth of invasion into the gallbladder wall and the extent of spread to surrounding organs and lymph nodes. In the revised 2010 AJCC staging system, stage groupings have been changed to distinguish hilar node involvement from other regional nodes and to better correlate with resectability of the tumor and patient outcome.[131] Lymph node metastasis is now classified as stage IIIB (N1) or stage IVB (N2), and locally unresectable T4 tumors have been reclassified as stage IV. An analysis of 10,705 patients diagnosed with gallbladder cancer between 1989 and 1996 in the National Cancer Data Base demonstrated that this revised staging system provided an improved prognostic discrimination of patients with stage III and stage IV disease.[407]

Tumor stage is the strongest prognostic factor for patients with gallbladder cancer.[408,409] In an analysis of about 2500 patients with gallbladder cancer from hospital cancer registries throughout the United States, the 5-year survival rates were 60%, 39%, and 15% for patients with stage 0, stage I, and stage III disease, respectively, whereas the corresponding survival rates were only 5% and 1% for patients with stage III and stage IV disease, respectively.[408] Results from a retrospective analysis of 435 patients treated at a single center showed a median OS of 10.3 months for the entire cohort of patients.[409] The median survival was 12.9 months and 5.8 months for those presenting with stage IA-III and stage IV disease, respectively. It is important to note, however, that these retrospective analyses did not control well for treatment-related variables. In a sample of 122 patients with gallbladder cancer identified in a prospectively maintained database, liver involvement at re-resection (after cholecystectomy) was associated with decreased RFS and disease-specific survival for patients with T2 tumors (median RFS was 12 months vs. not reached for patients without liver involvement, $P = .004$; median was 25 months vs. not reached for patients without liver involvement, $P = .003$) but not in patients with T1b tumors.[410]

Diagnosis

Gallbladder cancer is often diagnosed at an advanced stage due to the aggressive nature of the tumor, which can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation that mimics that of biliary colic or chronic cholecystitis. Hence, it is common for a diagnosis of gallbladder cancer to be an incidental finding at cholecystectomy for presumed benign gallbladder disease or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis. In a retrospective review of 435 patients diagnosed and treated with curative resection at a single center during the period of 1995 to 2005, 123 patients (47%) were diagnosed with gallbladder cancer as an incidental finding after laparoscopic cholecystectomy.[409] Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on US or biliary tract obstruction with jaundice or chronic right upper quadrant abdominal pain. The presence of jaundice in patients with gallbladder cancer is usually associated with a poor prognosis; patients with jaundice are more likely to have advanced-stage disease (96% vs. 60%; $P < .001$) and significantly lower disease-specific survival (6 months vs.16 months; $P < .0001$) than those without jaundice.[411] In a sample of 82 patients with gallbladder cancer who presented with jaundice, the resectability rate was low (7%), with even fewer having negative surgical margins (5%).[411]

Workup

The initial workup of patients presenting with a gallbladder mass or disease suspicious for gallbladder cancer should include liver function tests and an assessment of hepatic reserve. High-quality contrast-

enhanced cross-sectional imaging (CT and/or MRI) of the chest, abdomen, and pelvis is recommended to evaluate tumor penetration through the wall of the gallbladder and the presence of nodal and distant metastases, and to detect the extent of direct tumor invasion of other organs/biliary system or major vascular invasion.[412] CT is more useful than US for the detection of lymph node involvement, adjacent organ invasion, and distant metastasis; MRI may be useful for distinguishing benign conditions from gallbladder cancer.[391] Although the role of PET scan has not been established in the evaluation of patients with gallbladder cancer, emerging evidence from retrospective studies indicates that it may be useful for the detection of radiologically occult regional lymph node and distant metastatic disease in patients with otherwise potentially resectable disease.[413,414,415]

For patients presenting with jaundice, additional workup should include cholangiography to evaluate for hepatic and biliary invasion of tumor. Noninvasive magnetic resonance cholangiography (MRCP) is preferred over endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), unless a therapeutic intervention is planned.[412]

Carcinoembryonic antigen (CEA) and CA 19-9 testing could be considered as part of initial workup (in conjunction with imaging studies). Elevated serum CEA levels (higher than 4.0 ng/mL) or CA 19-9 levels (higher than 20.0 units/mL) could be suggestive of gallbladder cancer.[416] While CA 19-9 had higher specificity (92.7% vs. 79.2% for CEA), its sensitivity was lower (50% vs. 79.4% for CEA). However, these markers are not specific for gallbladder cancer and CA 19-9 could also be elevated in patients with jaundice from other causes. Therefore, the panel recommends carrying out these tests as part of a baseline assessment, and not for diagnostic purposes.

Surgical Management

The surgical approach for the management of all patients with resectable gallbladder cancer is the same, with the exception that in patients with an incidental finding of gallbladder cancer on pathologic review, the gallbladder has been removed. Complete resection with negative margins remains the only curative treatment for patients with gallbladder cancer.[417] The optimal resection consists of cholecystectomy with a limited hepatic resection (typically segments IVB and V) and portal lymphadenectomy to encompass the tumor with negative margins.[418] Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct if possible. Extended hepatic resections (beyond segments IV B and V) and resection of the bile duct may be necessary in some patients to obtain negative margins, depending on the stage and location of the tumor, depth of tumor invasion, proximity to adjacent organs, and expertise of the surgeon.

A simple cholecystectomy is an adequate treatment for patients with T1a tumors, with the long-term survival rates approaching 100%.[419] Cholecystectomy combined with hepatic resection and lymphadenectomy is associated with an improved survival for patients with T2 or higher tumors. There is some controversy regarding the benefit of radical resection over simple cholecystectomy for patients with T1b tumors, and there is some risk of finding residual nodal disease or hepatic disease when re-resecting these patients.[420-425] Some studies have demonstrated an associated improvement in cancer-specific survival for patients with T1b and T2 tumors and no improvement in survival for patients with T3 tumors.[421-423] Other reports suggest that survival benefit associated with extended resection and lymphadenectomy is seen only in patients with T2 tumors and some T3 tumors with localized hepatic invasion and limited regional node involvement.[424,425]

Empiric major hepatic resection and bile duct resection have been shown to increase morbidity without any demonstrable difference in survival.[418,426] An analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990 to 2002 showed that in a multivariate analysis, higher T and N stage, poor differentiation, and common bile duct involvement were independent predictors of poor disease-specific survival.[426] Major hepatectomy and common bile duct excision significantly increased overall perioperative morbidity (53%) and were not independently associated with long-term survival.[426] Fuks et al from the AFS-GBC-2009 study group also reported that bile duct resection resulted in a postoperative morbidity rate of 60% in patients with incidental finding of gallbladder cancer.[418] However, for patients with incidental finding of gallbladder cancer, Pawlik et al have suggested that common duct resection should be performed at the time of re-resection for those with positive cystic duct margins due to the presence of residual disease.[427] However, occasionally the cystic duct stump can be re-resected to a negative margin.

