National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Biliary Tract Cancers

Version 2.2023 — May 10, 2023

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2023
# Biliary Tract Cancers

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NCCN Guidelines Panel Disclosures

| | |
|---|---|
| ¤ Gastroenterology | ≠ Pathology |
| ‡ Hematology/Hematology oncology | § Radiotherapy/Radiation oncology |
| Þ Internal medicine | ¶ Surgery/Surgical oncology |
| ф Interventional radiology | ξ Transplantation |
| † Medical oncology | * Discussion section writing committee |
| ¥ Patient advocacy | |

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2023
# Biliary Tract Cancers

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Discussion



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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate. See NCCN Categories of Preference.

Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

**Updates in Version 2.2023 of the NCCN Guidelines for Biliary Tract Cancers from Version 1.2023 include:**

BIL-B (1 of 8)
- Recommendations
  - Bullet 1, 1st sentenced revised: Molecular profiling in BTCs: Comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC ~~appropriate~~ *who are candidates* for systemic therapy.

BIL-B (6 of 8)
- Other Biomarkers
  - Bullet 1, 1st sentence revised: In addition to the genomic aberrations reviewed above, NGS testing may uncover other potentially actionable molecular alterations that could determine eligibility for ongoing clinical trials in patients with advanced ~~hepatobiliary cancers~~ *BTCs*.

BIL-B (7 of 8)
- Reference 17 added: Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: Updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022;33:929-938. (Also for BIL-C 4 of 5)

BIL-C (2 of 5)
- Footnote g revised: Treatment selection depends on clinical factors including previous treatment regimen/agent, *somatic* molecular testing results, and extent of liver dysfunction. (Also for BIL-C 3 of 5)

BIL-C (4 of 5)
- Reference 9 revised: ~~Yoo C, Kim KP, Jeong JH, et al. Liposomal irinotecan plus fluorouracil and leucovorin versus fluorouracil and leucovorin for metastatic biliary tract cancer after progression on gemcitabine plus cisplatin (NIFTY): A multicentre, open-label, randomised, phase 2b study. Lancet Oncol 2021;22:1560–1572.~~ *Hyung J, Kim I, Kim KP, et al. Treatment with liposomal irinotecan plus fluorouracil and leucovorin for patients with previously treated metastatic biliary tract cancer: The phase 2b NIFTY randomized clinical trial. JAMA Oncol 2023:e230016.*

MS-1
- The discussion was updated to reflect the changes in the algorithm.

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**Updates in Version 1.2023 of the NCCN Guidelines for Biliary Tract Cancers from Version 5.2022 include:**

The NCCN Guidelines for Hepatobiliary Cancers have been reorganized to separate Guidelines for Biliary Tract Cancers and Hepatocellular Carcinoma.

Gallbladder Cancer

GALL-1
- Top pathway, column 3, Unresectable, Biopsy, if not previously performed
  - Bullet revised: ~~Additional~~ Molecular testing
  - Bullet removed: Microsatellite instability (MSI)/mismatch repair (MMR) testing
  - Bullet removed: Tumor mutational burden (TMB) testing
- After Unresectable, column 4, "See Postoperative Workup (above)" added before Primary Treatment options
- Footnote revised: ~~Testing may include NTRK gene fusion testing~~ Principles of Molecular Testing (BIL-B). (Also for GALL-2 through GALL-5)
- Footnote removed: For locoregionally advanced disease, consider neoadjuvant chemotherapy to rule out rapid progression and avoid futile surgery. There are limited clinical trial data to define a standard regimen or definitive benefit. See Principles of Systemic Therapy (BIL-C).

