National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Hepatobiliary Cancers

V.2.2008

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This manuscript is being updated to correspond with the newly updated algorithm.

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

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

Summary of the Guidelines Updates

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

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

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

Hepatocellular Carcinoma:

(HCC-1)

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

(HCC-2)

- **Surgical Evaluation, Bottom branch: Included "....or hepatitis C antigen positive."**
- **Footnote "i": Removed the word "cadaveric" so that text now reads "Criteria for transplantation." (Also for HCC-3)**

(HCC-3)

- **Footnote "k" that states, "For selected patients, a randomized clinical trial has demonstrated survival benefits" is new to the page.**
- **Treatment: The sorafenib recommendations now include Child-Pugh Class A *or B*, with corresponding footnote "l" that states, "There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels." Previously, the guidelines only recommended sorafenib for Child-Pugh Class A patients. (Also for HCC-4)**

(HCC-4)

- **Treatment, Top branch: Sorafenib was added as a treatment option for patients who are inoperable by performance status or comorbidity (local disease only) and who present with cancer-related symptoms.**

Gallbladder Cancer:

(GALL-1)

- **Top branch, second column: The phrase "Consider en bloc resection" was changed to "Consider extended cholecystectomy."**
- **Postoperative Workup; Bottom branch: The recommendation "Strongly consider staging laparoscopy" was added.**
- **Resectable; Primary Treatment: Panel deleted the recommendation "± resection of port sites for laparoscopic operations."**
- **Footnote "b" was amended with the following sentence: "Patients with nodal disease outside this area are unresectable."**

(GALL-3)

- **Under Adjuvant Treatment: The panel changed "...chemotherapy/RT" to "...chemotherapy ± RT"**

Intrahepatic Cholangiocarcinoma:

(INTRA-1)

- **Workup: After "Upper and lower endoscopy", the panel deleted the phrase "as indicated"**
- **Primary Treatment, Unresectable: The panel deleted the recommendation "Ablative or embolization therapy" along with its corresponding footnote.**

Extrahepatic Cholangiocarcinoma:

(EXTRA-1)

- **Unresectable and metastatic pathways; Primary Treatment: The panel changed the recommendation to "Biliary drainage, *if indicated*"**
- **Surgical Procedures for Resectable Disease box: Proximal Third: The panel changed "± en bloc liver resection" to "+" en bloc liver resection.**

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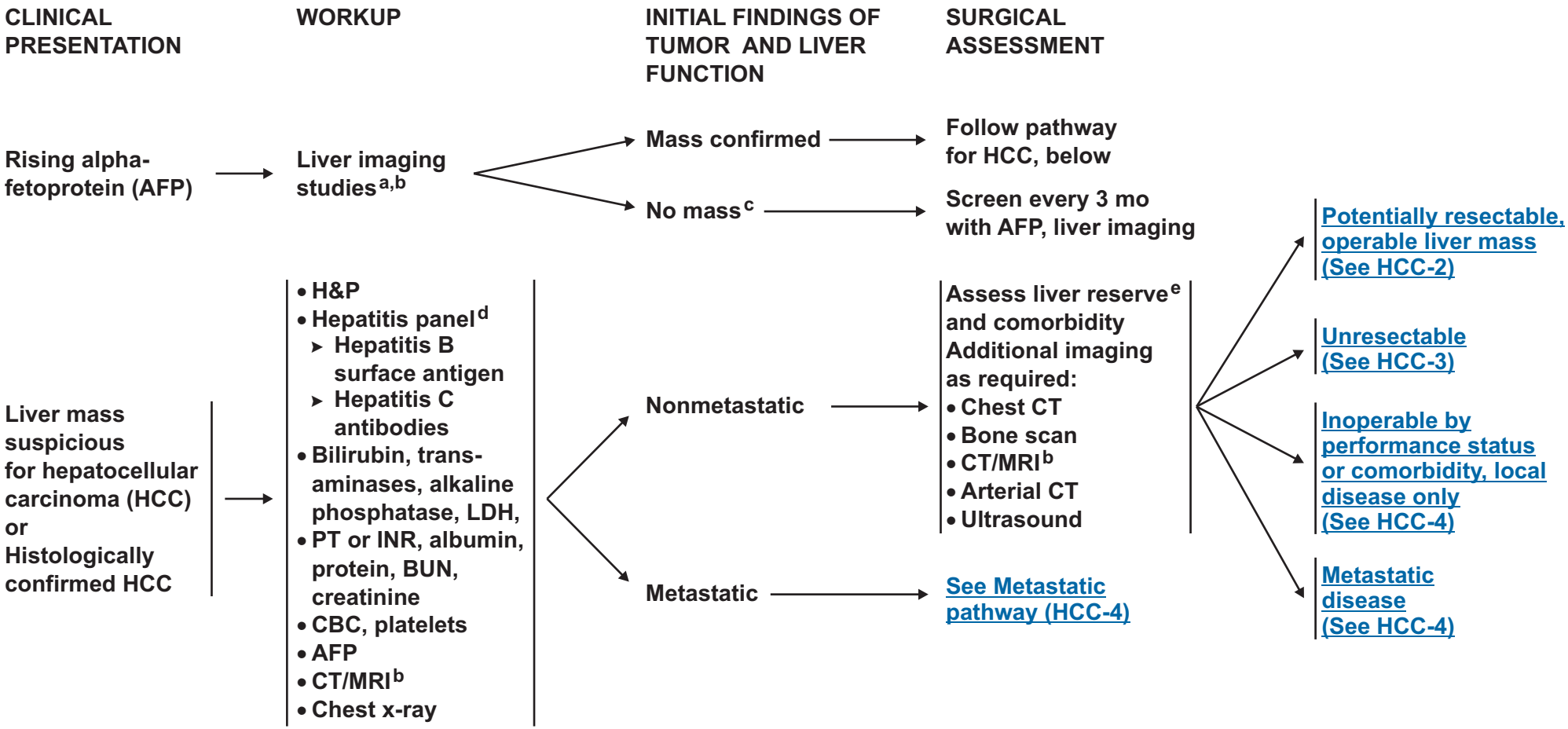
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Hepatocellular Carcinoma



[a] If ultrasound negative, CT/MRI should be performed.

[b] MRI/ CT scan to define extent and number of primary lesions, vascular anatomy, involvement with tumor, and extrahepatic disease; triphasic helical CT or MRI to include early arterial phase enhancement.

[c] Rule out germ cell tumor if clinically indicated. MRI or triple phase CT scan may be helpful.

[d] An appropriate hepatitis panel should preferably include:

- Hepatitis B surface antigen (HBsAg). HBe and anti-HBc (IgM) are included if HBsAg is positive
- Hepatitis B surface antibody (for HBIG or vaccine evaluation only)
- Hepatitis C virus antibodies. If low positive, recombinant immuno blot assay (RIBA) confirmation test is performed

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

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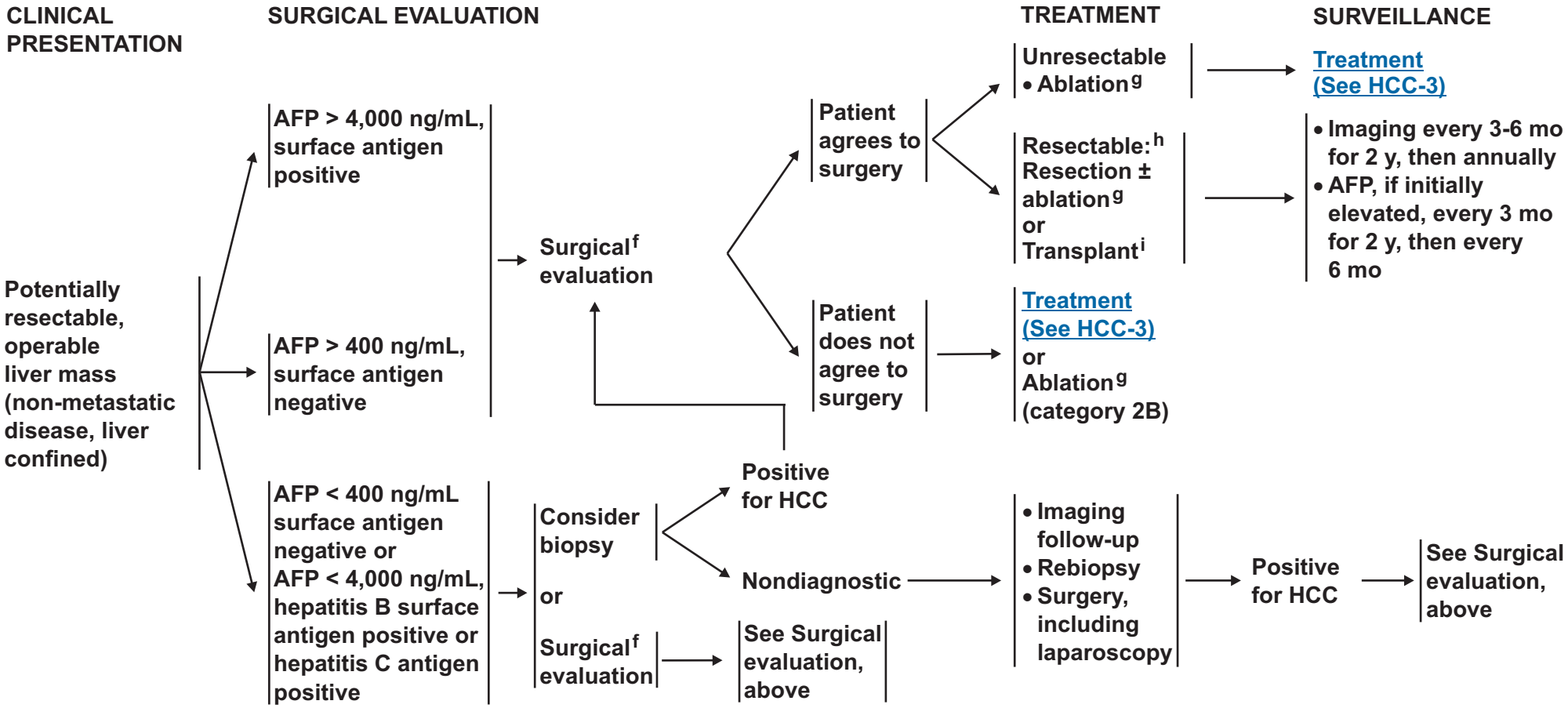
Hepatocellular Carcinoma



[f]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

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

[h]Consider interferon or other antiviral therapy for selected low risk hepatitis C patients with completely resected tumors and good performance status.

