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Hepatobiliary Cancers, Version 2.2014

Clinical Practice Guidelines in Oncology

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Overview: Biliary Tract Cancers

Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma [HCC]), gallbladder, and bile ducts (intrahepatic and extrahepatic cholangiocarcinoma). Gallbladder cancer and cholangiocarcinomas are collectively known as biliary tract cancers. In 2014, an estimated 33,190 people in the United States will be diagnosed with liver cancer and intrahepatic bile duct cancer and an additional 10,310 people will be diagnosed with gallbladder cancer or other biliary tract cancer. Approximately

Abstract

Hepatobiliary cancers include a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma), gall bladder, and bile ducts (cholangiocarcinomas). Gallbladder cancer and cholangiocarcinomas are collectively known as biliary tract cancers. Gallbladder cancer is the most common and aggressive type of all the biliary tract cancers. 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. This manuscript focuses on the clinical management of patients with gallbladder cancer and cholangiocarcinomas (intrahepatic and extrahepatic). (*J Natl Compr Canc Netw* 2014;12:1152–1182)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Hepatobiliary Cancers are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Hepatobiliary Cancers Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Hepatobiliary Cancers Panel members can be found on page 1182. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

23,000 deaths from liver or intrahepatic bile duct cancer will occur, and 3630 deaths will result from gallbladder cancer or other biliary tract cancer.[1] The types of hepatobiliary cancers covered in these guidelines include HCC, gallbladder cancer, and intrahepatic and extrahepatic cholangiocarcinoma. This manuscript discusses the recommendations for the clinical management of patients with biliary tract cancers. For other topics related to hepatobiliary cancers, please refer to the full NCCN Guidelines for Hepatobiliary Cancers (available at NCCN.org).

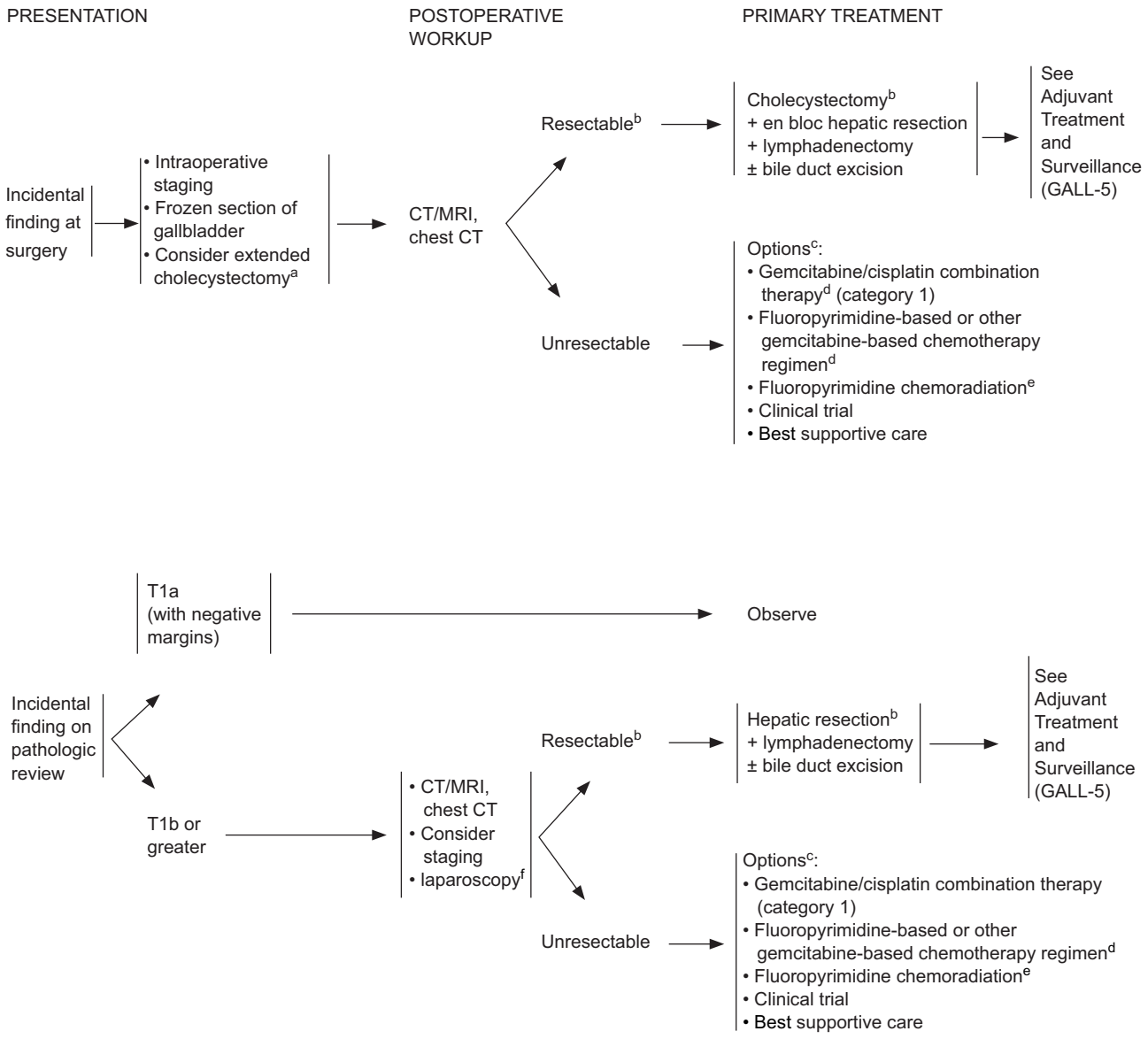
Gallbladder Cancer

Gallbladder cancer is the most common and aggressive type of all the biliary tract cancers. Most gallbladder cancers are adenocarcinomas and their incidence steadily increases with age; women are more likely than men to be diagnosed with gallbladder cancer, and it is more common in white women.[2,3] 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 time to recurrence, and shorter survival duration after recurrence than hilar cholangiocarcinoma.[4]

Risk Factors

Cholelithiasis with the presence of chronic inflammation is the most prevalent risk factor for gallbladder cancer and the risk increases with the stone size.[5,6] Calcification of the gallbladder (porcelain

Text cont. on page 1164.



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

[b]See Principles of Surgery (GALL-A).

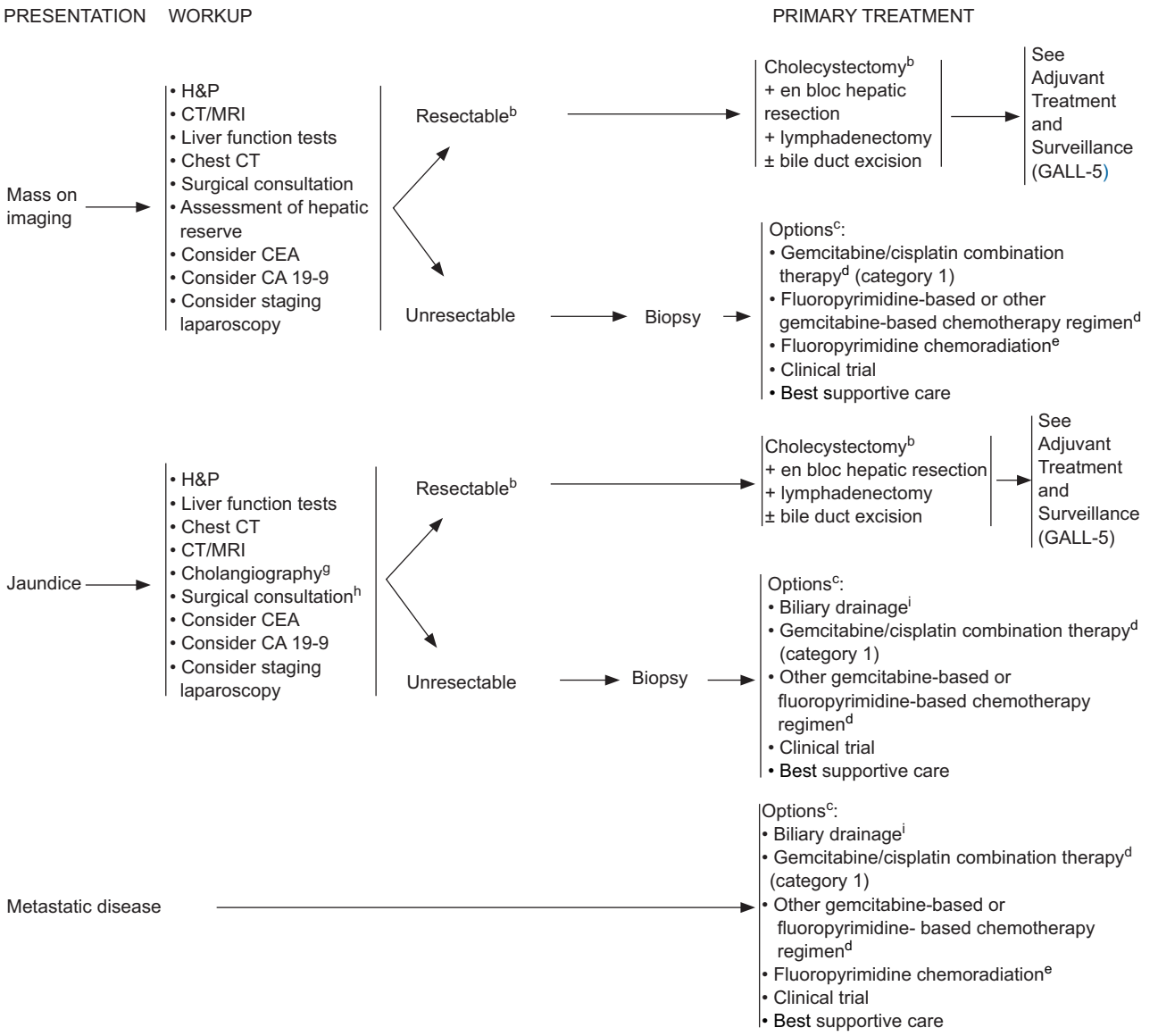
[c]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.

[d]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 Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[e]Limited clinical trial data are available 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.)

[f]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.

GALL-1,
GALL-2



[b]See Principles of Surgery (GALL-A).

[c]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, and institutional capabilites.