With these data in mind, the guidelines recommend that extended hepatic resections (beyond segments IV B and V) should be performed only when necessary to obtain negative margins (R0 resection) in well-selected clinical situations as discussed above.[421,423-425] Bile duct excision should only be performed in the presence of adherent nodal disease and/or locally invasive disease.[426]

Among patients with an incidental finding of gallbladder cancer, there is some evidence that a delayed resection due to referral to a tertiary cancer center or a radical resection following an initial noncurative procedure is not associated with a survival deficit compared with immediate resection.[428,429] However, these comparisons are difficult to interpret due to selection bias. Nevertheless, in all patients with a convincing clinical evidence of gallbladder cancer, the guidelines recommend that surgery should be performed by an experienced surgeon who is prepared to do a definitive resection of the tumor. If expertise is unavailable, patients should be referred to a center with available expertise. The panel is also of the opinion that surgery should not be performed in situations where the extent and resectability of the disease has not been established. Consultation with a pathologist with expertise in the hepatobiliary region should be considered, and careful review of the pathology report for T stage, cystic duct margin status, and other margins following surgery are crucial.

Management of Resectable Disease

All patients should undergo cross-sectional imaging (CT and/or MRI) of the chest, abdomen, and pelvis prior to surgery to evaluate for the presence of distant metastases. Staging laparoscopy has been shown to identify radiographically occult disseminated disease in patients with primary gallbladder cancer.[430] In a prospective study that evaluated the role of staging laparoscopy in 409 patients diagnosed with primary gallbladder cancer, Agarwal et al reported a significantly higher yield in locally advanced tumors compared with early-stage tumors (25.2% vs. 10.7%; $P = .02$); the accuracy for detecting unresectable disease and a detectable lesion in locally advanced tumors (56.0% and 94.1%, respectively) was similar to that in early-stage tumors (54.6% and 100%, respectively).[430] The use of staging laparoscopy obviated the need for laparotomy in 55.9% of patients with unresectable disease. Staging laparoscopy, however, is of relatively low yield in patients with incidental finding of gallbladder cancer, since disseminated disease is relatively uncommon; higher yields may be obtained in patients who are at higher risk for disseminated metastases (those with poorly differentiated, T3 or higher tumors or margin-positive tumors at cholecystectomy).[431] Since the risk of peritoneal metastases is high for patients with primary gallbladder cancer, staging laparoscopy should be

considered for this group of patients if no distant metastases are found on imaging or if there is any suspicion of metastatic disease on imaging that is not amenable to percutaneous biopsy.[430] In patients with incidental finding of gallbladder cancer, staging laparoscopy can be considered for patients who are at high risk for disseminated metastases.[431]

Radical cholecystectomy (cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision) is the preferred primary treatment for patients with incidental finding of gallbladder cancer at surgery. The guidelines also recommend intraoperative staging and consideration of intraoperative photography prior to definitive resection, and procurement of frozen section of gallbladder for biopsy in select cases where diagnosis is unclear. Frozen section of suspicious lymph node may also be obtained. Contraindications for resection include tumors with distant lymph node metastases in the celiac axis or aortocaval groove (retropancreatic) or metastatic disease (ie, distant metastases, nodal metastases beyond the porta hepatis, extensive involvement of the porta hepatis causing jaundice or vascular encasement).

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.[419] Extended hepatic resection and lymphadenectomy with or without bile duct excision is recommended for patients with T1b or greater lesions.[421,423,424] Re-resection to achieve negative margins is recommended for patients with an incidental finding of T1b, T2, or T3 gallbladder cancer since a significant percentage of these patients have been found to harbor residual disease within the liver and common bile duct.[409,427] Port site disease is associated with peritoneal metastases, and prophylactic port site resection is not associated with improved survival or disease recurrence in patients with incidental findings of gallbladder cancer and, thus, should not be considered during definitive resection.[432,433]

For patients with a suspicious mass detected on imaging or in patients presenting with jaundice, the guidelines recommend cholecystectomy plus en bloc hepatic resection, lymphadenectomy, and bile duct excision. A biopsy is not necessary and a diagnostic laparoscopy is recommended prior to definitive resection.[430] In selected patients where the diagnosis is not clear it may be reasonable to perform a cholecystectomy (including intraoperative frozen section) followed by the definitive resection during the same setting if pathology confirms cancer. However, jaundice in patients with gallbladder cancer is considered a relative contraindication to surgery and outcomes are generally poor in these patients; only a rare group of patients with localized node-negative disease potentially benefit from complete resection.[411,434,435] In patients with jaundice, if gallbladder cancer is suspected, surgery should only be performed if a complete resection is feasible. These patients should be carefully evaluated prior to surgery and referral to an experienced center should be considered. The guidelines recommend consideration of preoperative biliary drainage for patients with jaundice. However, caution should be exercised in patients with biliary obstruction as drainage is not always feasible and can be dangerous. Decisions regarding biliary drainage should be made by a multidisciplinary team.

Gallbladder cancer that is locally advanced or has lymph node involvement is associated with a poor prognosis, but neoadjuvant chemotherapy may allow one to evaluate the biology of the tumor and identify patients who are most likely to benefit from surgical intervention. In a recent prospective feasibility study, patients with

locally advanced gallbladder cancer received either neoadjuvant chemoradiation (*n* = 25) or neoadjuvant chemotherapy without RT if paraaortic node involvement was present (*n* = 15).[436] Eight percent of patients who received chemoradiation, and 27% of patients who received chemotherapy underwent extended cholecystectomy following neoadjuvant treatment. Out of the six patients who underwent resection, four (66.7%) were alive at 18-month follow-up. In a retrospective database analysis including 74 patients with locally advanced or lymph node-positive disease who received systemic therapy, 30% of patients underwent resection.[437] Out of the 22 patients who underwent resection, 45% underwent definitive resection, with OS being significantly greater for patients who underwent definitive resection compared to those who did not (51 months vs. 11 months, respectively; *P* = .003). In patients for whom there is evidence of locoregionally advanced disease (ie, nodal disease or evidence of other high-risk disease), neoadjuvant chemotherapy should be considered. However, more studies are needed in order to recommend specific regimens.

Fluoropyrimidine chemoradiation and fluoropyrimidine or gemcitabine chemotherapy are options for adjuvant treatment. See the section on *Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers*.

Management of Unresectable or Metastatic Disease

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

In patients with unresectable or metastatic gallbladder cancer and jaundice, biliary drainage is an appropriate palliative procedure and should be done before instituting chemotherapy if technically feasible.[434] However, caution should be exercised in patients with biliary obstruction as drainage is not always feasible and can be dangerous. Decisions regarding biliary drainage should be made by a multidisciplinary team. Biliary drainage followed by chemotherapy can result in improved quality of life. CA 19-9 testing can be considered after biliary decompression.

Surveillance

There are no data to support 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, then annually up to 5 years. Assessment of CEA and CA 19-9 may also be considered as clinically indicated. Re-evaluation according to the initial workup should be considered in the event of disease relapse or progression.