[i]Criteria for transplantion (UNOS criteria):

- Patient is not a liver resection candidate
- Patient has a tumor ≤ 5 cm in diameter or 2-3 tumors ≤ 3 cm each
- No macrovascular involvement
- No extrahepatic spread of tumor to surrounding lymph nodes, lungs, abdominal organs, or bone

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.

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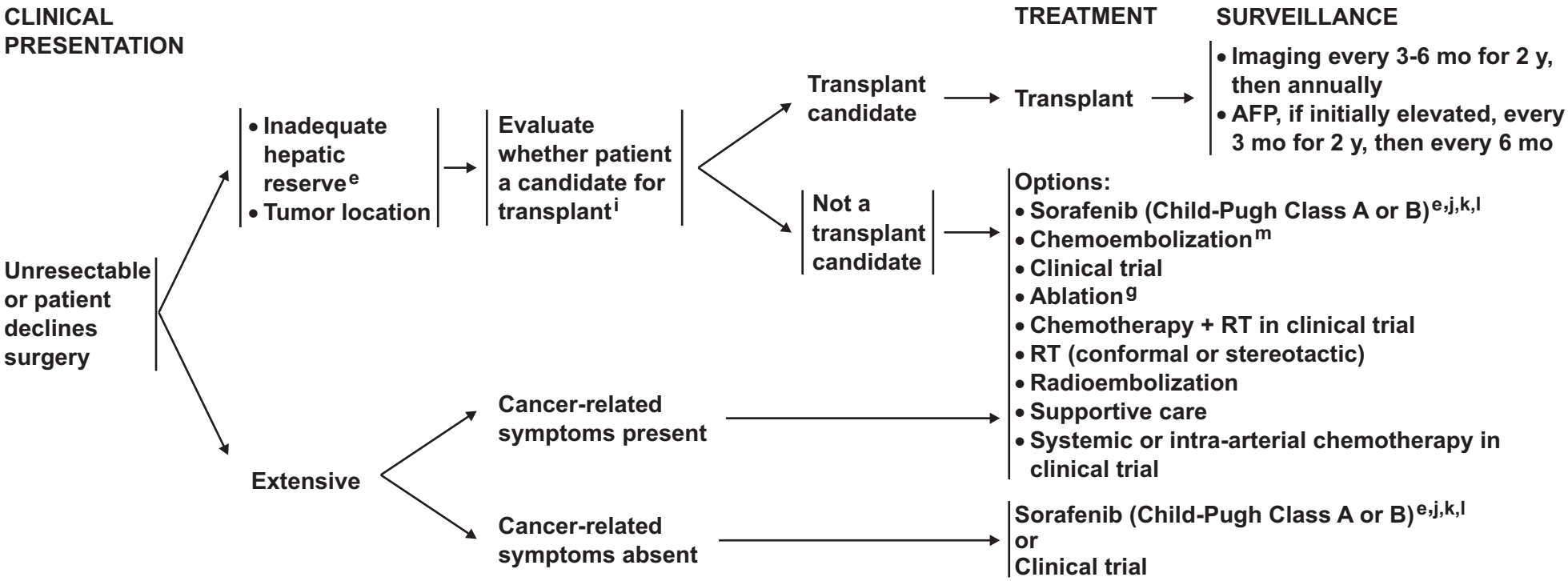
For relapse, see initial Workup (HCC-1)

Hepatocellular Carcinoma



[e] See Child-Pugh Score (HCC-A).

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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.

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

[k] For selected patients, a randomized clinical trial has demonstrated survival benefits. (Llovet J, Ricci S, Mazzaferro V, et al. Sorafenib improves survival in advanced Hepatocellular Carcinoma (HCC): Results of a Phase III randomized placebo-controlled trial (SHARP trial). 2007 ASCO Annual Meeting Proceedings Part I. J Clin Onc 2007, Vol 25, No. 18S (June 20 Supplement), 2007: LBA1)

[l] Caution: There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, Murry K, Owzar DR, et al. Pharmacokinetic (PK) phase I study of sorafenib (S) for solid tumors and hematologic malignancies with hepatic or renal dysfunction (HD or RD): CALGB 6031 2007 ASCO Annual Meeting Proceedings Part I. J Clin Onc 2007, Vol 25, No 18S (June 20 Supplement), 2007: 3538)

[m] Contraindicated in cases of main portal thrombosis or Child-Pugh Class C.

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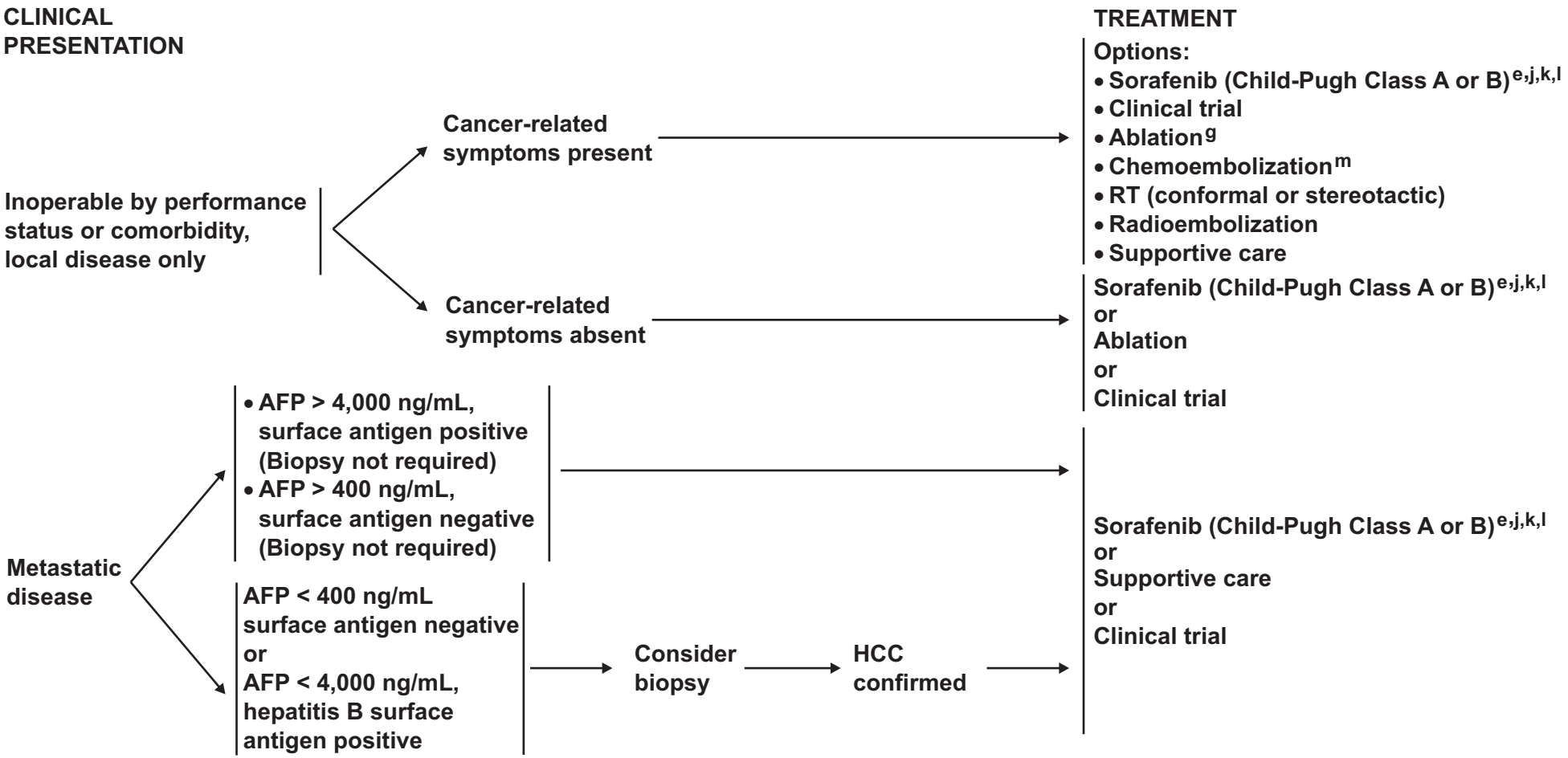
Hepatocellular Carcinoma



[e] See Child-Pugh Score (HCC-A).