[d]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 Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

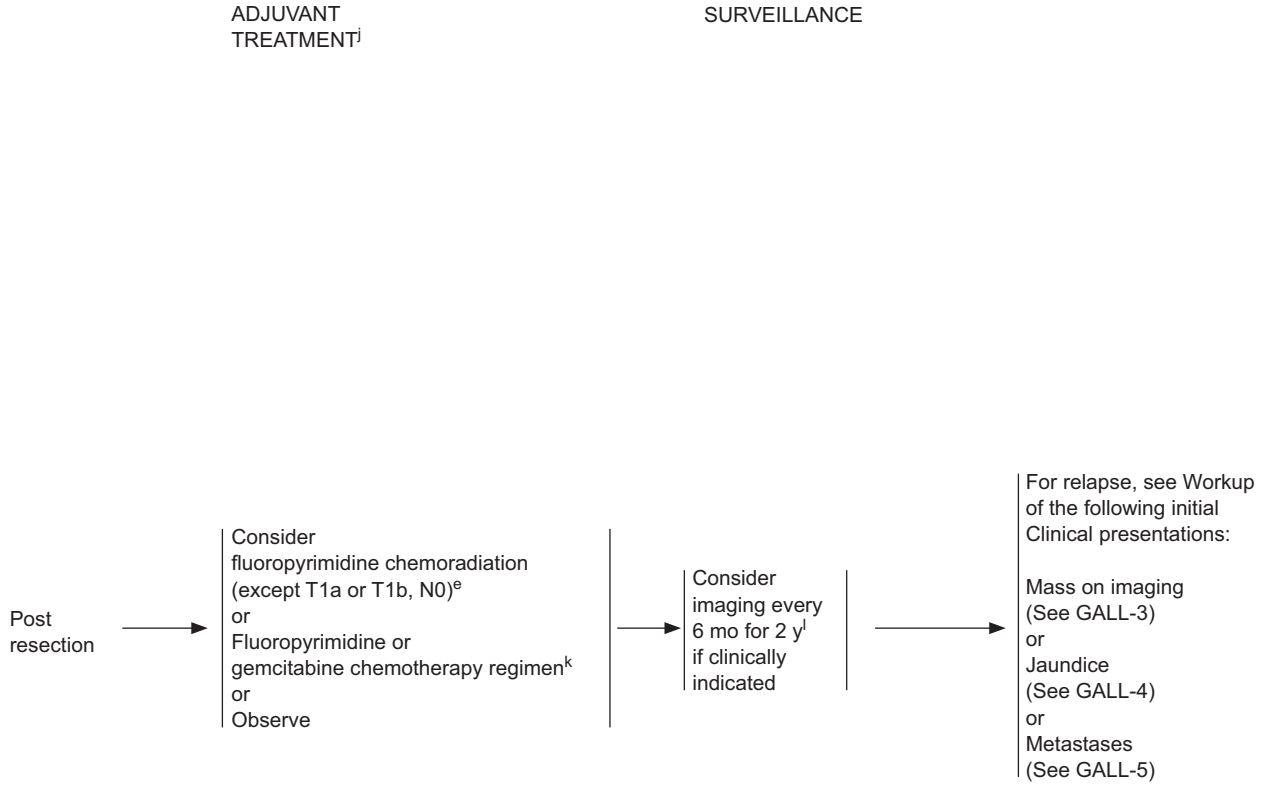
[e]Limited clinical trial data are available to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941-954.)

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

[h]Consult with a multidisciplinary team.

[i]It is expected that patients will have biliary drainage for jaundice before instituting chemotherapy. Consider baseline CA 19-9 after biliary decompression.

GALL-3,
GALL-4



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

[j]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 of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940.)

[k]No randomized phase III clinical trial data support a standard adjuvant regimen. Clinical trial participation is encouraged. Single-agent fluoropyrimidine or gemcitabine is generally recommended in the adjuvant setting.

[l]No data support aggressive surveillance. A patient/physician discussion should take place regarding appropriate follow-up schedules/imaging.

PRINCIPLES OF SURGERY

Incidental finding at surgery:

- If expertise is unavailable, all relevant findings should be documented and the patient referred to a center with available expertise. If a suspicious mass is present, a biopsy is not necessary because it can result in peritoneal dissemination.
- If expertise is available and convincing clinical evidence of cancer is present, a definitive resection should be performed as described 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 IVB and V and lymphadenectomy and extended hepatic or biliary resection as necessary to obtain a negative margin.

Incidental finding on pathologic review:

- Review the operative note and/or speak to surgeon to check for completeness of cholecystectomy, signs of disseminated disease, location of tumor, and any other pertinent information.
- Review the pathology report for T stage, cystic duct margin status, and other margins.
- Diagnostic laparoscopy can be performed but is of relatively low yield. Higher yields may be seen in patients with T3 or higher tumors, poorly differentiated tumors, or with a margin-positive cholecystectomy. Diagnostic laparoscopy should also be considered in patients with any suspicion of metastatic disease on imaging that is not amenable to percutaneous biopsy.[1]
- Repeat cross-sectional imaging of the chest, abdomen, and pelvis should be performed before definitive resection.
- Initial exploration should rule out distant lymph node metastases in the celiac axis or aortocaval groove, because these contraindicate further resection.
- Hepatic resection should be performed to obtain clear margins, which usually consists of segments IVB and V. Extended resections beyond segments IVB 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, because the presence of a port site implant is a surrogate marker of underlying disseminated disease and has not been shown to to improve outcomes.[4]

Mass on imaging: patients presenting with gallbladder mass/disease suspicious for gallbladder cancer

- Staging should be performed with cross-sectional imaging of the chest, abdomen, and pelvis.
- If a suspicious mass is present, a biopsy is not necessary and a definitive resection should be performed.
- Diagnostic laparoscopy is recommended before definitive resection.
- In selected cases in which 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] These patients require careful surgical evaluation.
- Although a relative contraindication, curative intent resection for resectable disease can be attempted in select patients in centers with available expertise.

[1]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.

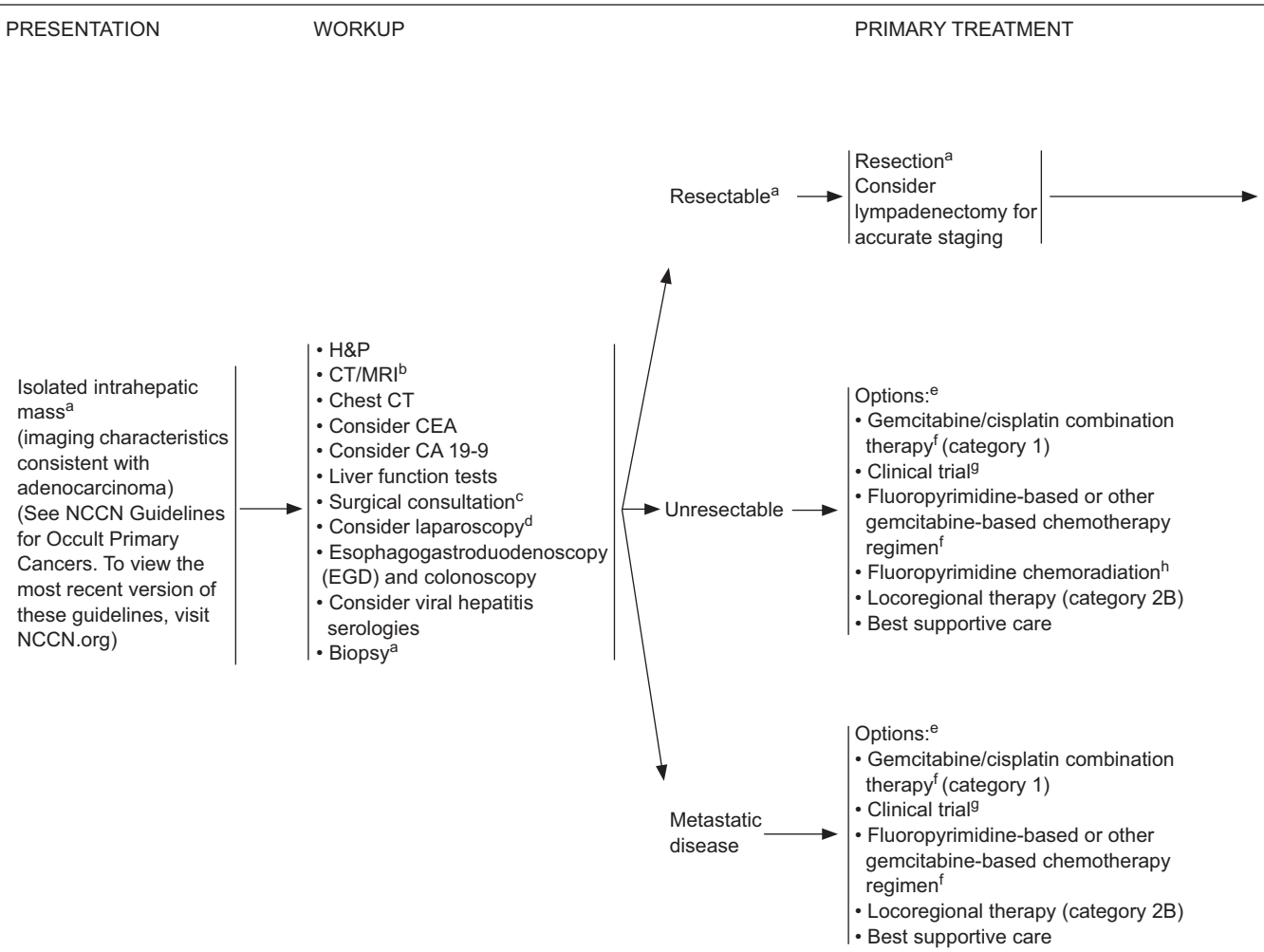
[2]Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 2011;35:1887-1897.

[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.

[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.



[a]See Principles of Surgery (INTRA-A).

[b]Recommend delayed contrast-enhanced imaging.

[c]Consult with a multidisciplinary team.

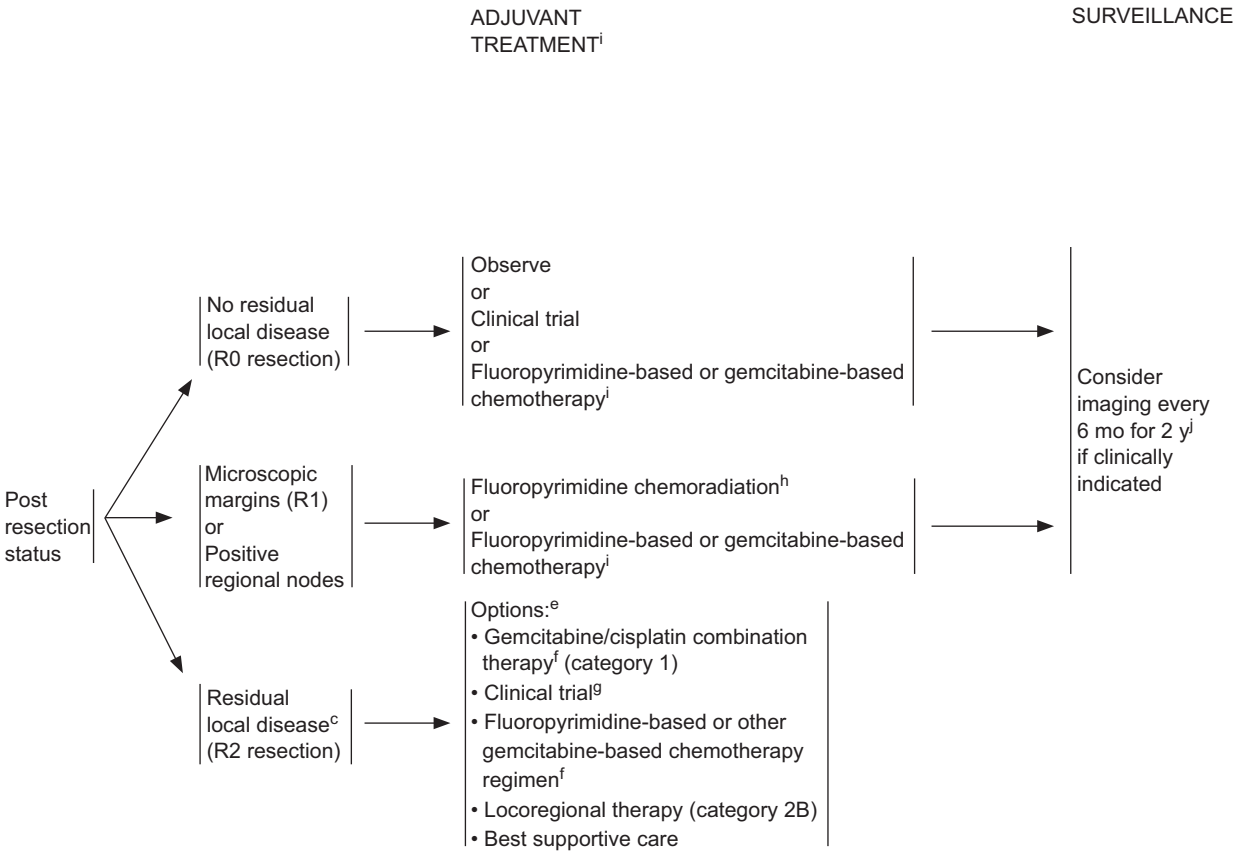
[d]Laparoscopy may be performed in conjunction with surgery if no distant metastases are found.