Cholangiocarcinomas

Cholangiocarcinomas encompass all tumors originating in the epithelium of the bile duct. More than 90% of cholangiocarcinomas are adenocarcinomas and are broadly divided into 3 histologic types based on their growth patterns: mass-forming, periductal-infiltrating, and intraductal-growing.[438] Cholangiocarcinomas are diagnosed throughout the biliary tree and are typically classified as either intrahepatic or

extrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas. Analyses of SEER data from 1973 to 2012 showed that incidence of intrahepatic cholangiocarcinoma is increasing [annual percentage change (APC), 2.3%], while incidence of extrahepatic cholangiocarcinoma has remained stable (APC, 0.14%).[439] Study investigators suggested that the increase in incidence of intrahepatic cholangiocarcinoma may be due to an improvement in the ability to accurately diagnose intrahepatic cholangiocarcinoma, such as with imaging, molecular diagnostics, and pathology. These cancers may have previously been diagnosed as cancers of unknown primary, in which incidence has decreased from 1973 to 2012 (APC, -1.87%).

Intrahepatic cholangiocarcinomas are located within the hepatic parenchyma and have also been called “peripheral cholangiocarcinomas” (Figure 1). Extrahepatic cholangiocarcinomas occur anywhere within the extrahepatic bile duct — from the junction of the right and left hepatic ducts to the common bile duct, including the intrapancreatic portion (Figure 1) — and are further classified into hilar or distal tumors. Hilar cholangiocarcinomas (also called Klatskin tumors) occur at or near the junction of the right and left hepatic ducts; distal cholangiocarcinomas are extrahepatic lesions arising in the extrahepatic bile ducts above the ampulla of Vater.[440] Hilar cholangiocarcinomas are the most common type of extrahepatic cholangiocarcinomas.

There is a potentially increasing role for molecular profiling of cholangiocarcinomas. Isocitrate dehydrogenase 1 and 2 (*IDH1/2)* mutations are found in 10% to 23% of intrahepatic cholangiocarcinomas.[441-446] The prognostic effect of this mutation is uncertain,[447] as is the clinical benefit of targeting this mutation therapeutically. Mutations in *FGFR2* fusions have been found in 8% to 14% of intrahepatic cholangiocarcinomas.[448-450] *FGFR* mutations may be associated with a favorable prognosis.[446,449] Ongoing phase II studies are currently investigating *FGFR* as a therapeutic target (NCT02924376, NCT02272998). *HER-2* gene amplification has been found in up to 18% of extrahepatic cholangiocarcinomas.[451] In patients with lymph node metastases, *HER-2* gene amplification may be associated with poor prognosis.[451]

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

Risk Factors

No predisposing factors are identified in most patients diagnosed with cholangiocarcinoma,[452] although there is evidence that particular risk factors may be associated with the disease in some patients. These risk factors, like those for gallbladder cancer, are associated with the presence of chronic inflammation. Primary sclerosing cholangitis, chronic calculi of the bile duct (hepatolithiasis), choledochal cysts, and liver fluke infections are well-established risk factors for cholangiocarcinoma. Unlike gallbladder cancer, however, cholelithiasis is not thought to be linked with cholangiocarcinoma.[453] Inflammatory bowel disease may also be a risk factor for cholangiocarcinoma, though this association may be confounded by primary sclerosing cholangitis.[454] Other risk factors for intrahepatic cholangiocarcinoma have been found to include HCV, HBV, cirrhosis, diabetes, obesity, alcohol, NAFLD, and tobacco.[455] Several case-controlled studies from Asian and Western countries have reported hepatitis C viral infection as a significant risk factor for intrahepatic cholangiocarcinoma.[456-459] This may be responsible for the increased incidence of intrahepatic

cholangiocarcinoma observed at some centers, although future studies are needed to further explore this putative association.[460]

Staging and Prognosis

Intrahepatic Cholangiocarcinoma

In the 6th edition of the AJCC staging system, intrahepatic cholangiocarcinoma was staged identically to HCC. However, this staging system did not include predictive clinicopathologic features (multiple hepatic tumors, regional nodal involvement, and large tumor size) that are specific to intrahepatic cholangiocarcinoma.[461] In other reports, tumor size had no effect on survival in patients undergoing complete resection.[462,463] In a SEER database analysis of 598 patients with intrahepatic cholangiocarcinoma who had undergone surgery, 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.[462] In this study, tumor size had no independent effect on survival. These findings were confirmed in a subsequent multi-institutional international study of 449 patients undergoing surgery for intrahepatic cholangiocarcinoma.[463] The 5-year survival rate was higher for patients who lacked all three risk factors (multiple tumors, vascular invasion, and N1 disease) than those with one or more risk factors (38.3%, 27.3%, and 18.1%, respectively) and, more importantly, tumor number and vascular invasion were of prognostic significance only in patients with N0 disease. Although tumor size was associated with survival in the univariate analysis, it was not of prognostic significance in a multivariate analysis.

In the revised 7th edition of the AJCC staging system, intrahepatic cholangiocarcinoma has a new staging classification that is independent of the staging classification used for HCC.[131] The new classification focuses on multiple tumors, vascular invasion, and lymph node metastasis. Farges et al from the AFC-IHCC study group validated the new staging classification in 163 patients with resectable intrahepatic cholangiocarcinoma.[464] The revised classification was useful in predicting survival according to the TNM staging. With a median follow-up of 34 months, the median survival was not reached for patients with stage I disease, was 53 months for those with stage II disease ($P = .01$), and was 16 months for those with stage III disease ($P < .0001$).

Extrahepatic Cholangiocarcinoma

In the previous AJCC classification, extrahepatic cholangiocarcinomas (hilar, middle, and distal tumors) were grouped together as a single entity. The 7th edition of AJCC staging system includes a separate TNM classification for hilar and distal bile duct tumors, based on the extent of liver involvement and distant metastatic disease.[131] Although the depth of tumor invasion is not part of the TNM classification, it has been identified as an independent predictor of outcome in patients with distal as well as hilar cholangiocarcinomas.[465,466]

The modified Bismuth-Corlette staging system[467] and the Blumgart staging system[468] are used for the classification of hilar cholangiocarcinomas. The modified Bismuth-Corlette staging system classifies hilar cholangiocarcinomas into 4 types based on the extent of biliary duct involvement. However, this does not include other clinicopathologic features such as vascular encasement, lymph node involvement, distant metastases, and liver atrophy. In addition, both the AJCC and the Bismuth-Corlette staging systems are not useful for predicting resectability or survival. The Blumgart staging system is a useful preoperative staging system that predicts resectability, likelihood of metastatic disease, and survival.[468,469] In this staging system, hilar cholangiocarcinomas are classified into 3 stages (T1-T3) based on the location and extent of bile duct involvement, the presence or absence

of portal venous invasion, and hepatic lobar atrophy.[468] Negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after resection; increasing T-stage significantly correlated with reduced R0 resection rate, distant metastatic disease, and lower median survival.[469]

Diagnosis

Early-stage cholangiocarcinomas may only manifest as mild changes in serum liver function tests. Patients with intrahepatic cholangiocarcinoma, due to their often late presentation, are more likely to present with nonspecific symptoms such as fever, weight loss, and/or abdominal pain; symptoms of biliary obstruction are uncommon because these tumors do not necessarily involve the common hepatic/bile duct. Intrahepatic cholangiocarcinoma may be detected incidentally as an isolated intrahepatic mass on imaging.[81] In contrast, patients with extrahepatic cholangiocarcinoma are likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.