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

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Hepatocellular Carcinoma

CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time prolonged (sec)	1-4	4-6	> 6
Bilirubin (mg/dL) • For primary biliary cirrhosis	1-2 1-4	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.
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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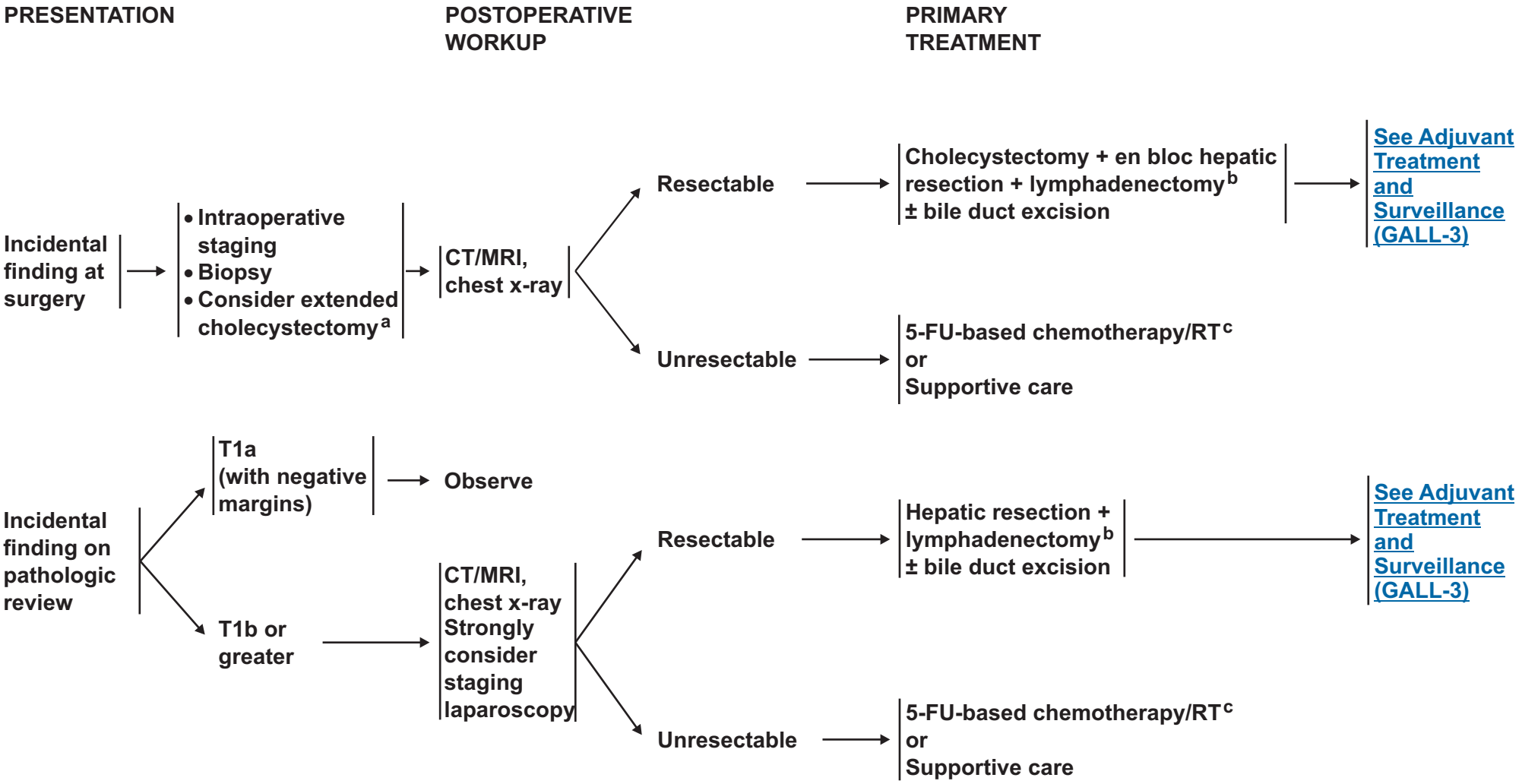
Gallbladder Cancer



Other Clinical Presentations (See GALL-2)

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

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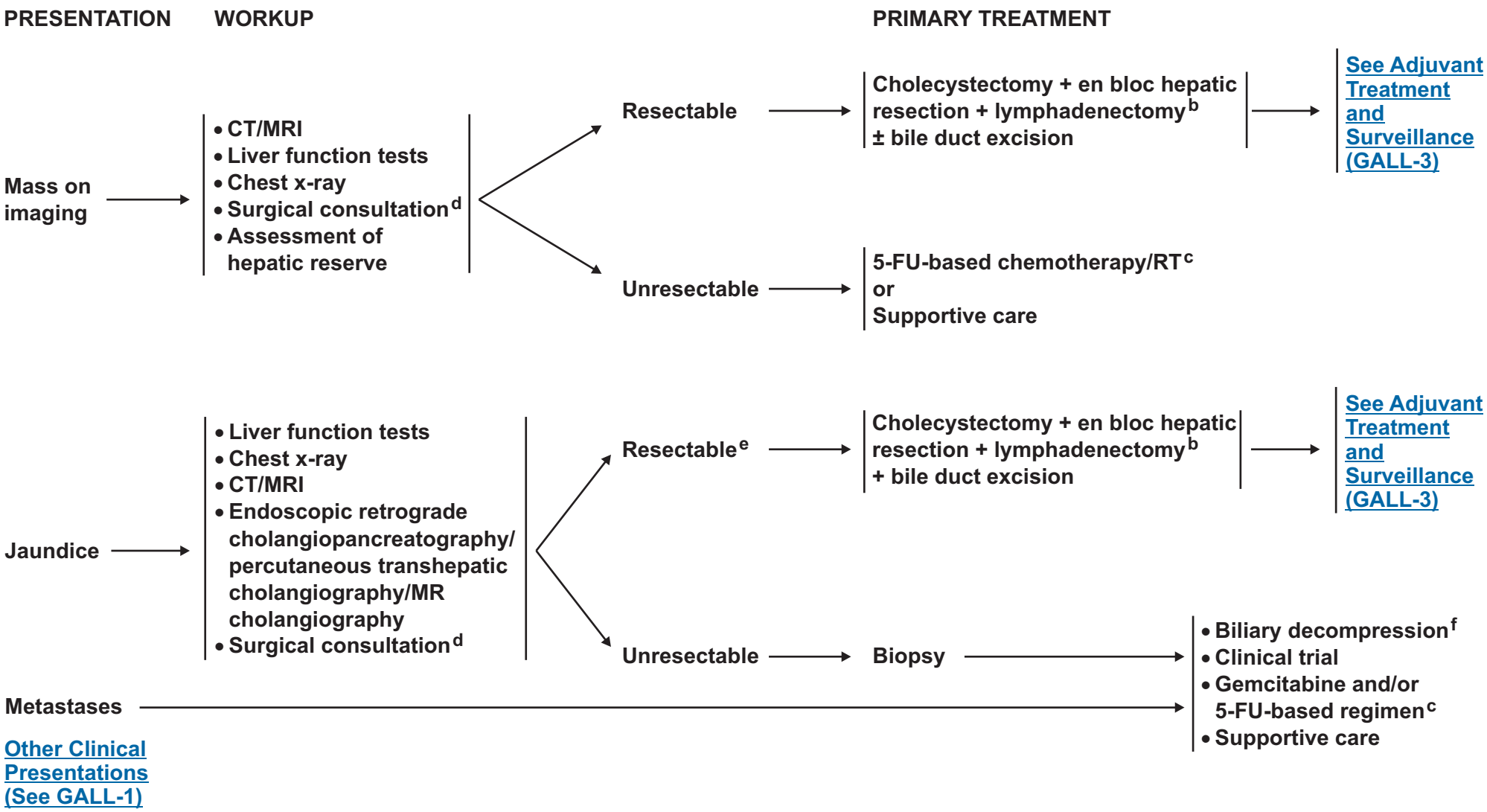
Gallbladder Cancer



[b] Include porta hepatis, gastrohepatic ligament, retroduodenal.
[c] There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.
[d] Laparoscopy can be done in conjunction with surgery if no distant metastases are found.
[e] These patients comprise only 5% of patients and carry a poor prognosis. Extensive surgery is often required.
[f] It is expected that patients will have biliary decompression for jaundice prior to instituting chemotherapy.