[e]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.

[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 Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[g]Systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers.

[h]Limited clinical trial data are available 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.)



[c]Consult with a multidisciplinary team.

[e]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.

[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 Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[g]Systemic or intra-arterial chemotherapy may be used in a clinical trial or at experienced centers.

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[i]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 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. No randomized phase III clinical trial data support a standard adjuvant regimen. Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[j]No data support aggressive surveillance. A patient/physician discussion should take place regarding appropriate follow-up schedules/imaging.

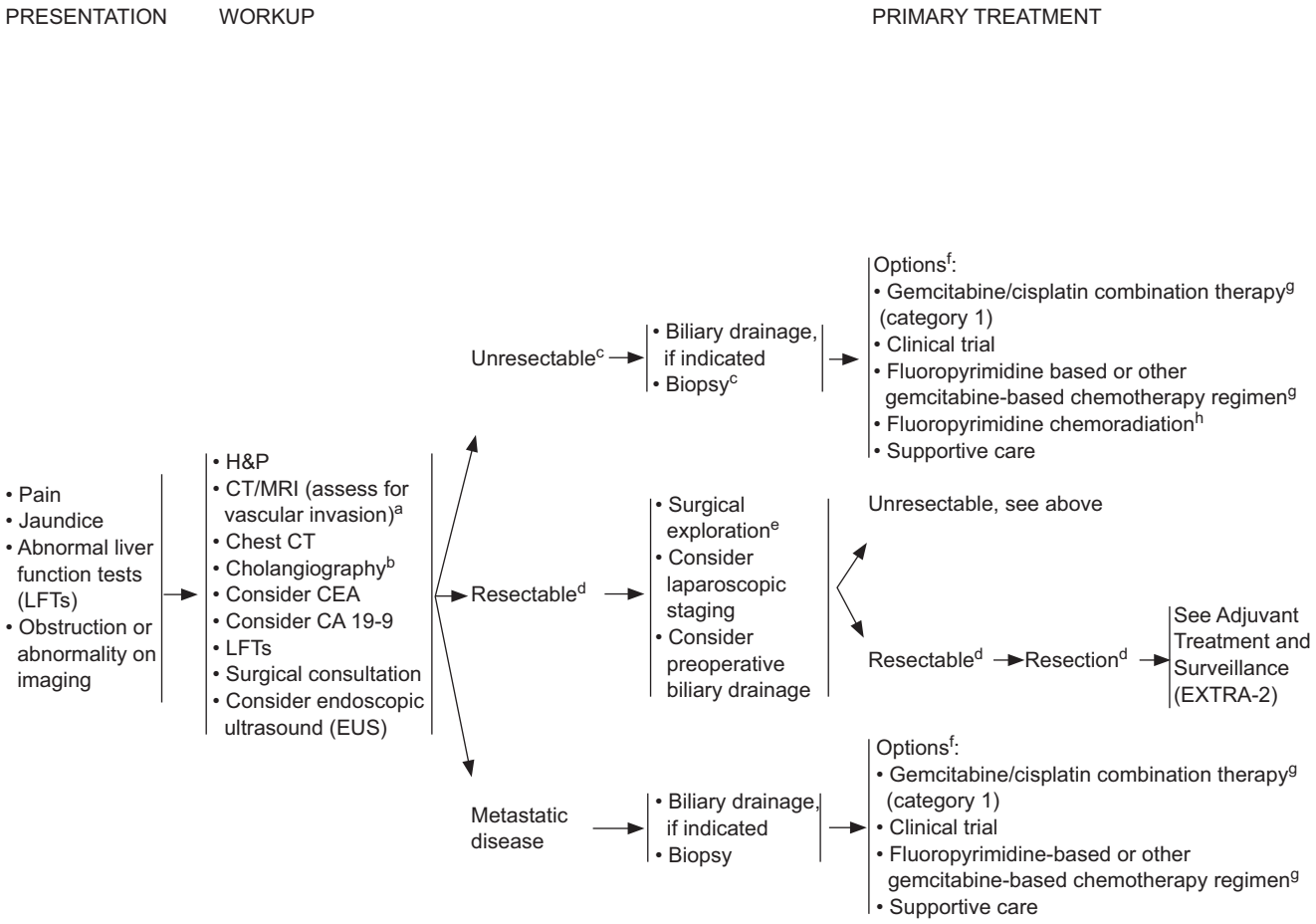
PRINCIPLES OF SURGERY[1,2]

- 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. Although 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 because it 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. Intraheptic 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. J Clin Oncol 2011;29:3140-3145.T.

INTRA-A



[a]Recommend delayed contrast-enhanced imaging.

[b]Noninvasive cholangiography with cross-sectional imaging.

[c]Before biopsy, evaluate if patient is a surgical or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy.

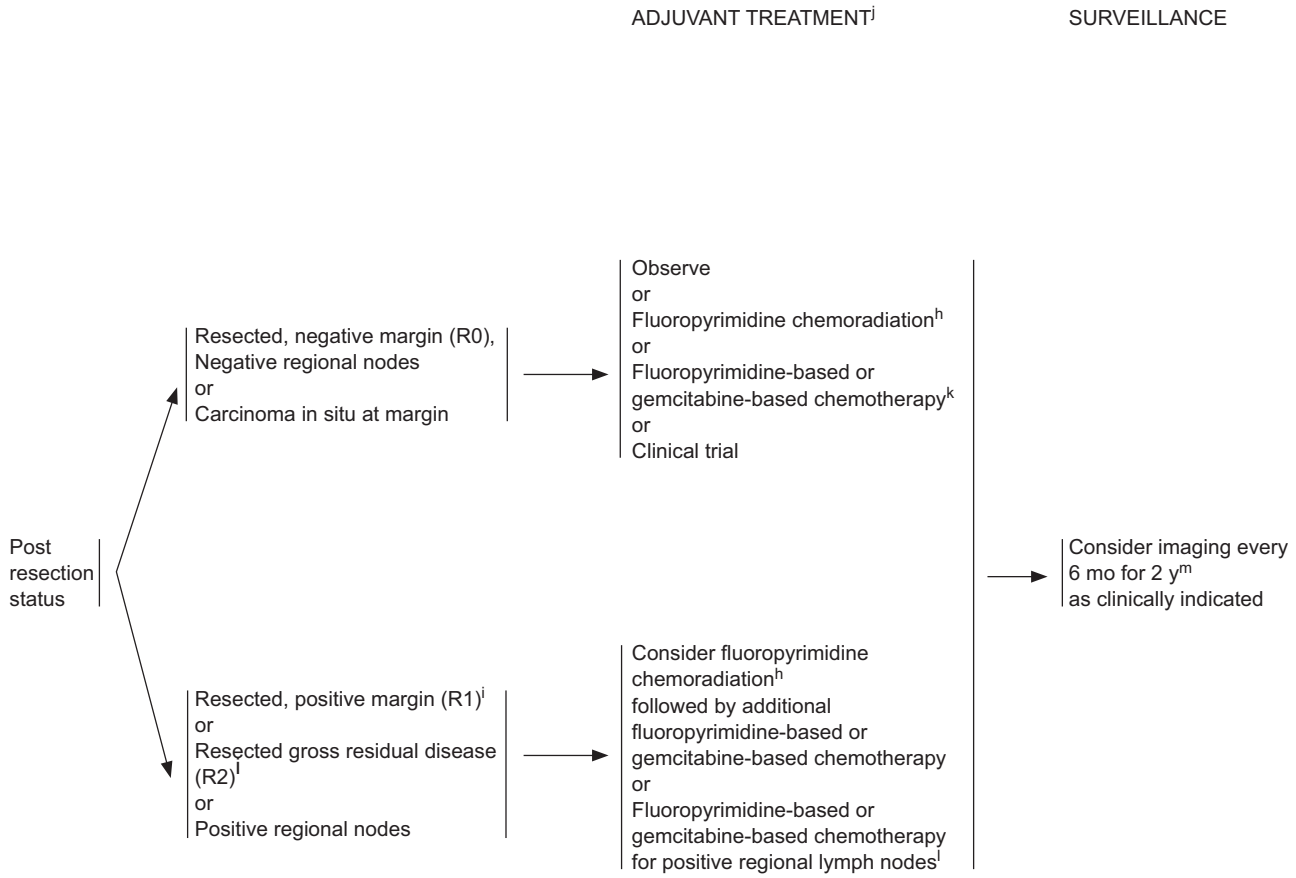
[d]See Principles of Surgery (EXTRA-A).

[e]Surgery may be performed when index of suspicion is high; biopsy not required.

[f]Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilites.

[g]A recent phase III trial supporting gemcitabine/cisplatin has been reported for patients with advanced or metastatic biliary tract cancer. (Valle JW, Wasan HS, Palmer DD, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-1281.) Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[h]Limited clinical trial data are available 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.)



[h]Limited clinical trial data are available 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.)

[i]R1 or R2 resections should be evaluated by a multidisciplinary team.

[j]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 of biliary tract cancer: a systemic review and meta-analysis. J Clin Oncol 2012;30:1934-1940).

[k]Limited clinical trial data are available to define a standard regimen. Clinical trial participation is encouraged.

[l]No randomized phase III clinical trial data support a standard adjuvant regimen. Clinical trial participation is encouraged. Phase II trials 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, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415-423.)

[m]No data support aggressive surveillance. A patient/physician discussion should take place regarding appropriate follow-up schedules/imaging.

EXTRA-2

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 performed 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 negativere section. 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 future liver remnant (FLR). This requires an assessment of biliary drainage and volumetrics of the FLR. Although 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 future liver remnant.[4,5]
- Initial exploration rules out distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis, because these findings contraindicate resection. Further exploration must confirm local resectability.
- Because 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 performed.
- Frozen section assessment of proximal and distal bile duct margins are recommended if further resection can be performed.

Distal cholangiocarcinoma

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

[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 outcomes 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 preoparative biliary drainage of live remnant prior to extended liver resection of hilar cholangiocarcinoma. HPB (Oxford) 2009;11:445-451.