Workup

The initial workup should include liver function tests. CEA and CA 19-9 testing can be considered for baseline assessment, although these markers are not specific for cholangiocarcinoma; they are also associated with other malignancies and benign conditions.[470] Further, CA 19-9 may be falsely elevated due to jaundice.[471] Since the diagnosis of HCC versus intrahepatic cholangiocarcinoma can be difficult, AFP testing may also be considered, especially in patients with chronic liver disease. Further, there are a number of mixed HCC/intrahepatic cholangiocarcinoma cases in which AFP may be elevated. Early surgical consultation with a multidisciplinary team is recommended as part of the initial workup for assessment of resectability in intrahepatic and extrahepatic cholangiocarcinomas. 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). Providers should only proceed with biopsy once transplant or resectability status has been determined. For patients who may be transplant candidates, transperitoneal biopsy is contraindicated and will likely preclude transplantation. For patients undergoing resection, biospy is usually not necessary. When necessary, intraluminal biopsy is the preferred biopsy approach for potential transplant patients.

In patients who are not resectable, direct visualization of the bile duct with directed biopsies is the ideal technique for the workup of cholangiocarcinoma. Multiphasic CT/MRI with IV contrast of the abdomen and pelvis to assess the involvement of the liver, major vessels, nearby lymph nodes, and distant sites is also recommended when extrahepatic cholangiocarcinoma is suspected.[472,473] There are no pathognomonic CT/MRI features associated with intrahepatic cholangiocarcinoma, but CT/MRI can indicate the involvement of major vessels and the presence of vascular anomalies and satellite lesions.[472] Therefore, multiphasic CT/MRI with IV contrast is used to help determine tumor resectability by characterizing the primary tumor, its relationship to nearby major vessels and the biliary tree, the presence of satellite lesions and distant metastases in the liver, and lymph node involvement, if present.[81,472] In addition, chest CT (with or without) should be performed, and staging laparoscopy may be considered in conjunction with surgery if no distant metastasis is found. Endoscopic US may be useful for distal common bile duct cancers for defining a mass or abnormal thickening, which can direct biopsies. For extrahepatic cholangiocarcinoma, endoscopic US should be done after

surgical consultation to prevent jeopardizing a patient's candidacy for transplantation. EGD and colonoscopy are recommended as part of initial workup for patients with intrahepatic cholangiocarcinoma since a mass diagnosed as adenocarcinoma can be metastatic disease. Pathologic workup can be suggestive of cholangiocarcinoma but is not definitive. IgG4-associated cholangitis, which presents with biliary strictures and obstructive jaundice, may mimic extrahepatic cholangiocarcinoma.[474,475] Therefore, serum IgG4 should be considered in patients for whom a diagnosis of extrahepatic cholangiocarcinoma is not clear, in order to avoid an unnecessary surgical resection.[476,477]

Contrast-enhanced MRCP and/or CT as a diagnostic modality is recommended over direct cholangiography for the diagnosis of bile duct cancers.[478,479] MRCP has been shown to have a higher sensitivity, specificity, and diagnostic accuracy compared to ERCP in the diagnosis and pre-treatment staging of hilar cholangiocarcinomas.[480] Data also support the use of MRCP and CT as the preferred method of cholangiography for the assessment of bile duct tumors.[481] Direct cholangiography should only be necessary as a diagnostic procedure in patients who are not resectable or in patients in whom a therapeutic intervention is necessary. ERCP/PTC is not recommended for the diagnosis of extrahepatic cholangiocarcinoma, since this is associated with complications and contamination of the biliary tree. For distal bile duct tumors in which a diagnosis is needed or where palliation is indicated, an ERCP allows for complete imaging of the bile duct and stenting of the obstruction. In addition, brush cytology of the bile duct can be obtained for pathologic evaluation. Since many of the patients with extrahepatic cholangiocarcinoma present with jaundice, workup should include noninvasive cholangiography with cross-sectional imaging to evaluate local tumor extent.[472] Although the role of PET imaging has not been established in the evaluation of patients with cholangiocarcinoma, emerging evidence indicates that it may be useful for the detection of regional lymph node metastases and distant metastatic disease in patients with otherwise potentially resectable disease.[413-415,482,483]

Management of Intrahepatic Cholangiocarcinoma

Complete resection is the only potentially curative treatment for patients with resectable disease, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis. The optimal surgical margin associated with improved survival and reduced risk of recurrence in patients undergoing surgery remains uncertain, with some reports documenting R0 resection as a significant predictor of survival and recurrence,[484-489] while others suggest that margin status is not a significant predictor of outcome.[490,491] Ribero et al from the Italian Intrahepatic Cholangiocarcinoma Study Group reported that margin-negative resection was associated with significantly higher survival rates (the estimated 5-year survival rates were 39.8% vs. 4.7% for patients with a positive margin) and significantly lower recurrence rates (53.9% vs. 73.6% for those with a positive margin); however, in patients resected with negative margins, the margin width had no long-term impact on survival (P = .61) or recurrence (P > .05) following resection.[489] Farges et al from the AFC-IHCC-2009 study group reported that although R1 resection was the strongest independent predictor of poor outcome in pN0 patients undergoing surgery, its impact on survival was very low in pN+ patients (median survival was 18 months and 13 months, respectively, after R0 and R1 resections; P = .1).[491] In this study, a margin width >5 mm was an independent predictor of survival among pN0 patients with R0 resections, which is in contrast to the findings reported by Ribero et al.[489] A retrospective analysis of 535 patients with intrahepatic cholangiocarcinoma who underwent resection showed that other factors associated with worse survival post-resection include multifocal disease (HR, 1.49; 95% CI,

1.19–1.86; *P* = .01), lymph node metastasis (HR, 2.21; 95% CI, 1.67–2.93; *P* < .01), and vascular invasion (HR, 1.39; 95% CI, 1.10–1.75; *P* = .006).[492]

Available evidence (although not conclusive) supports the recommendation that hepatic resection, regardless of extent, with negative margins should be the goal of surgical therapy for patients with potentially resectable disease.[493] Extensive hepatic resections are often necessary to achieve clear margins since the majority of tumors present as large masses.[489]

Initial surgical exploration should include assessment of multifocal liver disease, lymph node metastases, and distant metastases. Multifocal liver disease, distant (beyond the porta hepatis) nodal metastases, and distant metastases contraindicate surgery as these generally indicate advanced incurable disease. In highly selected situations, resection can be considered. A preoperative biopsy is not always necessary prior to definitive and potentially curative resection. Although multifocal liver tumors (including satellite lesions), lymph gross node metastases to the porta hepatis, and distant metastases are considered relative contraindications to surgery, surgical approaches can be considered in selected patients. Patient selection for surgery is facilitated by careful preoperative staging, which may include laparoscopy to identify patients with unresectable or disseminated metastatic disease.[494,495] Staging laparoscopy has been shown to identify peritoneal metastases and liver metastases with a yield of 36% and 67% accuracy in patients with potentially resectable intrahepatic cholangiocarcinoma.[494] A portal lymphadenectomy is reasonable as this provides accurate staging information. However, there are no data to support a therapeutic benefit of routine lymph node dissection in patients undergoing surgery, particularly in those with no lymph node involvement.[496-499] However, since lymph node metastasis is an important prognostic indicator of survival, lymphadenectomy could be considered at operation.[463,489]