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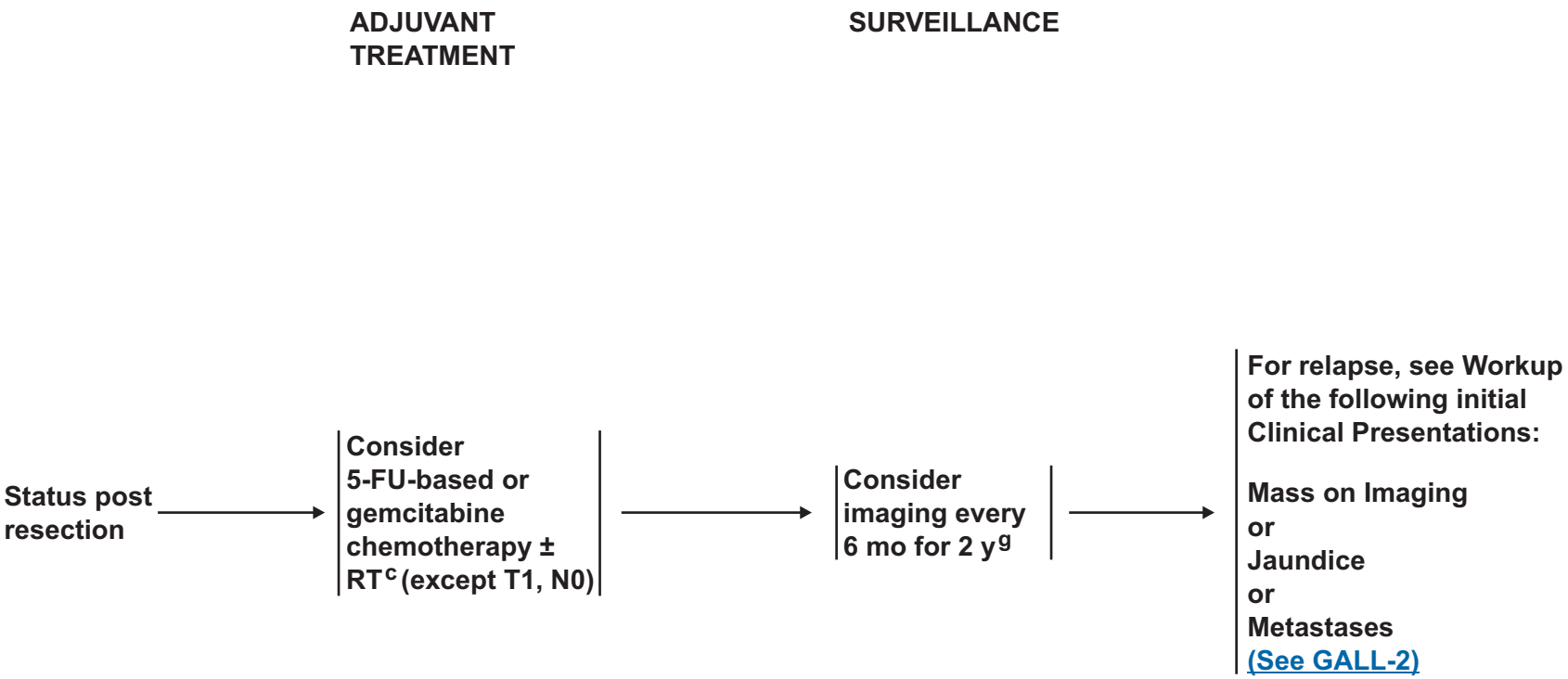

[c]There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.
[g]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

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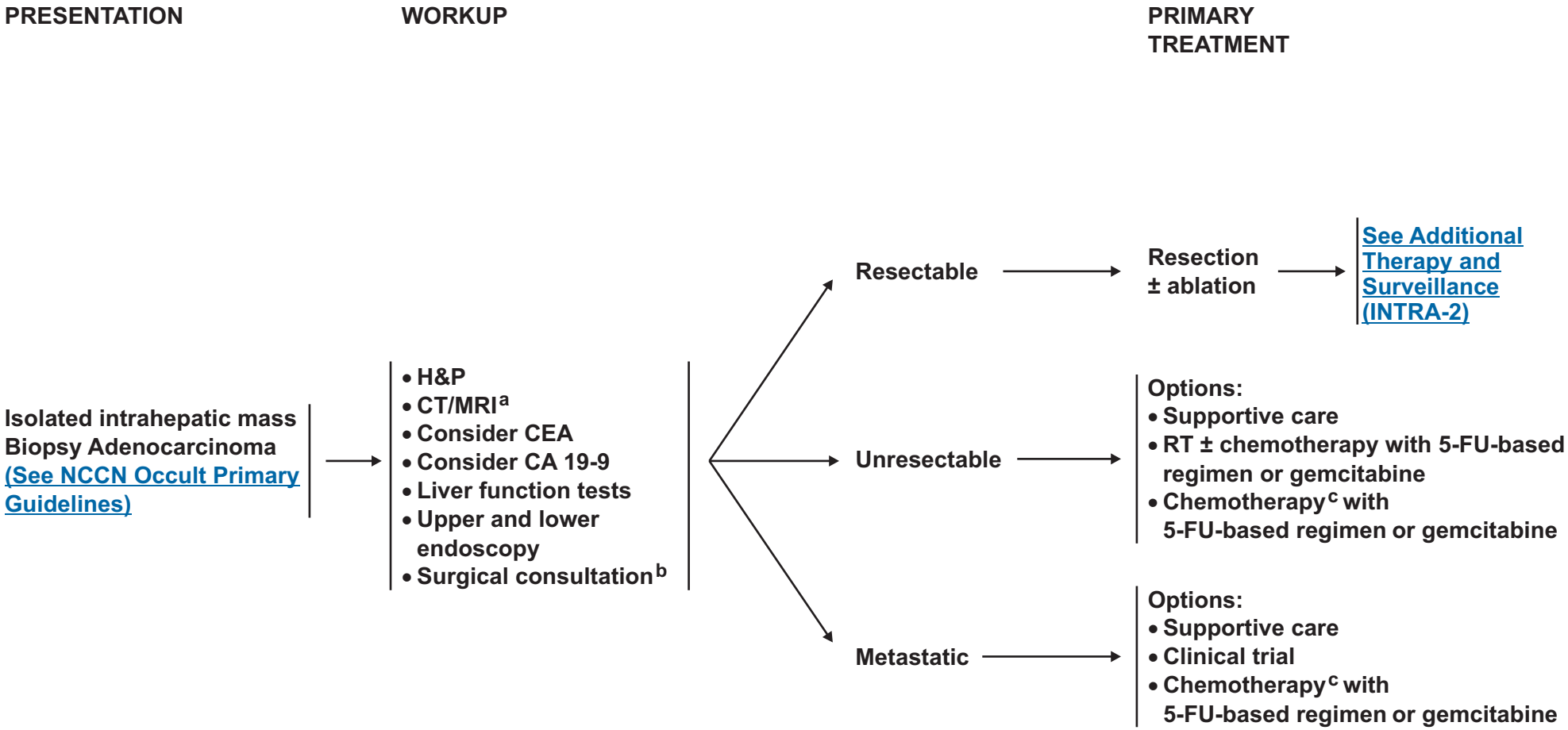
Intrahepatic Cholangiocarcinoma



[a]Recommend delayed contrast-enhanced imaging.
[b]Consult with multidisciplinary team.
[c]There are limited clinical trial data to define a standard regimen. Participation in clinical trials is encouraged.

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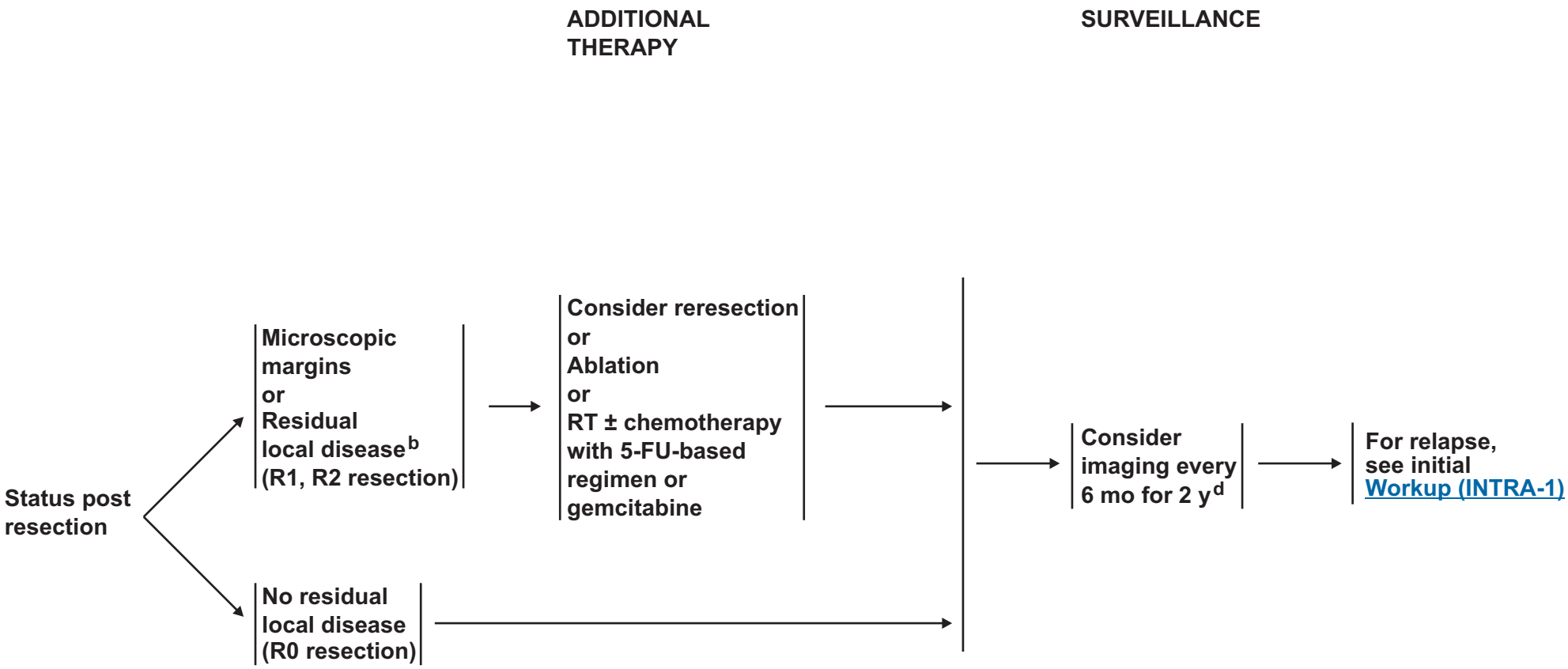
Intrahepatic Cholangiocarcinoma



[b] Consult with multidisciplinary team.