Text cont. from page 1153.

gallbladder), a result of chronic inflammation of the gallbladder, has also been regarded as a risk factor for gallbladder cancer.[5] Recent reports, however, suggest that the risk of developing gallbladder cancer in patients with gallbladder calcification is much lower than anticipated (6% compared with 1% in patients without gallbladder calcifications).[7,8] Other risk factors include anomalous pancreaticobiliary duct junctions, gallbladder polyps (solitary and symptomatic polyps >1 cm), chronic typhoid infection, adenomyomatosis of the gallbladder, and inflammatory bowel disease.[6,9,10] Prophylactic cholecystectomy may be beneficial for patients who are at high risk of developing gallbladder cancer.[5]

Staging and Prognosis

In the AJCC staging system, gallbladder cancer is classified into 4 stages based on the depth of invasion into the gallbladder wall and the extent of spread to surrounding organs and lymph nodes. In the revised 2010 AJCC staging system, stage groupings have been changed to better correlate with the extent of cystic duct and lymph node involvement, resectability of the tumor, and patient outcome.[11] Lymph node metastasis is now classified as stage IIIB (N1) or IVB (N2), and locally unresectable T4 tumors have been reclassified as stage IV. An analysis of 10,705 patients diagnosed with gallbladder cancer between 1989 and 1996 in the National Cancer Database showed that this revised staging system provided an improved prognostic discrimination of patients with stage III and IV disease.[12]

Tumor stage is the strongest prognostic factor for patients with gallbladder cancer.[2,13] In an analysis of approximately 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, I, and III disease, respectively, whereas the corresponding survival rates were only 5% and 1% for patients with stage III and IV disease, respectively.[2] Results from a retrospective analysis of 435 patients treated at a single center showed a median overall survival (OS) of 10.3 months for the entire cohort of patients.[13] The median survival was 12.9 and 5.8 months for those presenting with stage IA–III and stage IV disease, respectively. In a recent report of 122 patients with gallbladder cancer identified in a prospectively maintained database, liver involvement was associated with decreased relapse-free survival (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 disease-specific survival was 25 months vs not reached for patients without liver involvement, P=.003) but not in patients with T1b tumors.[14]

Diagnosis

Gallbladder cancer is often diagnosed at an advanced stage because of the aggressive nature of the tumor, which can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation that mimics that of biliary colic or chronic cholecystitis. Hence, it is not uncommon for a diagnosis of gallbladder cancer to be an incidental finding at cholecystectomy for a benign gallbladder disease or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis. In a retrospective review of 435 patients diagnosed and treated with curative resection at a single center during 1995 to 2005, 123 patients (47%) were diagnosed with gallbladder cancer as an incidental finding during laparoscopic cholecystectomy.[13] Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound or biliary tract obstruction with jaundice. The presence of jaundice in patients with 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 vs 16 months; P<.0001) than those without jaundice.[15]

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 cross-sectional imaging (ultrasound, CT, or MRI) of the chest, abdomen, and pelvis is recommended to evaluate tumor penetration within the wall of the gallbladder to determine the presence of nodal and distant metastases and to detect the extent of direct tumor invasion of other organs/biliary system or major vascular invasion.[16] CT is more useful than ultrasound for the detection of lymph node involvement, adjacent organ invasion, and distant metastasis; MRI may be useful for distinguishing benign conditions from gallbladder cancer.[3] Although the role of PET scan has not been established in the evaluation of

patients with gallbladder cancer, emerging evidence indicates that it may be useful for detecting regional lymph node metastases and distant metastatic disease in patients with otherwise potentially resectable disease.[17–19]

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.[16]

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 (>4.0 ng/mL) or CA 19-9 levels (>20.0 units/mL) could be suggestive of gallbladder cancer.[20] Although CA 19-9 had higher specificity than CEA (92.7% vs 79.2%), its sensitivity was lower (50.0% vs 79.4%). However, these markers are not specific for gallbladder cancer, and CA 19-9 could also be elevated in patients with jaundice from other benign causes.

Surgical Management

The surgical approach to the management of all patients with resectable gallbladder cancer is the same, except 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.[21] The optimal resection consists of cholecystectomy with a limited hepatic resection (segments IVB and V), and portal lymphadenectomy to encompass the tumor with negative margins.[22] 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 IVB 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%.[23] Although cholecystectomy combined with hepatic resection and lymphadenectomy is associated with an improved survival for patients with T2 or higher tumors, no definite evidence exists regarding the benefit of radical resection over simple cholecystectomy for patients with T1b tumors.[24–29] Some studies have demonstrated a significant improvement in cancer-specific survival among patients with T1b and T2 tumors, and no improvement in survival among patients with T3 tumors.[25–27] Other reports suggest that a survival benefit associated with extended resection and lymphadenectomy is seen only in patients with T2 tumors and some with T3 tumors with localized hepatic invasion and limited regional node involvement.[28,29] Major hepatic resection and bile duct resection have also been shown to increase morbidity without improvement in survival.[22,30] A multivariate analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990 to 2002 showed that higher T and N stage, poor differentiation, and common bile duct involvement were independent predictors of poor disease-specific survival.[30] Major hepatectomy and common bile duct excision significantly increased overall perioperative morbidity (53%) and were not independently associated with long-term survival.[30] Fuks et al[22] from the AFS-GBC-2009 study group also reported that bile duct resection resulted in a postoperative morbidity rate of 60% in patients with an incidental finding of gallbladder cancer. However, for patients with incidental findings of gallbladder cancer, Pawlik et al[31] reported that common duct resection should be performed at the time of re-resection for those with positive cystic duct margins, because of the presence of residual disease.

With these data in mind, the guidelines recommend that extended hepatic (beyond segments IVB and V) and bile duct resections should be performed only when necessary to obtain negative margins (R0 resection) in certain clinical situations, as discussed earlier.[25,27–29]

Among patients with an incidental finding of gallbladder cancer, some evidence shows 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.[32,33] However, these comparisons are difficult to interpret because of selection bias. Nevertheless, in all patients with convincing clinical evidence of gallblad-

der cancer, the guidelines recommend that surgery should be performed by an experienced surgeon who is prepared to perform a definitive resection of the tumor. If expertise is unavailable, patients should be referred to a center with available expertise. The panel is also of the opinion that surgery should not be performed in situations where the extent and resectability of the disease has not been established.

Management of Resectable Disease

All patients should undergo cross-sectional imaging (ultrasound, CT, or MRI) of the chest, abdomen, and pelvis before 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.[34] In a prospective study that evaluated the role of staging laparoscopy in 409 patients diagnosed with primary gallbladder cancer, Agarwal et al[34] 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 100.0%, respectively). 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 an incidental finding of gallbladder cancer, because 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).[35] Because the risk of peritoneal metastases is high for patients with primary gallbladder cancer, staging laparoscopy should be considered for if no distant metastases are found on imaging or if any suspicion exists of metastatic disease on imaging that is not amenable to percutaneous biopsy.[34] In patients with an incidental finding of gallbladder cancer, staging laparoscopy can be considered in those who are at high risk for disseminated metastases.[35]

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

Among patients with an incidental finding of gallbladder cancer on pathologic review, those with T1a lesions may be observed if the tumor margins are negative, because these tumors have not penetrated the muscle layer and long-term survival approaches 100% with simple cholecystectomy.[23] Extended hepatic resection and lymphadenectomy with or without bile duct excision is recommended for patients with T1b or greater lesions.[25,27,28] Aggressive re-resection to achieve negative margins is often performed for patients with an incidental finding of T1b, T2, or T3 gallbladder cancer, because a significant percentage of these patients have been found to harbor residual disease within the liver and common bile duct.[13,31] Port site resection was not associated with improved survival or disease recurrence in patients with incidental findings of gallbladder cancer and should not be considered during definitive resection.[36,37]

For patients with a suspicious mass detected on imaging or in patients presenting with jaundice, the guidelines recommend cholecystectomy plus en bloc hepatic resection and lymphadenectomy with or without bile duct excision. A biopsy is not necessary and a diagnostic laparoscopy is recommended before definitive resection.[34] 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 portion of those with node-negative disease potentially benefit from complete resection.[15,38] In patients with jaundice, if gallbladder cancer is suspected, surgery should only be performed with a curative intent. These patients should be carefully evaluated before surgery and referral to an experienced center should be considered.

The optimal adjuvant treatment strategy for patients with resected gallbladder cancer has not been determined and limited clinical trial data support a standard regimen for adjuvant treatment. A multivariate Cox proportional hazards model developed to make individualized predictions of survival from the addition of radiotherapy following gallbladder

cancer resection showed that the greatest benefit of radiotherapy was seen in patients with T2 or higher-stage tumors and node-positive disease.[39,40] Results of these studies support omitting adjuvant chemoradiation in the postsurgical treatment of patients with gallbladder cancer characterized as T1b, N0.

The guidelines have included consideration of fluoropyrimidine chemoradiation (except T1a or T1b,N0) and fluoropyrimidine or gemcitabine chemotherapy as options for adjuvant treatment. See "Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers," page 1172.

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 aortocaval 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) a 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," page 1174.

In patients with unresectable or metastatic gallbladder cancer and jaundice, biliary drainage is an appropriate palliative procedure and should be performed before instituting chemotherapy if technically feasible.[38] Biliary drainage followed by chemotherapy can result in improved quality of life. CA 19-9 testing can be considered after biliary decompression.

Surveillance

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

Cholangiocarcinomas

Cholangiocarcinomas encompass all tumors originating in the epithelium of the bile duct. More than 90% of cholangiocarcinomas are adenocarcinomas and are broadly divided into 3 histologic types based on their growth patterns: mass-forming, periductal-infiltrating, and intraductal-growing.[41] Cholangiocarcinomas are diagnosed throughout the biliary tree and are typically classified as either intrahepatic or extrahepatic cholangiocarcinoma. Extrahepatic cholangiocarcinomas are more common than intrahepatic cholangiocarcinomas.

Intrahepatic cholangiocarcinomas (also known as *peripheral cholangiocarcinomas*) are located within the hepatic parenchyma and have also been called *peripheral cholangiocarcinomas* (see Figure 1, available online, in these guidelines, at NCCN.org). Extrahepatic cholangiocarcinomas occur anywhere within the common hepatic duct, at or near the junction of the right and left hepatic ducts, or the common bile duct, including the intrapancreatic portion, and are further classified into hilar or distal tumors (see Figure 1). 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.[42] Hilar cholangiocarcinomas are the most common type of extrahepatic cholangiocarcinomas.

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

Risk Factors

No predisposing factors have been identified in most patients diagnosed with cholangiocarcinoma,[43] although evidence shows that particular risk factors may be associated with the disease in some patients. These risk factors, like those for gallbladder cancer, are associated with the presence of chronic inflammation. Primary sclerosing cholangitis, chronic calculi of the bile duct (hepatolithiasis), choledochal cysts, and liver fluke infections are well-established risk factors for cholangiocarcinoma. Unlike gallbladder cancer, however, cholelithiasis is not thought to be closely linked with cholangiocarcinoma.[44] Other potential but less-established risk factors include in-

flammatory bowel disease, hepatitis C virus, hepatitis B virus, cirrhosis, diabetes, obesity, alcohol, and tobacco. Recently, several case-controlled studies from Asian and Western countries have reported hepatitis C viral infection as a significant risk factor for intrahepatic cholangiocarcinoma.[45–48] This may be responsible for the increased incidence of intrahepatic cholangiocarcinoma recently observed at some centers, although future studies are needed to further explore this putative association.[49]

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.[50] In more recent reports, tumor size had no effect on survival in patients undergoing surgery.[51,52] In a SEER database analysis of 598 patients with intrahepatic cholangiocarcinoma who had undergone surgery, Nathan et al[51] first reported that multiple lesions and vascular invasion predicted an adverse prognosis following resection, and lymph node status was of prognostic significance among patients without distant metastases. 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.[52] The 5-year survival rate was higher for patients who lacked all 3 risk factors (multiple tumors, vascular invasion, and N1 disease) than for those with one or more risk factors (38.3%, 27.3%, and 18.1%, respectively), and, more importantly, tumor number and vascular invasion were of prognostic significance only in patients with N0 disease. Although tumor size was associated with survival in the univariate analysis, it was not of prognostic significance in the multivariate analysis.