GALL-2
- Unresectable pathway
  - Bullet revised: ~~Additional~~ Molecular testing
  - Bullet removed: MSI/MMR testing
  - Bullet removed: TMB testing

Continued

**Updates in Version 1.2023 of the NCCN Guidelines for Biliary Tract Cancers from Version 5.2022 include:**

GALL-3
- Postoperative Workup
  - Middle pathway
    - ◊ Bullet removed: MSI/MMR testing
- Unresectable pathway
  - Bullet revised: ~~Additional~~ Molecular testing
  - Bullet removed: MSI/MMR testing
  - Bullet removed: TMB testing

GALL-4
- Unresectable, Biopsy
  - Bullet revised: ~~Additional~~ Molecular testing
  - Bullet removed: MSI/MMR testing
  - Bullet removed: TMB testing

GALL-5
- Jaundice
  - Unresectable pathway
    - ◊ Bullet revised: ~~Additional~~ Molecular testing (Also for Metastatic disease pathway)
    - ◊ Bullet removed: MSI/MMR testing (Also for Metastatic disease pathway)
    - ◊ Bullet removed: TMB testing (Also for Metastatic disease pathway)

GALL-6
- Header revised: *Post-Surgical* Treatment (Also for INTRA-2 and EXTRA-2)
  - Top pathway, Options
    - ◊ Fluoropyrimidine-based chemoradiation changed from a category 2A to category 2B recommendation.

GALL-A (1 of 2)
- Principles of Surgery and Pathology
  - Incidental Finding *of Suspicious Mass During* ~~at~~ Surgery

Intrahepatic Cholangiocarcinoma

INTRA-1
- Resectable
  - Last column revised: *Adjuvant Treatment* ~~Additional Therapy~~ and Surveillance
- Unresectable
  - Biopsy, if not previously performed.
    - ◊ Bullet revised: ~~Additional~~ Molecular testing (Also for Metastatic disease pathway)
    - ◊ Bullet removed: MSI/MMR testing (Also for Metastatic disease pathway)
    - ◊ Bullet removed: TMB testing (Also for Metastatic disease pathway)
- Primary Treatment
  - Unresectable, Biopsy, if not previously performed pathway
    - ◊ Bullet 3 revised: ~~EBRT~~ *RT* with concurrent fluoropyrimidine
    - ◊ Bullet 4, sub-bullet 1 revised: ~~EBRT~~ *RT*
  - Metastatic disease pathway, bullet 3, sub-bullet 1 revised: ~~EBRT~~ *RT*
- Footnote h revised: ~~Testing may include NTRK gene fusion testing~~ Principles of Molecular Testing (BIL-B).
- Footnote removed: See NCCN Guidelines for Hepatocellular Carcinoma (Principles of Locoregional Therapy). See Principles of Locoregional Therapy (HCC-E).

Continued

**Updates in Version 1.2023 of the NCCN Guidelines for Biliary Tract Cancers from Version 5.2022 include:**

INTRA-A
- Principles of Surgery
  - General Principles
    - Last bullet added: Minimally invasive approaches in experienced hands have been proven to be safe and effective.

Extrahepatic Cholangiocarcinoma
EXTRA-1
- Column 4, Unresectable pathway
  - Bullet 2, sub-bullet 1 revised: ~~Additional~~ Molecular testing (Also for Metastatic disease pathway)
  - Bullet removed: MSI/MMR testing (Also for Metastatic disease pathway)
  - Bullet removed: TMB testing (Also for Metastatic disease pathway)
- Column 4, Unresectable pathway:
  - Bullet 3 revised: ~~EBRT~~ *RT* with concurrent fluoropyrimidine
  - Bullet 4, revised: Palliative ~~EBRT~~ *RT*

Biliary Tract Cancers
BIL-A
- Intrahepatic and Extrahepatic Cholangiocarcinoma
  - Bullet 4 revised: ~~Imaging for staging ideally should be performed prior to biopsy or biliary drainage.~~ *When biliary duct involvement is suspected, it is very important to obtain high-quality biliary protocol imaging (preferably CT) to evaluate the extent of tumor prior to stenting. Reactive changes from stenting could potentially compromise the ability to delineate the complete extent of biliary tract involvement.*