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

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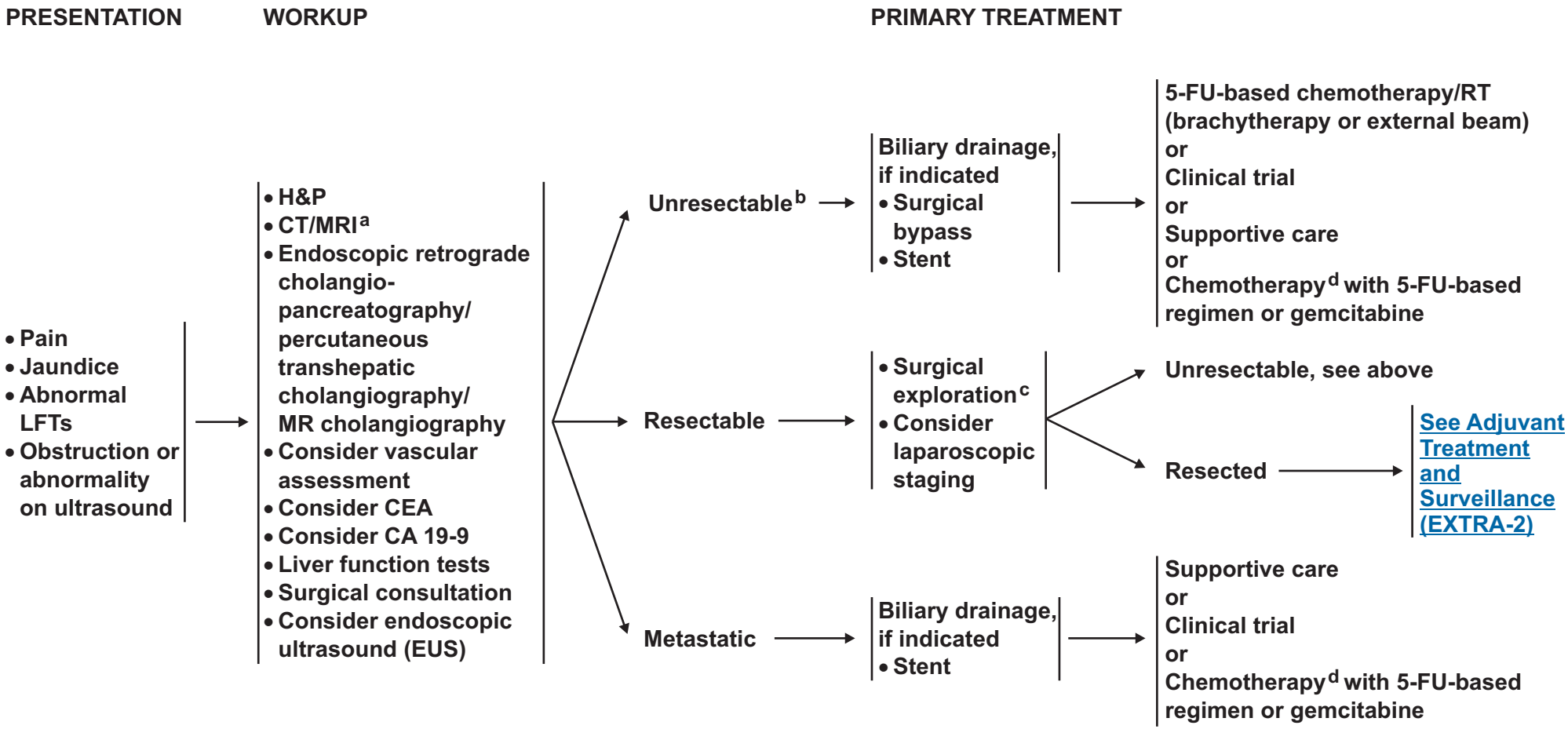
Extrahepatic Cholangiocarcinoma



[a] Recommend delayed contrast-enhanced imaging.
[b] Highly selected patients may be transplant candidates.
[c] Surgery may be performed when index of suspicion is high, biopsy not required.
[d] There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.

Surgical Procedures for Resectable Disease

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

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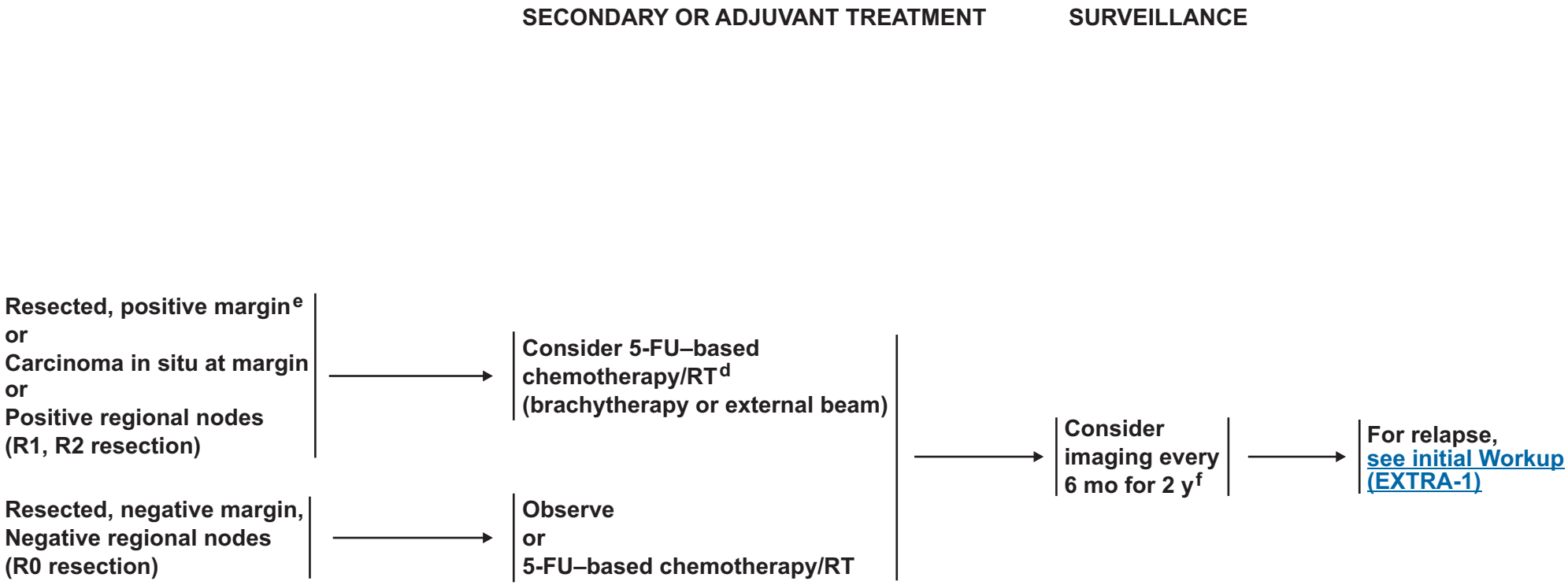
Extrahepatic Cholangiocarcinoma



[d]There are limited clinical trial data to define a standard regimen. Clinical trial participation is encouraged.
[e]Multidisciplinary team review.
[f]There are no data to support aggressive surveillance. There should be a patient/physician discussion regarding appropriate follow-up schedules/imaging.

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Staging

Table 1

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

Primary Tumor (T)

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	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
G4 Undifferentiated

Fibrosis Score (F)

The fibrosis score as defined by Ishak is recommended because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

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

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual, Sixth edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

Table 2

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

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 muscle layer
T1a Tumor invades lamina propria
T1b Tumor invades muscle layer
T2 Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3 Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4 Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

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

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Table 3

American Joint Committee on Cancer (AJCC) TNM Staging for Extrahepatic Bile Duct Tumors*

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor confined to the bile duct histologically
T2 Tumor invades beyond the wall of the bile duct
T3 Tumor invades the liver, gallbladder, pancreas, and/or ipsilateral branches of the portal vein (right or left) or hepatic artery (right or left)
T4 Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Histologic Grade (G)

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

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Manuscript

This manuscript is being updated to correspond with the newly **updated** algorithm. Last update 06/01/06

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Hepatobiliary cancers are both common and highly lethal worldwide. Hepatocellular carcinoma is the most common of the hepatobiliary malignancies.[1,2] However, in the United States, the incidence of hepatobiliary cancer is relatively low, with approximately 25,030 patients estimated to be diagnosed in 2005.[3] The incidence of hepatocellular carcinoma is increasing probably because of the current epidemic of hepatitis C in the United States (1.8% of population).[4] Along with summaries of the NCCN algorithm for the subtypes of hepatobiliary cancer, this manuscript includes a brief discussion of the epidemiology, pathology, etiology, staging, diagnosis, and treatment of each subtype as well as recommended readings. By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the members of the panel during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

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

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

Hepatocellular Carcinoma

Epidemiology and Risk Factors

Hepatocellular carcinoma is the seventh most common cancer in the world and the most common cancer diagnosed in men, with a male-female ratio of 7:1 in high-incidence regions, such as China and Korea.[5,6] The mean age at diagnosis worldwide is between 50 and 60 years.