In the revised 7th edition of the AJCC staging system, intrahepatic cholangiocarcinoma has a new staging classification that is independent of the staging classification used for HCC.[11] The new classification focuses on multiple tumors, vascular invasion, and lymph node metastasis. Farges et al[53] from the AFC-IHCC study group validated the new staging classification in 163 patients with resectable intrahepatic cholangiocarcinoma. The revised classification was useful in predicting survival according to the TNM staging. With 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.[11] 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 and hilar cholangiocarcinomas.[54,55]

The modified Bismuth-Corlette staging system[56] and the Blumgart staging system[57] are used to classify 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 atopy. In addition, both the AJCC and the Bismuth-Corlette staging systems are not useful for predicting resectability or survival. The Blumgart staging system developed by Jarnagin et al[57,58] is a useful preoperative staging system that predicts resectability, likelihood of metastatic disease, and survival. In this staging system, the hilar cholangiocarcinomas are classified into 3 stages (T1–3) based on the location and extent of bile duct involvement, the presence or absence of portal venous invasion, and hepatic lobar atrophy.[57] Negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after resection; increasing T stage correlated significantly with reduced R0 resection rate, distant metastatic disease, and lower median survival.[58]

Diagnosis

Early-stage cholangiocarcinomas are typically asymptomatic. Patients with intrahepatic cholangiocarcinoma are more likely to present with nonspecific symptoms, such as fever, weight loss, and/

or abdominal pain; symptoms of biliary obstruction are uncommon. Alternatively, intrahepatic cholangiocarcinoma may be detected incidentally as an isolated intrahepatic mass on imaging.[59] In contrast, patients with extrahepatic cholangiocarcinoma are likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.

Workup

The initial workup should include liver function tests. CEA and CA 19-9 testing can be considered, although these markers are not specific for cholangiocarcinoma; they are also associated with other malignancies and benign conditions.[60] Early surgical consultation with a multidisciplinary team is recommended as part of the initial workup for the 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).

Direct visualization of the bile duct with directed biopsies is the ideal technique for the workup of cholangiocarcinoma. Delayed-contrast CT/MRI to assess the involvement of the liver, major vessels, nearby lymph nodes, and distant sites is also recommended when extrahepatic cholangiocarcinoma is suspected.[61] Although no pathognomonic CT/MRI features are associated with intrahepatic cholangiocarcinoma, CT/MRI is used to help determine tumor resectability by characterizing the primary tumor, its relationship to nearby major vessels and the biliary tree, the presence of satellite lesions and distant metastases in the liver, and lymph node involvement, if present.[61] In addition, chest imaging should be performed, and laparoscopy may be performed in conjunction with surgery if no distant metastasis is found. Endoscopic ultrasound may be useful in distal common bile duct cancers for defining a mass or abnormal thickening, which can direct biopsies. Esophagogastroduodenoscopy and colonoscopy are recommended as part of the initial workup for patients with intrahepatic cholangiocarcinoma.

MRCP is increasingly being used as a noninvasive alternative to ERCP for the diagnosis of bile duct cancers.[62,63] It has been shown to have a higher sensitivity, specificity, and diagnostic accuracy than ERCP in the diagnosis and pretreatment staging of hilar cholangiocarcinomas.[64] Recent data also support the use of MRCP and CT as a noninvasive alternative to ERCP for the assessment of bile duct tumors.[65] ERCP/PTC should not be routinely recommended for the diagnosis of extrahepatic cholangiocarcinoma, because this is associated with complications and contamination of the biliary tree. For distal bile duct tumors in which a diagnosis is needed or when palliation is indicated, an ERCP allows for complete imaging of the bile duct and stenting of the obstruction. In addition, brushes of the bile duct can be obtained for pathologic evaluation. Because many of the patients with extrahepatic cholangiocarcinoma present with jaundice, additional workup should include noninvasive cholangiography with cross-sectional imaging to evaluate local tumor extent.[61] 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.[17–19,66,67]

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 because of 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,[68–73] whereas others suggest that margin status is not a significant predictor of outcome.[74,75] Ribero et al[73] from the Italian Intrahepatic Cholangiocarcinoma Study Group reported that margin-negative resection was associated with significantly higher survival rates (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 who had margin-negative resections, the margin width had no long-term impact on survival (P=.61) or recurrence (P>.05) after resection. Farges et al[75] from the AFC-IHCC-2009 study group reported that although R1 resection was the strongest independent predictor of poor outcome in patients with pN0 dis-

ease undergoing surgery, its survival benefit was very small in those with pN+ disease (median survival of 18 and 13 months, respectively, after R0 and R1 resections, respectively; *P*=.1). In this study, a margin width greater than 5 mm was an independent predictor of survival among patients with pN0 disease with R0 resections, which is in contrast to the findings reported by Ribero et al.[73]

Available evidence (although not conclusive) supports the recommendation that hepatic resection with negative margins (wedge resections and segmental resections) should be the goal of surgical therapy for patients with potentially resectable disease.[76] Extensive hepatic resections are often necessary to achieve clear margins, because most tumors present as large masses.[73] Initial surgical exploration should include assessment of multifocal liver disease, lymph node metastases, and distant metastases. A preoperative biopsy is not always necessary before definitive and potentially curative resection. Although multifocal liver tumors, lymph node metastases to the porta hepatis, and distant metastases are considered contraindications to surgery, surgical approaches can be considered in highly selected patients. Patient selection for surgery is facilitated by careful preoperative staging, which may include laparoscopy to identify patients with unresectable or disseminated metastatic disease.[77,78] 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.[77] A portal lymphadenectomy is reasonable because it provides accurate staging information. However, very few data support the therapeutic benefit of routine lymph node dissection in patients undergoing surgery, particularly in those with no lymph node involvement.[79–82] However, because lymph node metastasis is an important prognostic indicator of survival, lymphadenectomy could be considered for patients with lymph node metastases.[52,73]

The optimal adjuvant treatment strategy for patients with resected intrahepatic cholangiocarcinoma has not been determined and limited clinical trial data support a standard regimen for adjuvant treatment. Lymphovascular and perineural invasion, lymph node metastasis, and tumor size of 5 cm or greater have been reported as independent predictors of recurrence and reduced overall survival after resection.[83–85] Because recurrence after resection is common, these tumor-specific risk factors could be considered criteria for selecting 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 are included as options for patients with microscopic tumor margins (R1) or positive regional nodes (see "Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers," page 1172). Patients with residual local disease (R2) should be managed as described herein for unresectable or metastatic disease.

Primary treatment options for patients with unresectable or metastatic disease include (1) a 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," page 1174).

Locoregional therapies such as radiofrequency ablation (RFA),[86,87] transarterial chemoembolization (TACE),[88–90] TACE with drug-eluting microspheres (DEB-TACE),[89,91,92] and transarterial radioembolization (TARE) with yttrium-90 microspheres[90,93–98] have been shown to be safe and effective in a small series of patients with unresectable intrahepatic cholangiocarcinomas. In a series of 17 patients with primary unresectable intrahepatic cholangiocarcinoma, RFA resulted in a median progression-free survival (PFS) of 32 months and OS of 38.5 months.[87] The results of 2 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.[89] In another series of 24 patients with unresectable intrahepatic cholangiocarcinoma, TARE with yttrium-90 micro-

spheres induced greater than 50% tumor necrosis and 100% tumor necrosis in 77% and 9% of patients, respectively, with a median OS of 14.9 months.[93] Other series have also reported favorable response rates and a survival benefit for patients with unresectable intrahepatic cholangiocarcinoma treated with TARE with yttrium-90 microspheres.[96,98] However, because of the rarity of this disease, none of these approaches has been evaluated in randomized clinical trials. Nevertheless, based on the available evidence as discussed earlier, the panel has included locoregional therapy (category 2B) as an option for patients with unresectable or metastatic disease.

Photodynamic therapy (PDT) is a relatively new ablative therapy that involves intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation, and has been used for palliation in patients with cholangiocarcinoma. The combination of PDT with biliary stenting was reported to improve the OS of patients with unresectable cholangiocarcinoma in 2 small randomized clinical trials.[99,100]

Hepatic arterial infusion chemotherapy also has been used in select centers for the treatment of patients with advanced and unresectable intrahepatic cholangiocarcinoma.[101–104] However, this approach has not yet been evaluated in prospective randomized clinical trials.

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 after radical surgery are 20% to 42% and 16% to 52%, respectively, for patients with hilar and distal cholangiocarcinomas.[105]

Surgical margin status and lymph node metastases are independent predictors of survival after resection.[72,106] Regional lymphadenectomy of the porta hepatis should be considered along with curative resections.[107,108] Because these surgical procedures are associated with postoperative morbidity, they should be performed 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.

The type of surgical procedure for resectable disease is based on the tumor's anatomic location on the biliary tract. Hilar resection of the involved biliary tract and en bloc liver resection is recommended for hilar tumors. Major bile duct excision with frozen section assessment of proximal and distal bile duct margins and pancreaticoduodenectomy are recommended for mid and distal tumors, respectively. Very rare cases of small mid bile duct tumors can be resected with an isolated bile duct resection. A pancreaticoduodenectomy and a hepatic resection would be required, in rare instances, for a bile duct tumor with an extensive biliary tract involvement. Combined hepatic and pancreatic resections to clear distant nodal disease are not recommended.

In patients with hilar cholangiocarcinoma, extended hepatic resection (to encompass the biliary confluence) with caudate lobectomy is strongly encouraged, because hilar tumors, by definition, abut or invade the central portion of the liver. The recommendation for extended liver resection is supported by retrospective analyses showing a survival benefit and decreased hepatic recurrence associated with extended hepatic resections.[109–113] Because this association was maintained when only patients undergoing an R0 resection were considered, it cannot be solely attributed to the increased likelihood of an R0 resection when extended liver resection was performed, although some reports suggest that extended hepatic resections result in a higher probability of R0 resection.[111,114] Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection, especially in patients with more advanced disease.[115,116]

Patient selection for surgery is facilitated by careful preoperative staging, surgical exploration, biopsy, and 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 most patients with unresectable hilar cholangiocarcinoma, albeit with a lower yield.[117,118] Connor et al[117] reported that the yield of laparoscopy alone was 24% in identifying patients with unresectable hilar tumors, which increased to 42% with an overall accuracy of 53%, with the addition of intraoperative ultrasound. In another report, Weber et al[118] reported a higher yield for T2/T3 tumors (36%) than T1 tumors (9%), suggesting that staging laparoscopy may be more useful for patients who are at higher risk for occult unresectable disease.

Although not routinely used in all patients undergoing resection, the consensus of the panel is that preoperative treatments, including biliary drainage (using an endoscopic [ERCP] or percutaneous approach [PTC])[119–122] and contralateral portal vein embolization,[123,124] should be considered for patients with hilar cholangiocarcinoma with very low future liver remnant volumes.

Among patients with resectable disease, those who have undergone an R0 resection and 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, limited clinical trial data are available to define a standard regimen, and enrollment in a clinical trial is encouraged. Patients with microscopic positive tumor margins (R1), gross residual local disease (R2), or positive regional lymph nodes after resection should be evaluated by a multidisciplinary team to review the available treatment options on a case-by-case basis. Although the optimal treatment strategy has not been established, treatment options include fluoropyrimidine chemoradiation followed by additional fluoropyrimidine or gemcitabine chemotherapy; or fluoropyrimidine-based or gemcitabine-based chemotherapy for patients with positive regional nodes. Data to support particular chemoradiation and chemotherapy regimens are limited (see "Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers," opposite column).