The optimal adjuvant treatment strategy for patients with resected intrahepatic cholangiocarcinoma has not been determined and there are limited clinical trial data to support a standard regimen for adjuvant treatment. Lymphovascular and perineural invasion, lymph node metastasis, and tumor size ≥5 cm have been reported as independent predictors of recurrence and reduced OS following resection.[500-502] Since recurrence following resection is common, these tumor-specific risk factors could be considered as criteria for selection of patients for adjuvant treatment in clinical trials. Patients who have undergone an R0 resection may be followed with observation alone. For patients found to have microscopic tumor margins (R1) or residual local disease (R2) after resection, it is essential for a multidisciplinary team to review the available options on a case-by-case basis. Although the optimal treatment strategy has not been determined, adjuvant treatment options include fluoropyrimidine-based or gemcitabine-based chemotherapy for patients who have undergone R0 resection. Fluoropyrimidine chemoradiation or fluoropyrimidine-based or gemcitabine-based chemotherapy is included as options for patients with microscopic tumor margins (R1) or positive regional nodes. See *Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers* in this discussion. Patients with residual local disease (R2) should be managed as described below for unresectable or metastatic disease.

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

Locoregional therapies such as RFA,[503,504] TACE,[505-507] DEB-TACE, or TACE drug-eluting microspheres [506,508,509] and TARE with yttrium-90 microspheres[507,510-515] have been shown to be safe and effective in a small retrospective series of patients with unresectable intrahepatic cholangiocarcinomas. In a series of 17 patients with primary unresectable intrahepatic cholangiocarcinoma, RFA was associated with a median PFS of 32 months and OS of 38.5 months.[504] The results of two independent prospective studies showed that the efficacy of TACE with irinotecan DEB was similar to that of gemcitabine and oxaliplatin, but was superior to that of TACE with mitomycin in terms of PFS and OS for patients with unresectable intrahepatic cholangiocarcinoma.[506] In a systematic review of 12 studies with 298 patients, the effects of radioembolization with yttrium-90 microspheres in unresectable intrahepatic cholangiocarcinoma were assessed.[516] The overall weighted median survival for this treatment was 15.5 months, partial tumor response was seen for 28% of patients, and SD was seen for 54% of patients. Other smaller series have also reported favorable response rates and survival benefit for patients with unresectable intrahepatic cholangiocarcinoma treated with TARE with yttrium-90 microspheres.[510,513,515]Due to the rarity of this disease, none of these locoregional approaches has been evaluated in randomized clinical trials. Nevertheless, based on the available evidence as discussed above, the panel has included locoregional therapy (category 2B) as an option for patients with unresectable or metastatic disease.

Hepatic arterial infusion (HAI) chemotherapy also has been used in select centers for the treatment of patients with advanced and unresectable intrahepatic cholangiocarcinoma.[517-520] In one trial, 58% of patients with intrahepatic cholangiocellular carcinoma (ICC) had at least a PR when receiving HAI only.[520] In a meta-analysis including 20 studies (*N* = 657), HAI was compared to TACE, DEB-TACE, and TARE with yttrium-90 microspheres.[521] OS and tumor response were greatest for HAI, though grade III/IV toxicity was also highest, relative to the other arterially directed therapies. A retrospective analysis of 525 patients with ICC showed that patients who received a combined regimen of HAI and another chemotherapy agent (gemcitabine, irinotecan, or 5-FU) had greater OS, relative to patients receiving chemotherapy without HAI (30.8 vs. 18.4 months, $P < .001$).[522]

EBRT is a locoregional treatment option for unresectable intrahepatic cholangiocarcinoma. A non-randomized multi-institutional trial including 39 patients with unresectable intrahepatic cholangiocarcinoma showed that hypofractionated proton therapy resulted in a 2-year overall survival rate of 46.5% (median overall survival was 22.5 months) and a 2-year progression-free survival rate of 25.7%.[331] A single-institution study including 79 patients with unresectable intrahepatic cholangiocarcinoma showed that higher doses of RT (3D-CRT with photons or protons) was associated with better 3-year OS (73% vs. 38%, respectively; $P = .017$) and 3-year local control (78% vs. 45%, respectively; $P = .04$), compared with lower doses of RT.[523] SBRT may also be used for patients with unresectable intrahepatic cholangiocarcinoma.[327]

Additionally, data from a phase II trial of 44 patients with advanced cholangiocarcinoma suggested that the addition of cetuximab to gemcitabine-based chemotherapy may have activity in unresectable disease.[524] Randomized studies will be needed to confirm these data. The panel does not currently include cetuximab among its recommended treatments for cholangiocarcinoma.

Management of Extrahepatic Cholangiocarcinoma

Complete resection with negative margins is the only potentially curative treatment for patients with resectable disease. The reported

5-year survival rates following radical surgery are in the range of 20% to 42% and 16% to 52%, respectively, for patients with hilar and distal cholangiocarcinomas.[525]

Surgical margin status and lymph node metastases are independent predictors of survival following resection.[488,526,527] Regional lymphadenectomy of the porta hepatis (hilar cholangiocarcinoma) or in the area of the head of the pancreas (distal cholangiocarcinoma) are considered standard parts of curative resections.[528,529] Since these surgical procedures are associated with postoperative morbidity, they should be carried out in patients who are medically fit for a major operation. Surgery is contraindicated in patients with distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis (or head of the pancreas for distal tumors).

The type of surgical procedure for a resectable tumor is based on its anatomic location in the biliary tract. Resection of the involved biliary tract and en bloc liver resection (typically a major hepatectomy involving the right or left liver with the caudate lobe) is recommended for hilar tumors. Bile duct excision with frozen section assessment of proximal and distal bile duct margins and pancreaticoduodenectomy are recommended for mid and distal tumors, respectively. Mid bile duct tumors that can be completely resected with an isolated bile duct resection are uncommon. A combined pancreaticoduodenectomy and hepatic resection is required, in rare instances, for a bile duct tumor with extensive biliary tract involvement. Combined hepatic and pancreatic resections to clear distant nodal disease are not recommended, as these are highly morbid procedures with no obvious associated survival advantage. The guidelines recommend consideration of biliary drainage prior to definitive resection for patients with jaundice. However, caution should be exercised in patients with biliary obstruction as drainage is not always simple and can be associated with significant morbidity. Decisions about whether preoperative biliary drainage is appropriate should be made by a multidisciplinary team.