The incidence of hepatocellular carcinoma has been increasing in the United States mainly because of the rising incidence of hepatitis

C.[1,4,7,8] Currently, 3 to 4 million persons are infected with hepatitis C; it is estimated that 5% to 30% of these patients will develop chronic liver disease and of these, 30% will progress to cirrhosis. Once patients develop cirrhosis, the risk of hepatocellular carcinoma is 1% to 2% per year. Over the next 20 years, the number of patients with hepatitis C virus who progress to cirrhosis will double. Most patients who develop hepatocellular cancer in association with chronic hepatitis C virus infection have biopsy-proven cirrhosis or severe active hepatitis.[9] The latency period between hepatitis B or C exposure and the development of hepatocellular cancer varies between 30 and 50 years. A recent report indicates that the pathogenetic mechanism of hepatocarcinogenesis may differ between hepatitis B--associated and hepatitis C--associated hepatocellular carcinoma.[10] Chronic alcohol use by patients with hepatitis C may decrease the latency period between exposure and the development of cancer.[11]

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

Diagnosis and Initial Workup

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

The level of alpha-fetoprotein (AFP) is elevated in approximately 60% to 90% of patients with hepatocellular cancer and varies by geographic distribution. The highest percentage of AFP-secreting tumors is found in Asia. Proposed surveillance for the early detection of hepatocellular carcinoma among high-risk populations includes liver ultrasonography every 3 to 6 months and evaluation of alkaline phosphatase, albumin, and AFP.[12-14] It is not yet clear if early detection of hepatocellular cancer with routine screening improves the percentage of patients detected with disease at a potentially curative stage, but high-risk chronic hepatitis C virus--infected patients should be considered for ongoing recurrent screening until these issues have been resolved.

For patients with a rising AFP level but with negative liver imaging studies, screening should continue every 3 months. For patients with a suspicious mass, the evaluation should include a history and physical examination, complete blood count (CBC) and platelets, hepatitis screening, liver chemistries, prothrombin, albumin, protein, blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), and chest radiograph. Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed to better define the extent and number of primary lesions, vascular anatomy, vessel involvement, involvement with tumor, and extrahepatic disease.[15] Helical CT or MRI should include early arterial phase enhancement.

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

prognosis in patients with hepatocellular cancer who undergo resection. Of patients in the CRP-positive group, 75% had recurrence 1 year after surgery.[16]

Pathology and Staging

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

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

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

Management

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

Biopsy can be considered for patients with potentially resectable, operable disease who have (1) an AFP of less than 400 ng/mL and are negative for hepatitis B surface antigen, or (2) for those who have an AFP of less than 4000 ng/mL and are positive for hepatitis B surface antigen. Alternatively, surgical evaluation is an appropriate strategy, which includes a discussion of surgical treatment with the patient and determination of whether the patient is amenable to surgery. As mentioned, the presence of hepatitis can increase AFP in the absence of hepatocellular cancer. For selected low-risk patients with hepatitis C who have completely resected tumors and good performance status, interferon-based therapy or antiviral therapy may be considered.[8]

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

The Child-Pugh classification may be inaccurate in truly assessing the risk of postresection liver failure in cirrhotic patients with

hepatocellular carcinoma.[27] The hepatic venous pressure gradient (HVPG) may be a useful measurement of potential hepatic decompensation in patients with cirrhosis after resection of hepatocellular cancer.[27] Several other tests (including galactose elimination, aminopyrine clearance, and lidocaine metabolite [MEGX] clearance) can be combined with the HVPG and with CT volumetry to calculate the percentage of liver that will be resected as well as the liver remnant (which is termed *functional liver reserve*).[28]

A recent multicenter study compared the clinicopathologic characteristics and outcomes in patients with hepatocellular carcinoma who were treated with surgical resection in the United States, France, and Japan. Despite the significant difference among the three patient populations in the median tumor size and underlying liver damage (such as hepatitis C serology and severe fibrosis/cirrhosis in the adjacent liver), the post-resection 5-year survival of patients was not statistically different among the United States, France, and Japan (31% versus 31% versus 41%, respectively; $P = .3$).[29] A recent survey in Japan found that operative mortality was 0.9% and the 5-year survival rate after surgery was 52%.[30] However, future studies using uniform criteria on histopathologic differences are needed to allow better comparison of results.[29]

Portal vein embolization (PVE) has been used to induce hypertrophy of the anticipated liver remnant after a major hepatic resection.[31] PVE is safe (< 5% complication rate), causes little periportal reaction and fibrosis that would be problematic during a hepatic resection, and produces durable portal vein occlusion.[32] In cirrhotic patients or patients with chronic liver disease, PVE decreases the incidence of postoperative complications, length of total hospital stay, and incidence of liver dysfunction. The selective use of PVE may enable safe and potentially curative hepatic resection, including extended hepatectomy when necessary, in a subset of patients with cirrhosis and hepatocellular cancer who would have otherwise been marginal candidates for resection based on their chronic liver disease.

In liver transplantation recipients, 5-year survival has been reported to be as high as 75%, which exceeds survival after resection or ablation.[33] The United Network for Organ Sharing (UNOS) criteria for liver transplant include patients who are not candidates for resection who have (1) a single tumor that is 5 cm or less in diameter, or who have 2 to 3 tumors, each 3 cm or less in diameter; (2) no macrovascular invasion; and (3) no extrahepatic spread to surrounding lymph nodes, lungs, abdominal organs, or bone.[34] Liver transplantation is an option for the cirrhotic patient with hepatocellular carcinoma who will not tolerate liver resection and fulfills current UNOS criteria. Recent reports have suggested that patients with tumor size up to 6.5 cm may result in comparable outcomes after transplantation.[35] The model for end-stage liver disease (MELD) allocation system was designed to give priority status for the sickest patients to receive livers and does not appear to compromise survival.[36]

The single uniform negative prognostic finding for transplantation is histopathologic evidence of vascular invasion.[37] There are conflicting data regarding the role of ablative or resection therapy as a bridge to transplantation, although percutaneous radiofrequency ablation appears useful.[38,39] The major limit to transplantation is the lack of donor organs. Living donor liver transplantation is being performed with greater frequency in the United States with results similar to those individuals undergoing cadaveric donor transplantation.[40]

Patients With Unresectable and Inoperable Disease or Those Who Decline Surgery. Alternative therapies for patients with unresectable disease or those who decline surgery include clinical trial, ablative therapy (eg, radiofrequency, alcohol, cryotherapy, microwave), chemoembolization, chemotherapy plus radiation in a clinical trial, conformal radiation, radiotherapeutic microspheres, supportive care, and systemic or intra-arterial chemotherapy in a clinical trial.[41-56]

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

Surveillance

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

Gallbladder Cancer

Epidemiology and Risk Factors

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

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

Diagnosis and Initial Workup

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

A suspicious mass detected on ultrasound should warrant further evaluation, including CT or MRI, liver function tests, chest radiograph, and staging laparoscopy. Laparoscopy can be done in conjunction with surgery if no distant metastasis is found. If a polypoid mass is seen on ultrasound, the cholecystectomy should be performed by a surgeon who is prepared to do a cancer

operation. For patients presenting with jaundice, additional workup should include endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or magnetic resonance (MR) cholangiography.

Pathology and Staging

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

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

Management

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

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

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

Adjuvant 5-fluorouracil (5-FU)--based chemotherapy and radiation is recommended as postoperative therapy for resectable patients, except those with T1, N0 disease. A small trial showed the 5-year survival rate was improved (64% versus 33%) in completely resected patients (21) receiving concurrent 5-FU plus external-beam radiation.[62] Unfortunately, because there are relatively few patients with gallbladder cancer, only one randomized phase III trial of adjuvant therapy has been conducted. This trial assessed postoperative adjuvant chemotherapy using mitomycin/5-FU; the

5-year overall survival rate was increased with adjuvant chemotherapy (26% versus 14%, *P* = .03) in patients with gallbladder carcinoma.[63,64]

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

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

Surveillance

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

Cholangiocarcinomas

Epidemiology and Risk Factors

Although cholangiocarcinomas are diagnosed throughout the biliary tree, they are usually classified as intrahepatic or extrahepatic.[58,61,66-69] Intrahepatic cholangiocarcinomas have been called “peripheral carcinomas,” because they arise from intrahepatic small-duct radicals. Extrahepatic cholangiocarcinomas encompass hilar carcinomas (including Klatskin's tumors) and may occur anywhere within the major hepatic ducts, in the region of the junction of the right and left hepatic ducts, and in the common hepatic and the common bile ducts (including the intrapancreatic portion of the common bile duct).

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

Although the exact etiology of cholangiocarcinoma in the United States is often unknown, there are well-established risk factors for the development of the disease. These risk factors include hepatolithiasis (with or without infection or stasis), ulcerative colitis, sclerosing cholangitis, choledochal cysts, chemical carcinogens (eg, nitrosamines), and liver fluke infections.[61]

Diagnosis and Initial Workup

Most patients with cholangiocarcinoma present with jaundice. Symptoms may be nonspecific and may include weight loss, anorexia, abdominal pain, and fever. Most patients are initially evaluated with a

complete history and physical examination, liver function studies, and CT scan or MRI. For intrahepatic cholangiocarcinomas, upper and lower endoscopy is also recommended as indicated. The evaluation for extrahepatic cholangiocarcinomas should include a delayed-contrast CT scan, endoscopic retrograde cholangiopancreatography, percutaneous transhepatic cholangiography, or MR cholangiography. For vascular assessment, an angiogram may also be needed; endoscopic ultrasound should be considered.