BIL-B
- New section added: Principles of Molecular Testing

BIL-C (1 of 5)
- Principles of Systemic Therapy
  - Neoadjuvant Therapy, Other Recommended Regimens
    - Bullet 1 revised: ~~5-fluorouracil + oxaliplatin~~ *FOLFOX* (Also for Adjuvant Therapy and on BIL-C 2 of 5)
    - Bullet 5 added: Durvalumab + gemcitabine + cisplatin
    - Bullets removed:
      - Gemcitabine + oxaliplatin (category 2B)
      - Single agents:
        - 5-fluorouracil
        - Capecitabine
        - Gemcitabine
  - Footnote a revised: "...There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. *The listed regimens are extrapolated from the metastatic setting."*

BIL-C (2 of 5)
- Primary Treatment for Unresectable and Metastatic Disease
  - Gemcitabine + cisplatin moved from preferred regimens to other recommended regimens.
  - Other recommended regimens, recommendation removed: 5-fluorouracil + cisplatin (category 2B)
  - Other recommended regimens, recommendation removed: Capecitabine + cisplatin (category 2B)
  - Useful in Certain Circumstances (Also for Subsequent-Line Therapy For Biliary Tract Cancers if Disease Progression)
    - Targeted therapy on this page added and all recommendations for targeted therapy and associated footnotes were moved to BIL-C (3 of 5)
  - Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression
    - Other Recommended Regimens
      - Bullet removed: Durvalumab + gemcitabine + cisplatin (category 2B).
      - Durvalumab + gemcitabine + cisplatin changed from a category 2B to a category 1 recommendation.

Continued

**Updates in Version 1.2023 of the NCCN Guidelines for Biliary Tract Cancers from Version 5.2022 include:**

BIL-C (2 of 5) (continued)
- Footnote f revised: For patients who have not been previously treated with a checkpoint inhibitor *when used as subsequent-line therapy* because there is a lack of data for ~~subsequent~~ use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor. (Also for BIL-C 3 of 5)
- Footnote g revised: Treatment selection depends on clinical factors including previous treatment regimen/agent*, molecular testing results,* and extent of liver dysfunction. (Also for BIL-C 3 of 5)

BIL-C (3 of 5)
- Primary Treatment for Unresectable and Metastatic Disease
  - Nivolumab + ipilimumab was added as a category 2B recommendation for TMB-H tumors.
  - Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression
    - ◊ Nivolumab + ipilimumab was added as a category 2A recommendation for TMB-H tumors.
    - ◊ For CCA with IDH1 mutations
      - – Ivosidenib changed from a category 2A to a category 1 recommendation.
    - ◊ For CCA with FGFR2 fusions or rearrangements
      - – Infigratinib was removed.
  - Footnote j added: For patients with disease refractory to standard therapies or who have no standard treatment options available.

BIL-C (4 of 5) and (5 of 5)
- References
  - Reference 17 added: Schenker M, Burotto M, Richardet M, et al. CheckMate 848: A randomized, open-label, phase 2 study of nivolumab in combination with ipilimumab or nivolumab monotherapy in patients with advanced or metastatic solid tumors of high tumor mutational burden [abstract]. Cancer Res 2022;82:Abstract CT022.
  - Reference 18 revised: ~~Subbiah V, Hu MI, Gainor JF, et al. Clinical activity of the RET inhibitor pralsetinib (BLU-667) in patients with *RET* fusion-positive solid tumors [abstract]. J Clin Oncol 2021;39:Abstract 467.~~ *Subbiah V, Cassier PA, Siena S, et al. Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. Nat Med 2022;28:1640-1645.*
  - Reference 25 revised: ~~Goyal L, Meric-Bernstam F, Hollebeque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring *FGFR2* fusions/rearrangements. J Clin Oncol 2022;40:Abstract 4009.~~ *Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N Engl J Med 2023;388:228-239.*
  - Reference removed: Demetri GD, Paz-Ares LG, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) tumors: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. ESMO Congress 2018.
  - Reference removed: Javle M, Roychowdhury S, Kelley RK, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study. Lancet Gastroenterol Hepatol 2021;6:803-815.