In patients with hilar cholangiocarcinoma, extended hepatic resection (to encompass the biliary confluence) with caudate lobectomy is recommended, since hilar tumors, by definition, abut or invade the central portion of the liver. The recommendation for extended liver resection is supported by retrospective analyses showing a high rate of R0 resection, prolonged survival, and decreased hepatic recurrence associated with extended hepatic resections as compared to bile duct resections.[530-534] Since this association was maintained when only those patients undergoing an R0 resection were considered, it cannot be solely attributed to the increased likelihood of an R0 resection when extended liver resection was performed, although most reports suggest that extended hepatic resections result in higher probability of R0 resection.[532,535] Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection, especially in patients with more advanced disease. This approach requires substantial experience and appropriate surgical support for such technical operations.[536,537] For adjuvant treatment of resected hilar cholangiocarcinoma, see section on *Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers*.

Patient selection for surgery is facilitated by careful preoperative staging, surgical exploration, biopsy, and consideration of diagnostic laparoscopy to identify patients with unresectable or distant metastatic disease. A preoperative biopsy is not necessary if the index of suspicion is high. Laparoscopy can identify the majority of patients with unresectable hilar cholangiocarcinoma, albeit with a lower yield. A review including six studies of staging laparoscopy in patients with hilar cholangiocarcinoma showed a yield of 14% to 45% and an accuracy of

32% to 71%.[538] The yield of staging laparoscopy over time may be due to improvements in imaging techniques.[539]

While not routinely used in all patients undergoing resection, the consensus of the panel is that in patients with hilar cholangiocarcinoma, preoperative treatments including biliary drainage (using an endoscopic [ERCP] or percutaneous approach [PTC])[540-543] and contralateral PVE[544,545] should be considered for patients with low FLR volumes.

Patients with unresectable or metastatic disease should be considered for biliary drainage using either surgical bypass (although rarely used) or an endoscopic (ERCP) or percutaneous approach (PTC), most often involving biliary stent placement.[546-549] Biopsy is recommended to confirm the diagnosis prior to the initiation of further treatment and to determine transplant status. Primary treatment options include: 1) clinical trial; 2) fluoropyrimidine-based or gemcitabine-based chemotherapy; or 3) best supportive care. In addition, fluoropyrimidine chemoradiation is included as an option for patients with unresectable disease. Data to support particular chemoradiation and chemotherapy regimens are limited. See section on *Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers*.

Liver transplantation is a potentially curative option for selected patients with lymph node-negative, non-disseminated, locally advanced hilar cholangiocarcinomas, with the 5-year survival rates ranging from 25% to 42%.[550-553] There is retrospective evidence suggesting that neoadjuvant chemoradiation followed by liver transplantation is highly effective for selected patients with hilar cholangiocarcinoma.[554-556] Results from two studies suggest that the combination of liver transplantation and neoadjuvant and/or adjuvant chemoradiation is associated with higher RFS than a potentially curative resection.[557,558] However, in one of these studies, there were substantial differences in the characteristics of patients in the two treatment groups.[557] It is important to note that many of these reports include patients with primary sclerosing cholangitis, and some have not had a definitive histologic cancer diagnosis. Liver transplantation should be considered only for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. The panel encourages continuation of clinical research in this area, and referral of patients with unresectable disease to a transplant center should be considered.

Photodynamic therapy (PDT) is a relatively new ablative therapy that involves intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation, and has been used for palliation in patients with extrahepatic cholangiocarcinoma. The combination of PDT with biliary stenting was reported to be associated with prolonged OS in patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.[559,560]

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, then annually up to 5 years. Re-evaluation according to the initial workup should be considered in the event of disease progression.

Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers

Local recurrence following surgery is a primary limitation for cure in patients with biliary tract cancers, which provides an important justification for the use of adjuvant therapy. In a sample of 80 patients with extrahepatic cholangiocarcinoma who underwent resection, 48.8% died of disease by 28 months, while 11.3% died of other causes.[468] The role of adjuvant chemotherapy or chemoradiation therapy in patients with resected biliary tract cancers is poorly defined.[561]

Due to the low incidence of biliary tract cancers, the efficacy and safety of adjuvant chemotherapy or chemoradiation therapy in these patients has been evaluated mostly in retrospective studies that have included only a small number of patients. Further, these studies often combined patients with gallbladder and bile duct cancers (with a few exceptions), which is problematic since the biology of these tumors is completely different. Despite the challenges associated with the accrual of large numbers of patients with biliary tract cancer for randomized phase III trials, it is widely recognized that efforts should be made to conduct such studies in which the individual disease entities are evaluated separately.

Retrospective studies that have combined patients with gallbladder cancer and cholangiocarcinomas provide conflicting evidence regarding the role of adjuvant therapy.[396,562] A retrospective analysis of 177 patients with resected gallbladder cancer and hilar cholangiocarcinoma concluded that, based on the pattern of initial recurrence, adjuvant radiotherapy may not have a significant impact in the management of patients with gallbladder cancer, whereas it could be a reasonable approach for patients with hilar cholangiocarcinoma.[396] The initial recurrence rate involving a distant site was significantly higher for patients with gallbladder cancer than for those with hilar cholangiocarcinoma (85% and 41%, respectively; $P < .001$). In a retrospective review of a prospective database of 157 patients with resected gallbladder cancer (n = 63) and cholangiocarcinoma (n = 94), the authors reported that adjuvant therapy was not associated with survival for this group of patients but identified an early resection with 1-cm tumor-free margins as the best predictor of long-term survival.[562] A multivariate Cox proportional hazards model developed to make individualized predictions of survival from the addition of RT following gallbladder cancer resection showed that the greatest benefit of RT was seen in patients with T2 or higher stage tumors and node-positive disease.[563,564] Results of these studies provide support for omitting adjuvant chemoradiation in the post-surgical treatment of patients with gallbladder cancer characterized as T1b, N0.

In a systematic review and meta-analysis of 6,712 patients with biliary tract cancers, Horgan et al reported an associated improvement in OS (although nonsignificant) with adjuvant therapy compared with surgery alone, with no difference between patients with gallbladder cancer and bile duct cancers.[565] Chemotherapy or chemoradiation therapy was associated with statistically greater benefit than RT alone, with the greatest benefit observed in patients with lymph node-positive disease and macroscopic residual disease (R1 resection).

The phase II SWOG S0809 trial, which enrolled patients with extrahepatic cholangiocarcinoma or gallbladder cancer ($N = 79$), provided prospective data on adjuvant chemotherapy/chemoradiation (ie, capecitabine/gemcitabine followed by concurrent capecitabine and RT).[566] Two-year OS was 65%, and median survival was 35 months. A majority of patients enrolled in the trial (86%) completed therapy, and the regimen was generally tolerable. Confirmatory phase III trial data are needed.

In the only phase III randomized trial that evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer, 508 patients (139 patients had cholangiocarcinoma and 140 patients had gallbladder cancer) were randomly assigned to adjuvant chemotherapy with fluorouracil and mitomycin C or to a control arm.[567] Results from the subgroup analyses showed a significantly better 5-year DFS for patients with gallbladder cancer treated with chemotherapy (20.3% compared to 11.6% in the control group; *P* = .021), although no significant differences between the two treatment arms were observed for patients with biliary duct cancers. Results from this trial suggest that patients with gallbladder cancer undergoing resection may derive survival benefit with adjuvant chemotherapy.