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

Pathology and Staging

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

The AJCC has developed staging criteria for cholangiocarcinomas (see Table 1 and Table 3) comparable to the UICC staging system. Other staging systems, which include the extent of invasion into blood vessels and other organs have been used, particularly in Japan. The Bismuth-Corlette classification describes the extent of biliary ductal involvement by the tumor.[70] Jarnagin and colleagues have developed a useful preoperative staging system for hilar cholangiocarincoma that predicts respectability, likelihood of metastatic disease, and survival.[69]

Management

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

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

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

For patients with unresectable disease, the options include (1) supportive care; (2) ablative therapy with cryotherapy, radiofrequency, or microwave; (3) radiation with or without chemotherapy using either 5-FU--based regimen or gemcitabine; or (4) chemotherapy with either 5-FU--based regimen or gemcitabine.[71] For patients with metastatic disease, options include (1) supportive care; (2) clinical trials; or (3) chemotherapy with either 5-FU--based regimen or gemcitabine.

Extrahepatic Cholangiocarcinoma. The surgical procedures for resectable extrahepatic cholangiocarcinoma are outlined in the algorithm. Patients with disease of the proximal third of the duct

should undergo hilar resection and lymphadenectomy with or without en bloc liver resection. In addition, caudate resection is strongly encouraged. For patients in whom resection is not possible because of either underlying chronic liver disease (primary sclerosing cholangitis) or bilobar extension, liver transplantation can be considered.[72,73]

Pancreaticoduodenectomy with lymphadenectomy is the preferred surgery for disease of the distal third of the duct. Tumors located in the mid third of the duct should be treated with major bile duct excision with lymphadenectomy. In addition, a frozen section assessment of the bile duct margins is recommended.

Patients with positive margins after resection should receive the benefit of a multidisciplinary team review; 5-FU--based chemotherapy with radiation (external-beam therapy or brachytherapy) should be considered for these patients.[74] Again, no randomized trials have been conducted which support a standard regimen. Similar treatments should be considered for patients with carcinoma in situ at the margins or those with positive regional nodes. Individuals with negative margins after resection or with negative regional nodes can either be observed or receive 5-FU--based chemotherapy with radiation.

Patients whose disease is deemed unresectable at the time of surgery should undergo biliary drainage using either surgical bypass or stent.[75,76] Given their overall poor prognosis, further options include (1) a clinical trial; (2) chemoradiation (5-FU--based chemotherapy/RT); (3) chemotherapy alone using either a 5-FU--based regimen or gemcitabine;[71] or (4) best supportive care. Highly selected patients may be transplant candidates (ie, patients whose cholangiocarcinomas are < 1 cm).[72,73]

Those with metastatic disease should undergo biliary drainage by stent placement. Further options include clinical trial, best supportive care, or chemotherapy with either 5-FU--based regimen or gemcitabine, depending on performance status.[77] Given the lack of clinical trial data, there is no standard regimen for these patients, although new therapies appear encouraging.[78,79]

Surveillance

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

Disclosures for the NCCN Hepatobiliary Cancers Guidelines Panel

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

References

1. Pawlik TM, Scoggins CR, Thomas MB, et al. Advances in the surgical management of liver malignancies. Cancer J 2004;10;74-87.

2. de Groen P, Gores G, LaRusso N, et al. Biliary tract cancers. N Engl J Med 1999;341:1368-1378.

3. Jemal A, Murray T, Ward E, et al. Cancer Statistics, 2005. CA Cancer J Clin 2005;55:10-30.

4. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer 1975-2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst 2005;97:1407-1427.

5. Okuda K, Odata H, Nakajina Y et al. Prognosis of primary hepatocellular cancer. Hepatology 1984;4:3.

6. Colombo M. Hepatocellular carcinoma. J Hepatol 1992;15:225-236.

7. El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817-823. [Erratum in: Ann Intern Med 2004;140:151.].

8. Cusnir M, Patt YZ. Novel systemic therapy options for hepatocellular carcinoma. Cancer J 2004;10:97-103.

9. Izzo F, Cremona F, Ruffolo F, et al. Outcome of 67 patients with hepatocellular cancer detected during screening of 1125 patients with chronic hepatitis. Ann Surg 1998;227:513-518.

10. Kim W, Oe Lim S, Kim JS, et al. Comparison of proteome between hepatitis B virus- and hepatitis C virus-associated hepatocellular carcinoma. Clin Cancer Res 2003;9:5493-5500.

11. Tagger A, Donato F, Ribero ML, et al. Case-control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. J Cancer 1999;81:695-699.

12. Muto Y, Moriwaki H, Ninomiya M et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. N Engl J Med 1996;334:1561-1567.

13. Shafritz DA. Synthetic retinoids for the secondary prevention of hepatocellular carcinoma. N Engl J Med 1996;334:1600-1601.

14. Zoli M, Magalotti D, Bianchi G et al. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996;78:977-985.

15. Fung KT, Li FT, Raimondo ML, et al. Systematic review of radiological imaging for hepatocellular carcinoma in cirrhotic patients. Br J Radiol 2004;77:633-640.

16. Hashimoto K, Ikeda Y, Korenaga D, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with hepatocellular carcinoma. Cancer 2005;103:1856-1864.

17. Greene FL, Page DL, Fleming ID, et al, eds. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002.

18. Vauthey JN, Lauwers GY, Esnaola NF et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol 2002;20:1527-1536.

19. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BLCL staging classification. Semin Liver Dis 1999;19:329-338.

20. The Cancer of the Liver Italian Program (CLIP) Investigators: Prospective validation of the CLIP score: a new prognostic system

for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000;31:840-845.

21. Falkson G, Cnaan A, Schutt AJ et al. Prognostic factors for survival in hepatocellular carcinoma. Cancer Res 1988;48:7314-7318.

22. Fan ST, Lo CM, Lai EC et al. Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 1994;331:1547-1552.

23. Farmer DG, Busuttil RW. The role of multimodal therapy in the treatment of hepatocellular carcinoma. Cancer 1994;73:2669-2670.

24. Venook AP. Treatment of hepatocellular carcinoma: Too many options? J Clin Oncol 1994;12:1323-1334.

25. Cha CH, Ruo L, Fong Y, et al. Resection of hepatocellular carcinoma in patients otherwise eligible for transplantation. Ann Surg 2003;238:315-321; discussion 321-323.

26. Ueno S, Tanabe G, Nuruki K, et al. Prognosis of hepatocellular carcinoma associated with Child class B and C cirrhosis in relation to treatment: a multivariate analysis of 411 patients at a single center. J Hepatobiliary Pancreat Surg 2002;9:469-477.

27. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-1022.

28. Wakabayashi H, Okada S, Maeba T, et al. Effect of preoperative portal vein embolization on major hepatectomy for advanced-stage hepatocellular carcinomas in injured livers: a preliminary report. Surg Today 1997;27:403-410.

29. Esnaola NF, Mirza N, Lauwers GY et al. Comparison of clinicopathologic characteristics and outcomes after resection in patients with hepatocellular carcinoma treated in the United States, France, and Japan. Ann Surg 2003;238:711-719.

30. Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. Liver Transpl 2004;10:S46-52.

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

32. Madoff DC, Hicks ME, Abdalla EK, et al. Portal vein embolization with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy: safety and effectiveness--study in 26 patients. Radiology 2003;227:251-260.

33. Regalia E, Coppa J, Pulvirenti A, et al. Liver transplantation for small hepatocellular carcinoma in cirrhosis: analysis of our experience. Transplant Proc 2001;33:1442-1444.

34. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.

35. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001;33:1394-1403.

36. Kanwal F, Dulai GS, Spiegel BM, et al. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. Aliment Pharmacol Ther 2005;21:169-177.

37. Roayaie S, Frischer JS, Emre SH, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the

treatment of hepatocellular carcinomas larger than 5 centimeters. Ann Surg 2002;235:533-539.

38. Lu DS, Yu NC, Raman SS, et al. Percutaneous radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. Hepatology. 2005;41:1130-1137.

39. Adam R, Azoulay D, Castaing D, et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003;238:508-518.

40. Gondolesi GE, Roayaie S, Munoz L, et al. Adult living donor liver transplantation for patients with hepatocellular carcinoma: Extending UNOS priority criteria. Ann Surg 2004;239:142-149.

41. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226:441-451.

42. Mazzanti R, Arena U, Pantaleo P, et al. Survival and prognostic factors in patients with hepatocellular carcinoma treated by percutaneous ethanol injection: a 10-year experience. Can J Gastroenterol 2004;18:611-618.

43. Greten TF, Papendorf F, Bleck JS, et al. Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients. Br J Cancer 2005;92:1862-1868.

44. Lu DS, Yu NC, Raman SS, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology 2005;234:954-960. Epub 2005 Jan 28.

45. Venook AP, Stagg RJ, Lewis BJ et al. Chemoembolization for hepatocellular carcinoma. J Clin Oncol 1990;8:1108-1114.

46. Ikeda K, Kumada H, Saitoh S et al. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma: An analysis of the Cox proportional hazard model. Cancer 1991;68:2150-2154.

47. Yamashita Y, Takahasi M, Koga Y, et al. Prognostic factors in the treatment of hepatocellular carcinoma with transcatheter arterial embolization and arterial infusion. Cancer 1991;67:385-391.