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.[125–128] Biopsy is recommended to confirm the diagnosis before the initiation of further treatment. Primary treatment options include (1) a 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 "Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers," page 1174).

Liver transplantation is the only other potentially curative option for selected patients with non-disseminated locally advanced hilar cholangiocarcinomas, with the 5-year survival rates ranging from 25% to 42%.[129–132] There is retrospective evidence suggesting that neoadjuvant chemoradiation followed by liver transplantation is highly effective for selected patients with hilar cholangiocarcinoma.[133–135] Results from 2 studies suggest that the combination of liver transplantation and neoadjuvant and/or adjuvant chemoradiation is associated with higher RFS than a potentially curative resection.[136,137] However, in one of these studies substantial differences were seen in the characteristics of patients in the 2 treatment groups.[136] The panel encourages the continuation of clinical research in this area. Liver transplantation should be considered only for highly selected patients with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. The panel encourages continuation of clinical research in this area.

Surveillance

No data 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. Reevaluation according to the initial workup should be considered in the event of disease progression.

Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers

Local recurrence after surgery is a primary limitation for cure in patients with biliary tract cancers, which provides an important justification for the use of adjuvant therapy. Nevertheless, the role of adjuvant chemotherapy or chemoradiation therapy in patients with resected biliary tract cancers is poorly defined.[138]

Because of the low incidence of biliary tract cancers, the efficacy and safety of adjuvant chemotherapy or chemoradiation therapy has been evaluated mostly in retrospective studies that have included only a small number of patients; these studies often combined patients with gallbladder and bile duct cancers, with a few exceptions. Despite the chal-

lenges associated with accruing large numbers of patients with biliary tract cancer for randomized phase III trials, it is widely recognized that efforts should be made to conduct studies in which the individual disease entities are evaluated separately.

Retrospective studies that have combined patients with gallbladder cancer and those with cholangiocarcinomas provide conflicting evidence regarding the role of adjuvant therapy.[4,139] A retrospective analysis of 177 patients with either resected gallbladder cancer or hilar cholangiocarcinoma concluded that based on the pattern of initial recurrence, adjuvant treatment may not have a significant effect in patients with gallbladder cancer, whereas it could be a reasonable approach for patients with hilar cholangiocarcinoma. The initial recurrence rate involving a distant site was significantly higher for patients with gallbladder cancer than for those with hilar cholangiocarcinoma (85% and 41%, respectively; $P<.001$).[4] In a more recent retrospective review of a prospective database of 157 patients with resected gallbladder cancer (n=63) and cholangiocarcinoma (n=94), the authors reported that adjuvant therapy did not significantly prolong survival for this group of patients but identified an early resection with 1-cm tumor-free margins as the best predictor of long-term survival.[139] Conversely, in a recent systematic review and meta-analysis of 6712 patients with biliary tract cancers, Horgan et al[140] reported an improvement in OS (although nonsignificant) with adjuvant therapy compared with surgery alone, with no difference between patients with gallbladder cancer and bile duct cancers. Chemotherapy or chemoradiation therapy was associated with statistically greater benefit than radiotherapy alone, with the greatest benefit observed in patients with lymph node–positive disease and macroscopic residual disease (R1 resection).

In the only phase III randomized trial that evaluated adjuvant chemotherapy in patients with resected pancreaticobiliary cancer, 508 patients (139 had cholangiocarcinoma and 140 had gallbladder cancer) were randomly assigned to adjuvant chemotherapy with fluorouracil and mitomycin C or to a control arm.[141] Results from the subgroup analyses showed a significantly better 5-year disease-free survival rate for patients with gallbladder cancer treated with chemotherapy (20.3% vs 11.6% in the control group; $P=.02$), although no significant differences between the treatment arms were observed for patients with biliary duct cancers, suggesting that patients with gallbladder cancer undergoing noncurative resection may derive survival benefit with adjuvant chemotherapy.

Among the retrospective studies that included only the patients with gallbladder cancer, 2 large analyses did not show a clear benefit for adjuvant chemotherapy alone,[13,142] although in one study the number of patients who received adjuvant chemotherapy was very limited (only 24 of 123 patients who underwent curative resection received adjuvant chemotherapy or chemoradiation or both),[13] and the other study, which included patients treated during 1988 to 1997, did not include chemotherapy with newer agents.[142] In contrast, more-recent retrospective studies have concluded that adjuvant chemoradiation after R0 resection might improve OS in selected patients with T2 or T3 tumors and lymph node–positive gallbladder cancer.[143–145] In a series of 47 patients with gallbladder cancer who underwent resection followed by adjuvant chemoradiation, the 5-year OS rate was significantly higher after R0 resection (52.8% vs 20.0%, and 0% for those with R1 and R2 resections, respectively; $P=.0038$).[145] Adjuvant chemoradiation after R0 resection was associated with a 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.[146–149] 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.[149] 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).[148,150,151] A nonrandomized, 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 re-

sulted in a significant survival benefit, especially in patients with R1 resection or negative lymph nodes, compared with 5-FU–based adjuvant concurrent chemoradiation alone.[148] 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, these findings were not observed for patients with R0 resection or positive lymph nodes and those with T1 or T2 tumors.

Most of the collective experience of chemoradiation in biliary tract cancers involves concurrent chemoradiation and fluorouracil. More recently, concurrent chemoradiation with capecitabine has also been used.[148,152] Concurrent chemoradiation with gemcitabine is not recommended because of the limited experience and toxicity associated with this treatment.[153] Because of the limited data and the heterogeneity of patient populations included in many of the published studies, in most cases the recommendations in these 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 these NCCN Guidelines are based on the extrapolation of data from studies of patients with advanced disease. Additionally, some of the recommendations are primarily based on practice patterns at NCCN Member Institutions and retrospective studies from single-center experiences.

Chemotherapy and Chemoradiation for Advanced Biliary Tract Cancers

The prognosis of patients with advanced biliary tract cancers is poor and the median survival for those undergoing supportive care alone is short.[154] 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.[155] In a recent single-center randomized study of 81 patients with unresectable gallbladder cancer, Sharma et al[156] reported that modified gemcitabine and oxaliplatin (GEMOX) improved PFS and OS compared with best supportive care or fluorouracil. 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 in the treatment of patients with advanced biliary tract cancers.[157,158] The results of a pooled analysis of 104 trials that included 2810 patients with advanced biliary tract cancers showed that response and tumor control rates were higher for the subgroup of patients receiving a combination of gemcitabine and platinum-based agents.[159] 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, those receiving gemcitabine were shown to have a lower risk of death.[160] 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.[161–164]

In a randomized phase II study of 51 patients, Kornek et al[161] established the efficacy and tolerance of mitomycin in combination with gemcitabine or capecitabine in previously untreated patients with advanced biliary tract cancers. Mitomycin and capecitabine was associated with superior complete response rate (31% vs 20%), median PFS (5.3 vs 4.2 months), and OS (9.25 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 and 5 months, respectively), but the PFS was similar in both treatment arms (3.3 months).[162] The randomized, controlled, phase III ABC-02 study, which enrolled 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer, showed that the combination of gemcitabine and cisplatin improved OS and PFS by 30% over gemcitabine alone.[163] Median OS was 11.7 versus 8.1 months, respectively (hazard ratio, 0.64; 95% CI, 0.52–0.80; *P*<.001), and median PFS was 8.0 versus 5.0 months, respectively (hazard ratio, 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, no

significant difference was seen in the rate of neutropenia-associated infections between the arms. Okusaka et al[164] also reported similar findings in a phase II randomized study of 84 patients with advanced biliary tract cancers. 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-based (fluorouracil or capecitabine) regimens with demonstrated activity in phase II trials include gemcitabine and cisplatin or oxaliplatin[165–173]; gemcitabine and fluoropyrimidine[174–179]; and fluoropyrimidine and oxaliplatin or cisplatin.[180–183] 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.[184–186] 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 vs 9 months, respectively) in patients with advanced biliary tract cancers, although the trial was underpowered to detect such a difference.[184] In a phase II trial, the combination of gemcitabine and irinotecan with panitumumab (a monoclonal anti–epidermal growth factor receptor antibody) showed encouraging efficacy with good tolerability in patients with advanced cholangiocarcinoma, with a 5-month PFS rate of 69%.[187] The median PFS and OS were 9.7 and 12.9 months, respectively.

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 because of the increased toxicity and decreased efficacy observed with this regimen when compared with results of studies of the gemcitabine and capecitabine regimen in the setting of advanced biliary tract cancer.[174]

Chemoradiation in the setting of advanced biliary tract cancers can provide control of symptoms caused by local tumor effects and may prolong OS. However, limited clinical trial data are available 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 most patients during this period (actuarial local control rates of 90% and 71% at 1 and 2 years, respectively).[188] Fluorouracil is the most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of biliary tract cancers,[189,190] although capecitabine has been substituted for fluorouracil in some studies.[152] The panel recommends that concurrent chemoradiation should be limited to either fluorouracil or capecitabine, and that this treatment should be restricted to patients without evidence of metastatic disease. Concurrent chemoradiation with gemcitabine is not recommended because of the limited experience and toxicity associated with this treatment.

Summary

Hepatobiliary cancers are associated with a poor prognosis, 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. 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.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
2. Donohue JH, Stewart AK, Menck HR. The National Cancer Data Base report on carcinoma of the gallbladder, 1989-1995. Cancer 1998;83:2618–2628.
3. Levy AD, Murakata LA, Rohrmann CA Jr. Gallbladder carcinoma: radiologic-pathologic correlation. Radiographics 2001;21:295–314; questionnaire, 549–255.

4. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer 2003;98:1689–1700.
5. Sheth S, Bedford A, Chopra S. Primary gallbladder cancer: recognition of risk factors and the role of prophylactic cholecystectomy. Am J Gastroenterol 2000;95:1402–1410.
6. Tazuma S, Kajiyama G. Carcinogenesis of malignant lesions of the gall bladder. The impact of chronic inflammation and gallstones. Langenbecks Arch Surg 2001;386:224–229.
7. Khan ZS, Livingston EH, Huerta S. Reassessing the need for prophylactic surgery in patients with porcelain gallbladder: case series and systematic review of the literature. Arch Surg 2011;146:1143–1147.
8. Schnelldorfer T. Porcelain gallbladder: a benign process or concern for malignancy? J Gastrointest Surg 2013;17:1161–1168.
9. Elnemr A, Ohta T, Kayahara M, et al. Anomalous pancreaticobiliary ductal junction without bile duct dilatation in gallbladder cancer. Hepatogastroenterology 2001;48:382–386.
10. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. J Gastrointest Surg 2007;11:671–681.
11. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.
12. Fong Y, Wagman L, Gonen M, et al. Evidence-based gallbladder cancer staging: changing cancer staging by analysis of data from the National Cancer Database. Ann Surg 2006;243:767–771; discussion 771–764.
13. Duffy A, Capanu M, Abou-Alfa GK, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008;98:485–489.
14. Ito H, Ito K, D'Angelica M, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. Ann Surg 2011;254:320–325.
15. 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.
16. Furlan A, Ferris JV, Hosseinzadeh K, Borhani AA. Gallbladder carcinoma update: multimodality imaging evaluation, staging, and treatment options. AJR Am J Roentgenol 2008;191:1440–1447.
17. Petrowsky H, Wildbrett P, Husarik DB, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma. J Hepatol 2006;45:43–50.
18. 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.
19. Lee SW, Kim HJ, Park JH, et al. Clinical usefulness of 18F-FDG PET-CT for patients with gallbladder cancer and cholangiocarcinoma. J Gastroenterol 2010;45:560–566.
20. Strom BL, Maislin G, West SL, et al. Serum CEA and CA 19-9: potential future diagnostic or screening tests for gallbladder cancer? Int J Cancer 1990;45:821–824.
21. Dixon E, Vollmer CM Jr, Sahajpal A, et al. An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. Ann Surg 2005;241:385–394.
22. 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.
23. Lee SE, Jang JY, Lim CS, et al. Systematic review on the surgical treatment for T1 gallbladder cancer. World J Gastroenterol 2011;17:174–180.
24. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: Defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol 2007;14:833–840.
25. Coburn NG, Cleary SP, Tan JC, Law CH. Surgery for gallbladder cancer: a population-based analysis. J Am Coll Surg 2008;207:371–382.
26. You DD, Lee HG, Paik KY, et al. What is an adequate extent of resection for T1 gallbladder cancers? Ann Surg 2008;247:835–838.
27. Jensen EH, Abraham A, Habermann EB, et al. A critical analysis of the surgical management of early-stage gallbladder cancer in the United States. J Gastrointest Surg 2009;13:722–727.
28. Downing SR, Cadogan KA, Ortega G, et al. Early-stage gallbladder cancer in the surveillance, epidemiology, and end results database: effect of extended surgical resection. Arch Surg 2011;146:734–738.
29. Shirai Y, Sakata J, Wakai T, et al. "Extended" radical cholecystectomy for gallbladder cancer: long-term outcomes, indications and limitations. World J Gastroenterol 2012;18:4736–4743.
30. D'Angelica M, Dalal KM, DeMatteo RP, et al. Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 2009;16:806–816.
31. Pawlik TM, Gleisner AL, Vigano L, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. J Gastrointest Surg 2007;11:1478–1486; discussion 1486–1477.
32. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. Ann Surg 2000;232:557–569.
33. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg 2007;245:893–901.
34. Agarwal AK, Kalayarasan R, Javed A, et al. Role of staging laparoscopy in primary gall bladder cancer—an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer. Ann Surg 2013;258:318–323.
35. 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.
36. 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.
37. Fuks D, Regimbeau JM, Pessaux P, et al. Is port-site resection necessary in the surgical management of gallbladder cancer? J Visc Surg 2013;150:277–284.
38. 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.
39. Wang SJ, Fuller CD, Kim JS, et al. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. J Clin Oncol 2008;26:2112–2117.

40. 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;29:4627–4632.
41. Lim JH. Cholangiocarcinoma: morphologic classification according to growth pattern and imaging findings. AJR Am J Roentgenol 2003;181:819–827.
42. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. Ann Surg 2007;245:755–762.
43. Chapman RW. Risk factors for biliary tract carcinogenesis. Ann Oncol 1999;10(Suppl 4):308–311.
44. Tyson GL, El-Serag HB. Risk factors for cholangiocarcinoma. Hepatology 2011;54:173–184.
45. Donato F, Gelatti U, Tagger A, et al. Intrahepatic cholangiocarcinoma and hepatitis C and B virus infection, alcohol intake, and hepatolithiasis: a case-control study in Italy. Cancer Causes Control 2001;12:959–964.
46. Yamamoto S, Kubo S, Hai S, et al. Hepatitis C virus infection as a likely etiology of intrahepatic cholangiocarcinoma. Cancer Sci 2004;95:592–595.
47. Shaib YH, El-Serag HB, Davila JA, et al. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case-control study. Gastroenterology 2005;128:620–626.
48. Welzel TM, Mellemkjaer L, Gloria G, et al. Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. Int J Cancer 2007;120:638–641.
49. Chang KY, Chang JY, Yen Y. Increasing incidence of intrahepatic cholangiocarcinoma and its relationship to chronic viral hepatitis. J Natl Compr Canc Netw 2009;7:423–427.
50. Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84–96.
51. Nathan H, Aloia TA, Vauthey JN, et al. A proposed staging system for intrahepatic cholangiocarcinoma. Ann Surg Oncol 2009;16:14–22.
52. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. J Clin Oncol 2011;29:3140–3145.
53. Farges O, Fuks D, Le Treut YP, et al. AJCC 7th edition of TNM staging accurately discriminates outcomes of patients with resectable intrahepatic cholangiocarcinoma. Cancer 2011;117:2170–2177.
54. de Jong MC, Hong SM, Augustine MM, et al. Hilar cholangiocarcinoma: tumor depth as a predictor of outcome. Arch Surg 2011;146:697–703.
55. Hong SM, Pawlik TM, Cho H, et al. Depth of tumor invasion better predicts prognosis than the current American Joint Committee on Cancer T classification for distal bile duct carcinoma. Surgery 2009;146:250–257.
56. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg 1992;215:31–38.
57. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–517; discussion 517–509.
58. 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.
59. Miller G, Schwartz LH, D'Angelica M. The use of imaging in the diagnosis and staging of hepatobiliary malignancies. Surg Oncol Clin N Am 2007;16:343–368.
60. Aljiffry M, Walsh MJ, Molinari M. Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. World J Gastroenterol 2009;15:4240–4262.
61. Sainani NI, Catalano OA, Holalkere NS, et al. Cholangiocarcinoma: current and novel imaging techniques. Radiographics 2008;28:1263–1287.
62. Halefoglu AM. Magnetic resonance cholangiopancreatography: a useful tool in the evaluation of pancreatic and biliary disorders. World J Gastroenterol 2007;13:2529–2534.
63. Hekimoglu K, Ustundag Y, Dusak A, et al. MRCP vs. ERCP in the evaluation of biliary pathologies: review of current literature. J Dig Dis 2008;9:162–169.
64. Vogl TJ, Schwarz WO, Heller M, et al. Staging of Klatskin tumours (hilar cholangiocarcinomas): comparison of MR cholangiography, MR imaging, and endoscopic retrograde cholangiography. Eur Radiol 2006;16:2317–2325.
65. Hyodo T, Kumano S, Kushihata F, et al. CT and MR cholangiography: advantages and pitfalls in perioperative evaluation of biliary tree. Br J Radiol 2012;85:887–896.
66. Kim JY, Kim MH, Lee TY, et al. Clinical role of 18F-FDG PET-CT in suspected and potentially operable cholangiocarcinoma: a prospective study compared with conventional imaging. Am J Gastroenterol 2008;103:1145–1151.
67. Ruys AT, Bennink RJ, van Westreenen HL, et al. FDG-positron emission tomography/computed tomography and standardized uptake value in the primary diagnosis and staging of hilar cholangiocarcinoma. HPB (Oxford) 2011;13:256–262.
68. Nakagohri T, Asano T, Kinoshita H, et al. Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma. World J Surg 2003;27:289–293.
69. Konstadoulakis MM, Roayaie S, Gomatos IP, et al. Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome. Surgery 2008;143:366–374.
70. Paik KY, Jung JC, Heo JS, et al. What prognostic factors are important for resected intrahepatic cholangiocarcinoma? J Gastroenterol Hepatol 2008;23:766–770.
71. Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. J Am Coll Surg 2009;208:218–228.
72. Murakami Y, Uemura K, Sudo T, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. Ann Surg Oncol 2011;18:651–658.
73. Ribero D, Pinna AD, Guglielmi A, et al. Surgical Approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. Arch Surg 2012;147:1107–1113.
74. Tamandl D, Herberger B, Gruenberger B, et al. Influence of hepatic resection margin on recurrence and survival in intrahepatic cholangiocarcinoma. Ann Surg Oncol 2008;15:2787–2794.
75. Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group. Ann Surg 2011;254:824–829; discussion 830.

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

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

78. Joseph S, Connor S, Garden OJ. Staging laparoscopy for cholangiocarcinoma. HPB (Oxford) 2008;10:116–119.

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

80. Choi SB, Kim KS, Choi JY, et al. The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 2009;16:3048–3056.

81. Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, et al. Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. HPB (Oxford) 2011;13:612–620.

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

83. Fisher SB, Patel SH, Kooby DA, et al. Lymphovascular and perineural invasion as selection criteria for adjuvant therapy in intrahepatic cholangiocarcinoma: a multi-institution analysis. HPB (Oxford) 2012;14:514–522.

84. Hyder O, Hatzaras I, Sotiropoulos GC, et al. Recurrence after operative management of intrahepatic cholangiocarcinoma. Surgery 2013;153:811–818.

85. Ribero D, Rosso S, Pinna AD, et al. Postoperative nomogram for predicting survival after resection for intrahepatic cholangiocarcinoma [abstract]. J Clin Oncol 2013;31(Suppl):Abstract 4129.

86. Carrafiello G, Lagana D, Cotta E, et al. Radiofrequency ablation of intrahepatic cholangiocarcinoma: preliminary experience. Cardiovasc Intervent Radiol 2010;33:835–839.

87. Kim JH, Won HJ, Shin YM, et al. Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma. AJR Am J Roentgenol 2011;196:W205–209.

88. Kiefer MV, Albert M, McNally M, et al. Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol: a 2-center study. Cancer 2011;117:1498–1505.

89. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma: conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. Eur J Gastroenterol Hepatol 2012;24:437–443.

90. Hyder O, Marsh JW, Salem R, et al. Intra-arterial therapy for advanced intrahepatic cholangiocarcinoma: a multi-institutional analysis. Ann Surg Oncol 2013;20:3779–3786.

91. Poggi G, Quaretti P, Minoia C, et al. Transhepatic arterial chemoembolization with oxaliplatin-eluting microspheres (OEM-TACE) for unresectable hepatic tumors. Anticancer Res 2008;28:3835–3842.

92. Schiffman SC, Metzger T, Dubel G, et al. Precision hepatic arterial irinotecan therapy in the treatment of unresectable intrahepatic cholangiocellular carcinoma: optimal tolerance and prolonged overall survival. Ann Surg Oncol 2011;18:431–438.

93. Ibrahim SM, Mulcahy MF, Lewandowski RJ, et al. Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. Cancer 2008;113:2119–2128.

94. Saxena A, Bester L, Chua TC, et al. Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. Ann Surg Oncol 2010;17:484–491.

95. Wijlemans JW, Van Erpecum KJ, Lam MG, et al. Trans-arterial (90)yttrium radioembolization for patients with unresectable tumors originating from the biliary tree. Ann Hepatol 2011;10:349–354.

96. Hoffmann RT, Paprottka PM, Schon A, et al. Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. Cardiovasc Intervent Radiol 2012;35:105–116.

97. Rafi S, Piduru SM, El-Rayes B, et al. Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. Cardiovasc Intervent Radiol 2013;36:440–448.

98. Mouli S, Memon K, Baker T, et al. Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: safety, response, and survival analysis. J Vasc Interv Radiol 2013;24:1227–1234.

99. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology 2003;125:1355–1363.

100. Zoepf T, Jakobs R, Arnold JC, et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol 2005;100:2426–2430.

101. Mambrini A, Guglielmi A, Pacetti P, et al. Capecitabine plus hepatic intra-arterial epirubicin and cisplatin in unresectable biliary cancer: a phase II study. Anticancer Res 2007;27:3009–3013.

102. Shitara K, Ikami I, Munakata M, et al. Hepatic arterial infusion of mitomycin C with degradable starch microspheres for unresectable intrahepatic cholangiocarcinoma. Clin Oncol (R Coll Radiol) 2008;20:241–246.