In studies that included only patients with gallbladder cancer, a meta-analysis including 10 retrospective studies with 3,191 patients showed that adjuvant chemotherapy improves OS, compared to resection alone (HR, 0.42; 95% CI, 0.22–0.80).[568] Subgroup analyses showed that the patients who are most likely to benefit from adjuvant therapy include those with a positive margin, those with nodal disease, and those with at least stage II disease. Retrospective studies have concluded that adjuvant chemoradiation following R0 resection might improve OS in selected patients with T2 or T3 tumors and lymph node-positive gallbladder cancer.[569-571] In a series of 47 patients with gallbladder cancer who underwent resection followed by adjuvant chemoradiation, the 5-year OS rate was significantly higher following R0 resection (52.8% vs. 20.0%, and 0% for those with R1 and R2 resections, respectively; *P* = .0038).[571] Adjuvant chemoradiation after R0 resection was associated with good long-term survival rate even in patients with lymph node metastases.

Retrospective studies that included only patients with resected extrahepatic cholangiocarcinoma suggest that adjuvant chemoradiation may improve local control and survival, although distant metastases was the most common pattern of failure.[572-575] In one retrospective study of 168 patients with extrahepatic cholangiocarcinoma treated with curative resection followed by adjuvant chemoradiation, the 5-year local control (58.5% vs. 44.4%; *P* = .007), DFS (32.1% vs. 26.1%, *P* = .041), and OS rates (36.5% vs. 28.2%, *P* = .049) were significantly better for patients who received chemoradiation than for those who were treated with surgery alone.[575] Other studies have suggested that adjuvant chemoradiation may have a significant survival benefit only in a subgroup of patients with T3 or T4 tumors or those with a high risk of locoregional recurrence (R1 resection or positive lymph nodes).[574,576,577] A non-randomized, single-center study of 120 patients with curatively resected extrahepatic cholangiocarcinoma also showed that 5-FU–based adjuvant concurrent chemoradiation followed by 5-FU–based adjuvant chemotherapy resulted in a significant survival benefit, especially in patients with R1 resection or negative lymph nodes compared to 5-FU–based adjuvant concurrent chemoradiation alone.[574] The 3-year DFS rates for concurrent chemoradiation therapy alone and concurrent chemoradiation therapy followed by adjuvant chemotherapy were 27% and 45.2% (*P* = .04), respectively. The corresponding OS rates were 31% and 63% (*P* < .01), respectively. However, this was not observed for patients with R0 resection or positive lymph nodes as well as those with T1 or T2 tumors.

Most of the collective experience of chemoradiation in biliary tract cancers involves concurrent chemoradiation and fluorouracil. Concurrent chemoradiation with capecitabine has also been used.[574,578] Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.[579] Due to the limited data and the heterogeneity of patient populations included in many of the published studies, in most cases the

recommendations in the NCCN Guidelines on the use of adjuvant chemotherapy or chemoradiation therapy are not specific to the particular type of biliary tract cancer. Specific recommendations for fluoropyrimidine-based or gemcitabine-based chemotherapy listed in the NCCN Guidelines are based on the extrapolation of data from studies of patients with advanced disease. Additionally, some of the recommendations are primarily based on practice patterns at NCCN Member Institutions and retrospective studies from single-center experiences.

Among patients with resectable disease of the gallbladder or extrahepatic bile duct, those who have undergone an R0 resection and who have negative regional nodes or those with carcinoma in situ at margin may be followed with observation alone, receive fluoropyrimidine chemoradiation, or receive fluoropyrimidine or gemcitabine chemotherapy. However, there are limited clinical trial data to define a standard regimen, and enrollment in a clinical trial is encouraged. Patients with microscopic positive tumor margins (R1), gross residual local disease (R2), or positive regional lymph nodes after resection should be evaluated by a multidisciplinary team to review the available treatment options on a case-by-case basis. Although the optimal treatment strategy has not been established, treatment options include: fluoropyrimidine chemoradiation followed by additional fluoropyrimidine or gemcitabine chemotherapy; or fluoropyrimidine-based or gemcitabine-based chemotherapy for patients with positive regional nodes. If radiotherapy is used, then EBRT using 3D-CRT and IMRT are options.[564,566] Data to support particular chemoradiation and chemotherapy regimens for adjuvant treatment of resected biliary tract cancer are limited.

Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers

The prognosis of patients with advanced biliary tract cancers is poor and the median survival for those undergoing supportive care alone is short.[580] The survival benefit of chemotherapy (fluorouracil, leucovorin, and etoposide) over best supportive care for patients with advanced biliary tract cancers was initially suggested in a phase III trial of 90 patients with advanced pancreatic and biliary tract cancers, 37 of whom had advanced biliary tract cancers.[581] In a single-center randomized study of 81 patients with unresectable gallbladder cancer, Sharma et al reported that modified gemcitabine and oxaliplatin (GEMOX) improved PFS and OS compared to best supportive care or fluorouracil.[582] Median OS was 4.5, 4.6, and 9.5 months, respectively, for the best supportive care, fluorouracil, and modified GEMOX arms (P = .039). The corresponding PFS was 2.8, 3.5, and 8.5 months (P < .001).

Several phase II studies have also demonstrated the efficacy of chemotherapy for the treatment of patients with advanced biliary tract cancers.[583,584] The results of a pooled analysis of 104 trials that have included 2810 patients with advanced biliary tract cancers showed that response rates and tumor control were higher for the subgroup of patients receiving a combination of gemcitabine and platinum-based agents.[585] In a retrospective study of 304 patients with unresectable biliary tract cancers who were treated with gemcitabine alone, a cisplatin-based regimen, or a fluoropyrimidine-based regimen, patients receiving gemcitabine were shown to have a lower risk of death.[586] Most importantly, the support for the use of gemcitabine-based or fluoropyrimidine-based chemotherapy for patients with advanced biliary tract cancers comes from 4 randomized studies.[587-590]

The randomized, controlled, phase III ABC-02 study, which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma,

gallbladder cancer, or ampullary cancer, demonstrated that the combination of gemcitabine and cisplatin improved OS and PFS by 30% over gemcitabine alone.[589] Median OS was 11.7 months and 8.1 months (HR, 0.64; 95% CI, 0.52–0.80; *P* < .001), and median PFS was 8.0 months vs. 5.0 months (HR, 0.63; 95% CI, 0.51–0.77; *P* < .001), both in favor of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the 2 arms. Okusaka et al also reported similar findings in a phase II randomized study of 84 patients with advanced biliary tract cancers.[590] Combined analyses from both of these trials (*n* = 227) showed that derived neutrophil-to-lymphocyte ratio assessed at baseline was associated with greater long-term survival in those randomized to receive gemcitabine/cisplatin (*P* < .01).[591] Based on these results, the combination of gemcitabine and cisplatin is considered to be the standard of care for first-line chemotherapy for patients with advanced or metastatic biliary tract cancers.