48. Raoul JL, Heresbach D, Bretagne et al. Chemoembolization of hepatocellular carcinomas. Cancer 1992;70:585-590.

49. Taguchi T, Nakamura H. Chemoembolization therapy for hepatocellular carcinoma in Japan. J Infus Chemother 1992;2:124-127.

50. Lyster MT, Benson AB, Vogelzang R et al. Chemoembolization: Alternative for hepatic tumors. Contemp Oncol 1993;3:17-28.

51. Bronowicki JP, Vetter D, Dumas F et al. Transcatheter oily chemoembolization for hepatocellular carcinoma. Cancer 1994;74:16-24.

52. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995;332:1256-1261.

53. Levin B, Amos C. Therapy of unresectable hepatocellular carcinoma. N Engl J Med 1995;332:1294-1296.

54. Alexander HR, Bartlett DL, Fraker DL et al. Regional treatment strategies for unresectable primary or metastatic cancer confined to the liver. PPO Updates: Principles and Practice of Oncology 1996;10:1-19.

55. Ishii H, Okada S, Nose H et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. Cancer 1996;77:1792-1796.

56. Dawson L, McGinn C, Normolle D et al. Escalated focal liver radiation and hepatic artery floxuridine for unresectable liver malignancies. J Clin Oncol 2000;18:2210-2218.

57. Jones RS. Carcinoma of the gallbladder. Surg Oncol Clin North Am 1990;70:1419.

58. Nakeeb A, Pitt HA. The role of preoperative biliary decompression in obstructive jaundice. Hepatogastroenterology 1995;42:332.

59. Fong Y. Aggressive therapy is warranted for gallbladder cancer. Cancer Invest 1998;16:64.

60. Maibenco DC, Smith JL, Nava HR, et al. Carcinoma of the gallbladder. Cancer Invest 1998;16:33.

61. Rajagopalan V, Daines WP, Grossbard ML, et al. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 1. Oncology 2004;18:889-896.

62. Kresl JJ, Schild SE, Henning GT, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002;52:167-175.

63. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002;95:1685-1695.

64. Daines WP, Rajagopalan V, Grossbard ML, et al. Gallbladder and biliary tract carcinoma: A comprehensive update, Part 2. Oncology (Huntingt) 2004;18:1049-1059.

65. Patt YZ, Hassan MM, Aguayo A, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 2004;101:578-586.

66. Vogt DP. Current management of cholangiocarcinoma. Oncology 1988;2:37-43.

67. Altaee MY, Johnson PJ, Farrant JM, et al. Etiologic and clinical characteristics of peripheral and hilar cholangiocarcinoma. Cancer 1991;68:2051-2055.

68. Pitt HA, Dooley WC, Yeo CJ, et al: Malignancies of the biliary tree. Curr Probl Surg 1995;32:1.

69. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507-517; discussion 517-519.

70. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis carcinoma of the hilus of the liver. Surg Gynecol Obstet 1975;140:170-178.

71. Kubicka S, Rudolph K, Tietze M, et al. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepatogastroenterology. 2001; 39:783-789.

72. Sudan D, DeRoover A, Chinnakotla S, et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. Am J Transplant 2002;2:774-779.

73. Heimbach JK, Haddock MG, Alberts SR, et al. Transplantation for hilar cholangiocarcinoma. Liver Transpl 2004;10:S65-68.

74. McMasters KM, Tuttle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. Am J Surg 1997;174:605-608.

75. Davids PH, Groen AK, Rauws EA, et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet 1992;340:1488-1492.

76. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc 1998;47:1-7.

77. Schiefke I, Zabel-Langhennig A, Wiedmann M, et al. Self-expandable metallic stents for malignant duodenal obstruction caused by biliary tract cancer. Gastrointest Endosc 2003;58:213-219.

78. Kim TW, Chang HM, Kang HJ, et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. Ann Oncol 2003;14:1115-1120.

79. Wiedmann M, Berr F, Schiefke I, et al. Photodynamic therapy in patients with non-resectable hilar cholangiocarcinoma: 5-year follow-up of a prospective phase II study. Gastrointest Endosc 2004;60:68-75.

Recommended Reading

Cance WG, Stewart AK, Menck HR. The National Cancer Data Base Report on treatment patterns for hepatocellular carcinomas: Improved survival of surgically resected patients, 1985-1996. Cancer 2000;88:912-920.

de Groen P, Gores G, LaRusso N, et al. Biliary tract cancers. N Engl J Med 1999;341:1368-1378.

Fujiyama S, Tanaka M, Maeda S, et al. Tumor markers in early diagnosis, follow-up and management of patients with hepatocellular carcinoma. Oncology 2002;62:57-63.

Greene FL, Page DL, Fleming ID, et al, eds. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002.

Hain SF, Fogelman I. Recent advances in imaging hepatocellular carcinoma: Diagnosis, staging, and response assessment: Functional imaging. Cancer J 2004;10:121-127.

Hayashi N, Kasahara A. Interferon for decreasing the incidence of hepatocellular carcinoma in patients with chronic hepatitis C. Oncology 2002;6287-93.

Hussain SA, Ferry DR, El-Gazzaz G, et al. Hepatocellular carcinoma. Ann Oncol 2001;12:161-172.

Iino S. Natural history of hepatitis B and C virus infections. Oncology 2002;62:18-23.

Ikeda K, Kobayashi M, Saitoh S, et al. Recurrence rate and prognosis of patients with hepatocellular carcinoma that developed after elimination of hepatitis C virus RNA by interferon therapy. Oncology 2003;65:204-210.

Kaneko S, Urabe T, Kobayashi K. Combination chemotherapy for advanced hepatocellular carcinoma complicated by major portal vein thrombosis. Oncology 2002;6269-73.

Kiyosawa K, Tanaka E. Characteristics of hepatocellular carcinoma in Japan. Oncology 2002;62:5-7.

Koike K, Tsutsumi T, Fujie H, et al. Molecular mechanism of viral hepatocarcinogenesis. Oncology 2002;62:38-42.

Kojiro M. Pathological evolution of early hepatocellular carcinoma. Oncology 2002;62:43-47.

Kubo S, Nishiguchi S, Hirohashi K, et al. Effect of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. Ann Intern Med 2001;134:963-967.

Kudo M. Imaging blood flow characteristics of hepatocellular carcinoma. Oncology 2002;62:48-56.

Kurnada H. Long-term treatment of chronic hepatitis C with glycyrrhizin [stronger neo-minophagen C (SNMC)] for preventing liver cirrhosis and hepatocellular carcinoma. Oncology 2002;62:94-100.

Levin B. Gallbladder carcinoma. Ann Oncol 1999;10:129-130.

Makuuchi M, Imamura H, Sugawara Y, et al. Progress in surgical treatment of hepatocellular carcinoma. Oncology 2002;62:74-81.

Marsh JW, Geller DA, Finkelstein SD, et al. Role of liver transplantation for hepatobiliary malignant disorders. Lancet Oncol 2004;5:480-488.

Matsunami H, Shimizu Y, Lynch SV, et al. Liver transplantation as a therapeutic option for hepatocellular carcinoma. Oncology 2002;62:82-86.

Mor E, Kaspa RT, Sheiner P, et al. Treatment of hepatocellular carcinoma associated with cirrhosis in the era of liver transplantation. Ann Intern Med 1998;129:643-653.

Nakakura EK, Choti MA. Management of hepatocellular carcinoma. Oncology 2000;14:1805-1098.

Nissen NN, Cavazzoni E, Tran TT, et al. Emerging role of transplantation for primary liver cancers. Cancer J 2004;10:88-96.

O'Brien TR, Kirk G, Zhang M. Hepatocellular carcinoma: Paradigm of preventive oncology. Cancer J 2004;10:67-73.

Oda T. Leading edge research studies of hepatocellular carcinoma in Japan. Oncology 2002;62:2-4.

Ogunbiyi JO. Hepatocellular carcinoma in the developing world. Semin Oncol 2001 28:179-197.

Okita K, Sakaida I, Hinko K. Current strategies for chemoprevention of hepatocellular carcinoma. Oncology 2002;62:24-28.

Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. Oncology 2004;66:167-179.

Poon RT, Ng IO, Fan ST, et al. Clinicopathologic features of long-term survivors and disease-free survivors after resection of hepatocellular carcinoma: A study of a prospective cohort. J Clin Oncol 2001;19:3037-3044.

Randi G, Altieri A, Gallus S, et al. History of cirrhosis and risk of digestive tract neoplasms. Ann Oncol 2005;16:1551-1555. Epub 2005 May 26.

Sarli L, Costi R, Roncoroni L. Laparoscopy and gallbladder cancer. Am J Gastroenterol 2002;97:206.

Shiina S, Teratani T, Obi S, et al. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology 2002;62:64-68.

Toyoda H, Kumada T, Nakano S, et al. Effect of the dose and duration of interferon-alpha therapy on the incidence of hepatocellular carcinoma in noncirrhotic patients with a nonsustained response to interferon for chronic hepatitis C. Oncology 2001;61:134-142.

Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. N Engl J Med 1966;274:473-481.

Venook AP. Regional strategies for managing hepatocellular carcinoma. Oncology 2001;14:347-354.

Weber SM, DeMatteo RP, Fong Y, et al. Staging laparoscopy in patients with extrahepatic biliary carcinoma analysis of 100 patients. Ann Surg 2002;235:392-399.

Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: Projection to other countries in the foreseeable future. Oncology 2002;62:8-17.

Yuen MF, Lai CL. Screening for hepatocellular carcinoma: survival benefit and cost-effectiveness. Ann Oncol 2003;14:1463-1467.