103. Inaba Y, Arai Y, Yamaura H, et al. Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301). Am J Clin Oncol 2011;34:58–62.

104. Kemeny NE, Schwartz L, Gonen M, et al. Treating primary liver cancer with hepatic arterial infusion of floxuridine and dexamethasone: does the addition of systemic bevacizumab improve results? Oncology 2011;80:153–159.

105. Akamatsu N, Sugawara Y, Hashimoto D. Surgical strategy for bile duct cancer: advances and current limitations. World J Clin Oncol 2011;2:94–107.

106. Qiao QL, Zhang TP, Guo JC, et al. Prognostic factors after pancreatoduodenectomy for distal bile duct cancer. Am Surg 2011;77:1445–1448.

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

108. Ito K, Ito H, Allen PJ, et al. Adequate lymph node assessment for extrahepatic bile duct adenocarcinoma. Ann Surg 2010;251:675–681.

109. Nishio H, Nagino M, Nimura Y. Surgical management of hilar cholangiocarcinoma: the Nagoya experience. HPB (Oxford) 2005;7:259–262.

110. Ito F, Agni R, Rettammel RJ, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence. Ann Surg 2008;248:273–279.

111. van Gulik TM, Kloek JJ, Ruys AT, et al. Multidisciplinary management of hilar cholangiocarcinoma (Klatskin tumor): extended resection is associated with improved survival. Eur J Surg Oncol 2011;37:65–71.

112. Cheng QB, Yi B, Wang JH, et al. Resection with total caudate lobectomy confers survival benefit in hilar cholangiocarcinoma of Bismuth type III and IV. Eur J Surg Oncol 2012;38:1197–1203.

113. Cho MS, Kim SH, Park SW, et al. Surgical outcomes and predicting factors of curative resection in patients with hilar cholangiocarcinoma: 10-year single-institution experience. J Gastrointest Surg 2012;16:1672–1679.

114. Lee SG, Song GW, Hwang S, et al. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. J Hepatobiliary Pancreat Sci 2010;17:476–489.

115. de Jong MC, Marques H, Clary BM, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases. Cancer 2012;118:4737–4747.

116. Wu XS, Dong P, Gu J, et al. Combined portal vein resection for hilar cholangiocarcinoma: a meta-analysis of comparative studies. J Gastrointest Surg 2013;17:1107–1115.

117. Connor S, Barron E, Wigmore SJ, et al. The utility of laparoscopic assessment in the preoperative staging of suspected hilar cholangiocarcinoma. J Gastrointest Surg 2005;9:476–480.

118. 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.

119. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). HPB (Oxford) 2008;10:130–133.

120. Kennedy TJ, Yopp A, Qin Y, et al. Role of preoperative biliary drainage of liver remnant prior to extended liver resection for hilar cholangiocarcinoma. HPB (Oxford) 2009;11:445–451.

121. Liu F, Li Y, Wei Y, Li B. Preoperative biliary drainage before resection for hilar cholangiocarcinoma: whether or not? A systematic review. Dig Dis Sci 2011;56:663–672.

122. Farges O, Regimbeau JM, Fuks D, et al. Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma. Br J Surg 2013;100:274–283.

123. Abulkhir A, Limongelli P, Healey AJ, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008;247:49–57.

124. Shindoh J, Vauthey JN, Zimmitti G, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg 2013;217:126–133.

125. 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.

126. 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.

127. Abraham NS, Barkun JS, Barkun AN. Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life. Gastrointest Endosc 2002;56:835–841.

128. Paik WH, Park YS, Hwang JH, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest Endosc 2009;69:55–62.

129. Robles R, Figueras J, Turrion VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. Ann Surg 2004;239:265–271.

130. Becker NS, Rodriguez JA, Barshes NR, et al. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. J Gastrointest Surg 2008;12:117–122.

131. Kaiser GM, Sotiropoulos GC, Jauch KW, et al. Liver transplantation for hilar cholangiocarcinoma: a German survey. Transplant Proc 2008;40:3191–3193.

132. Friman S, Foss A, Isoniemi H, et al. Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results. Scand J Gastroenterol 2011;46:370–375.

133. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88–98.

134. Panjala C, Nguyen JH, Al-Hajjaj AN, et al. Impact of neoadjuvant chemoradiation on the tumor burden before liver transplantation for unresectable cholangiocarcinoma. Liver Transpl 2012;18:594–601.

135. Duignan S, Maguire D, Ravichand CS, et al. Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience. HPB (Oxford) 2014;16:91–98.

136. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005;242:451–458.

137. Hong JC, Jones CM, Duffy JP, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. Arch Surg 2011;146:683–689.

138. Cereda S, Belli C, Reni M. Adjuvant treatment in biliary tract cancer: to treat or not to treat? World J Gastroenterol 2012;18:2591–2596.

139. Glazer ES, Liu P, Abdalla EK, et al. Neither neoadjuvant nor adjuvant therapy increases survival after biliary tract cancer resection with wide negative margins. J Gastrointest Surg 2012;16:1666–1671.

140. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012;30:1934–1940.

141. 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.

142. Kayahara M, Nagakawa T. Recent trends of gallbladder cancer in Japan: an analysis of 4,770 patients. Cancer 2007;110:572–580.

143. Gold DG, Miller RC, Haddock MG, et al. Adjuvant therapy for gallbladder carcinoma: the Mayo Clinic Experience. Int J Radiat Oncol Biol Phys 2009;75:150–155.

144. Cho SY, Kim SH, Park SJ, et al. Adjuvant chemoradiation therapy in gallbladder cancer. J Surg Oncol 2010;102:87–93.

145. Kim K, Chie EK, Jang JY, et al. Postoperative chemoradiotherapy for gallbladder cancer. Strahlenther Onkol 2012;188:388–392.

146. Hughes MA, Frassica DA, Yeo CJ, et al. Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. Int J Radiat Oncol Biol Phys 2007;68:178–182.

147. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2009;73:148–153.

148. Lim KH, Oh DY, Chie EK, et al. Adjuvant concurrent chemoradiation therapy (CCRT) alone versus CCRT followed by adjuvant chemotherapy: which is better in patients with radically resected extrahepatic biliary tract cancer?: a non-randomized, single center study. BMC Cancer 2009;9:345.

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

150. Borghero Y, Crane CH, Szklaruk J, et al. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. Ann Surg Oncol 2008;15:3147–3156.

151. Park JH, Choi EK, Ahn SD, et al. Postoperative chemoradiotherapy for extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys 2011;79:696–704.

152. Das P, Wolff RA, Abbruzzese JL, et al. Concurrent capecitabine and upper abdominal radiation therapy is well tolerated. Radiat Oncol 2006;1:41–41.

153. Lin LL, Picus J, Drebin JA, et al. A phase II study of alternating cycles of split course radiation therapy and gemcitabine chemotherapy for inoperable pancreatic or biliary tract carcinoma. Am J Clin Oncol 2005;28:234–241.

154. Park J, Kim MH, Kim KP, et al. Natural history and prognostic factors of advanced cholangiocarcinoma without surgery, chemotherapy, or radiotherapy: a large-scale observational study. Gut Liver 2009;3:298–305.

155. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol 1996;7:593–600.

156. Sharma A, Dwary AD, Mohanti BK, et al. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. J Clin Oncol 2010;28:4581–4586.

157. Hezel AF, Zhu AX. Systemic therapy for biliary tract cancers. Oncologist 2008;13:415–423.

158. Geynisman DM, Catenacci DV. Toward personalized treatment of advanced biliary tract cancers. Discov Med 2012;14:41–57.

159. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 2007;96:896–902.

160. Yonemoto N, Furuse J, Okusaka T, et al. A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. Jpn J Clin Oncol 2007;37:843–851.

161. Kornek GV, Schuell B, Laengle F, et al. Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. Ann Oncol 2004;15:478–483.

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

163. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281.

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

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

166. Thongprasert S, Napapan S, Charoentum C, Moonprakan S. Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. Ann Oncol 2005;16:279–281.

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

168. Lee J, Kim TY, Lee MA, et al. Phase II trial of gemcitabine combined with cisplatin in patients with inoperable biliary tract carcinomas. Cancer Chemother Pharmacol 2008;61:47–52.

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

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

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

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

173. Jang JS, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. Cancer Chemother Pharmacol 2010;65:641–647.

174. Alberts SR, Al-Khatib H, Mahoney MR, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. Cancer 2005;103:111–118.

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

176. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332–2338.

177. Riechelmann RP, Townsley CA, Chin SN, et al. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 2007;110:1307–1312.

178. Koeberle D, Saletti P, Borner M, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2008;26:3702–3708.

179. Iqbal S, Rankin C, Lenz HJ, et al. A phase II trial of gemcitabine and capecitabine in patients with unresectable or metastatic gallbladder cancer or cholangiocarcinoma: Southwest

Oncology Group study S0202. Cancer Chemother Pharmacol 2011;68:1595–1602.

180. Nehls O, Klump B, Arkenau HT, et al. Oxaliplatin, fluorouracil and leucovorin for advanced biliary system adenocarcinomas: a prospective phase II trial. Br J Cancer 2002;87:702–704.

181. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. Br J Cancer 2008;98:309–315.

182. 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.

183. Kobayashi K, Tsuji A, Morita S, et al. A phase II study of LFP therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and low-dose consecutive (Cisplatin) CDDP) in advanced biliary tract carcinoma. BMC Cancer 2006;6:121–121.

184. Rao S, Cunningham D, Hawkins RE, et al. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. Br J Cancer 2005;92:1650–1654.

185. Yamashita Y, Taketomi A, Fukuzawa K, et al. Gemcitabine combined with 5-fluorouracil and cisplatin (GFP) in patients with advanced biliary tree cancers: a pilot study. Anticancer Res 2006;26:771–775.

186. Wagner AD, Buechner-Steudel P, Moehler M, et al. Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials. Br J Cancer 2009;101:1846–1852.

187. Sohal DP, Mykulowycz K, Uehara T, et al. A phase II trial of gemcitabine, irinotecan and panitumumab in advanced cholangiocarcinoma. Ann Oncol 2013;24:3061–3065.

188. Ghafoori AP, Nelson JW, Willett CG, et al. Radiotherapy in the treatment of patients with unresectable extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2011;81:654–659.

189. Macdonald OK, Crane CH. Palliative and postoperative radiotherapy in biliary tract cancer. Surg Oncol Clin N Am 2002;11:941–954.

190. Czito BG, Anscher MS, Willett CG. Radiation therapy in the treatment of cholangiocarcinoma. Oncology (Williston Park) 2006;20:873–884.

Individual Disclosure for the NCCN Hepatobiliary Cancers Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Thomas A. Abrams, MD	None	None	None	None	9/2/13
Chandrakanth Are, MD	None	None	None	None	9/9/13
Al B. Benson III, MD	Amgen Inc.; Bayer HealthCare; Genentech, Inc.; Novartis Pharmaceuticals Corporation; Advanced Accelerator Applications SA; Alchemia; Astellas; Gilead; and Infinity	Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; Genomic Health, Inc.; National Cancer Institute; Cleveland Biolabs; Gilead; McKinsey; Spectrum Pharmaceuticals; and Precision Therapeutics, Inc.	None	None	9/5/13
P. Mark Bloomston, MD	None	Covidien AG	None	None	7/24/13
Daniel T. Chang, MD	None	None	None	None	7/25/14
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David Linehan, MD	Novartis Pharmaceuticals Corporation	None	None	None	3/5/13
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