Examples of other gemcitabine-based or fluoropyrimidine (fluorouracil or capecitabine)-based regimens with demonstrated activity in phase II trials include: gemcitabine and cisplatin or oxaliplatin;[592-600] gemcitabine and fluoropyrimidine;[601-606] and fluoropyrimidine and oxaliplatin or cisplatin.[607-610] Triple-drug chemotherapy regimens also have been shown to be effective in patients with advanced biliary tract cancers, albeit in a very small number of patients.[611-613] The phase III trial that evaluated fluorouracil, leucovorin, and etoposide versus fluorouracil, cisplatin, and epirubicin did not show one regimen to be significantly superior with respect to OS (12 months vs. 9 months, respectively) in patients with advanced biliary tract cancers, although the trial was underpowered to detect such a difference.[611] In a phase II trial, the combination panitumumab, a monoclonal anti-EGFR antibody, with gemcitabine and irinotecan showed encouraging efficacy with good tolerability in patients with advanced cholangiocarcinoma, with a 5-month PFS rate of 69%.[614] The median PFS and OS were 9.7 months and 12.9 months, respectively.

The effects of other gemcitabine combination therapies have been examined in phase II trials. In a randomized phase II study of 51 patients, Kornek et al established the efficacy and tolerance of mitomycin in combination with gemcitabine or capecitabine in previously untreated patients with advanced biliary tract cancers.[587] Mitomycin and capecitabine were associated with superior CR rate (31% vs. 20%), median PFS (5.3 months vs. 4.2 months), and OS (9.25 months vs. 6.7 months). The results of the 40955 EORTC trial showed that cisplatin and fluorouracil was more active than high-dose fluorouracil in terms of overall response rates (19% and 7.1%, respectively) and OS (8 months and 5 months, respectively), but the PFS was similar in both treatment arms (3.3 months).[588] In a randomized phase II trial, the combination of gemcitabine and sorafenib was compared to gemcitabine with a placebo in 102 patients with unresectable or metastatic biliary tract cancer.[615] There were no significant between-group differences for OS and PFS rates, but patients who developed liver metastases following resection survived longer if they received sorafenib, relative to patients who received the placebo (*P* = .019). The gemcitabine/sorafenib combination was well-tolerated. Data from phase III trials are needed.

The panel has included combination therapy with gemcitabine and cisplatin with a category 1 recommendation for patients with unresectable or metastatic biliary tract cancers. Based on the experiences from phase II studies, the following gemcitabine-based and fluoropyrimidine-based combination chemotherapy regimens are included with a category 2A recommendation for the treatment of

patients with advanced biliary tract cancer: gemcitabine with oxaliplatin or capecitabine; capecitabine with cisplatin or oxaliplatin; fluorouracil with cisplatin or oxaliplatin; and single-agent fluorouracil, capecitabine, and gemcitabine. The combination of gemcitabine and fluorouracil is not included due to the increased toxicity and decreased efficacy observed with this regimen[601] when compared with results of studies of the gemcitabine and capecitabine regimen in the setting of advanced biliary tract cancer.

In a systematic review including 23 studies (14 phase II clinical trials and 9 retrospective studies) with 761 patients with advanced biliary tract cancer, the efficacy of second-line chemotherapy was examined.[616] There is insufficient evidence to recommend second-line therapy in this group of patients, and prospective randomized trials are needed.

Chemoradiation in the setting of advanced biliary tract cancers can provide control of symptoms due to local tumor effects and may prolong OS. However, there are limited clinical trial data to define a standard regimen or definitive benefit. In a retrospective analysis of 37 patients treated with chemoradiation for unresectable extrahepatic cholangiocarcinoma, the actuarial OS rates at 1 and 2 years were 59% and 22%, respectively, although effective local control was observed in the majority of patients during this time period (actuarial local control rates of 90% and 71% at 1 and 2 years, respectively).[617] The most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers has been fluorouracil,[618,619] although capecitabine has been substituted for fluorouracil in some studies.[578] The panel recommends that concurrent chemoradiation (EBRT using 3D-CRT, IMRT, or SBRT) should be limited to either fluorouracil or capecitabine, and that such treatment should be restricted to patients without evidence of metastatic disease. Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.

In a retrospective review of 8 patients with advanced gallbladder cancer and *HER2/neu* gene amplification or overexpression, 5 of the 8 patients who received HER2/neu-directed therapy (trastuzumab) experienced a PR or CR. No response was seen in 5 patients with cholangiocarcinoma who also received HER2/neu-directed therapy.[620] Phase II studies are currently ongoing to investigate HER2-directed treatment options for solid tumors (eg, NCT02465060, NCT02693535).

Summary

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

Complete resection of well-selected patients is currently the best available potentially curative treatment. Liver transplantation is a curative option for select resectable patients. Bridge therapy can be considered for patients with HCC to decrease tumor progression and the dropout rate from the liver transplantation waiting list.

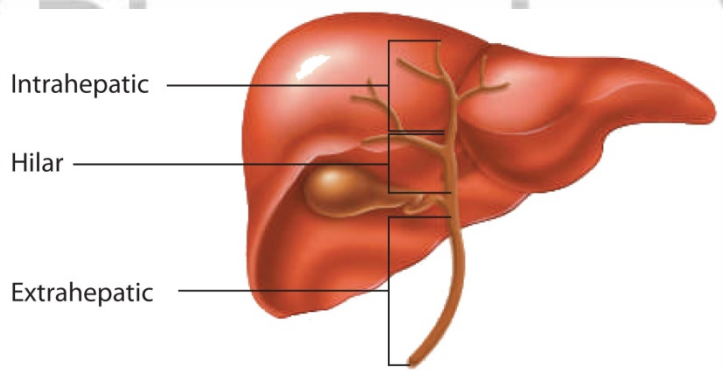
Locoregional therapies (ablation, arterially directed therapies, and EBRTs) are often the initial approach for patients with HCC who are not candidates for surgery or liver transplantation. Ablation should be considered as definitive treatment in the context of a multidisciplinary review in well-selected patients with small properly located tumors. Arterially directed therapies (TACE, DEB-TACE, or TARE with yttrium-90 microspheres) are appropriate for patients with unresectable or inoperable tumors that are not amenable to ablation therapy. SBRT

can be considered as an alternative to ablation and/or embolization techniques (especially for patients with 1–3 tumors and minimal or no extrahepatic disease) or when these therapies have failed or are contraindicated. Though it is currently rarely used, there are emerging data supporting its usefulness. PBT may also be used in select settings. Locoregional therapy is also included as an option for patients with unresectable or metastatic intrahepatic cholangiocarcinoma.

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

It is essential that all patients should be evaluated prior to initiation of treatment. Careful patient selection for treatment and active multidisciplinary cooperation are essential. There are very few high-quality randomized clinical trials of patients with hepatobiliary cancers, and patient participation in prospective clinical trials is the preferred option for the treatment of patients with all stages of disease.

Figure 1: Classification of Cholangiocarcinoma



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