BIL-D
- General Principles
  - All instances of "EBRT" have been replaced with "RT".

ABBR-1
- New section added: Abbreviations

# NCCN Guidelines Version 2.2023
# Gallbladder Cancer

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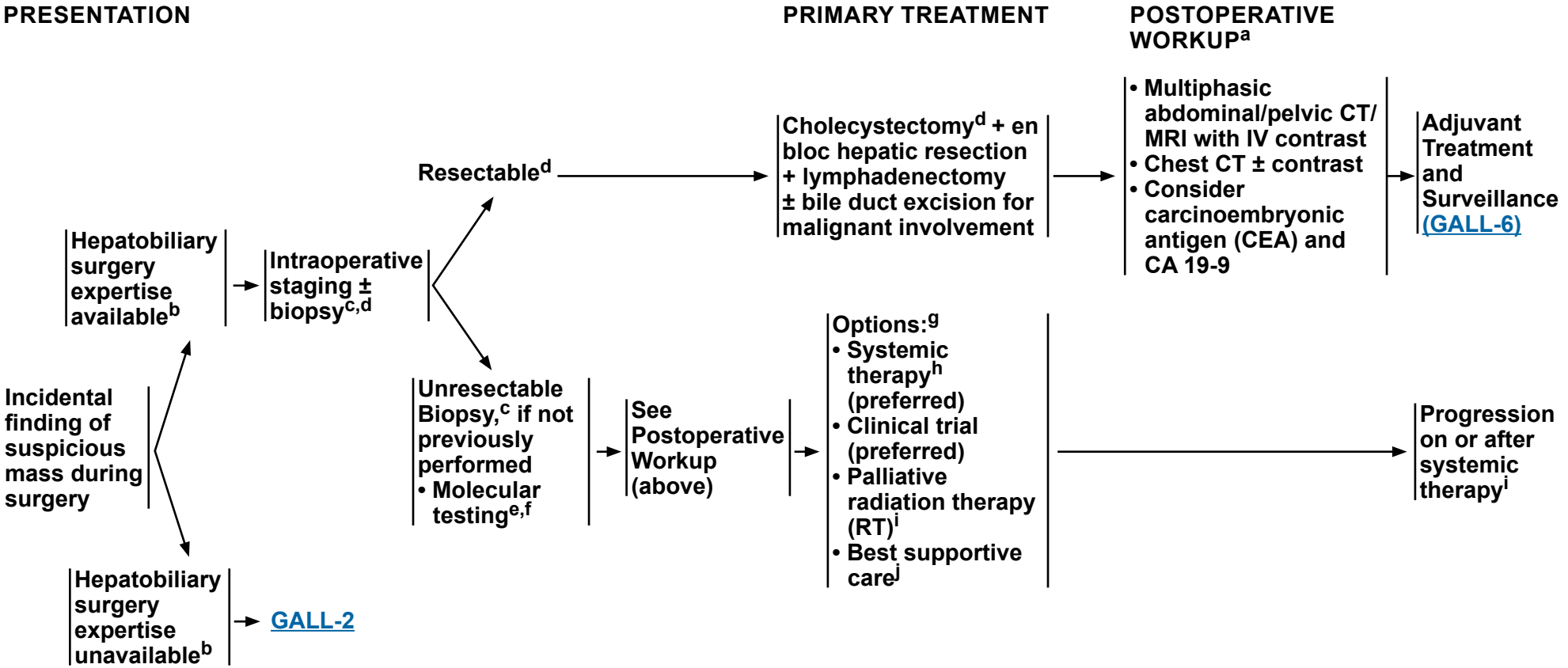


[a] Principles of Imaging (BIL-A).
[b] If expertise unavailable or resectability unclear, visually inspect the abdomen, document all findings, and refer to surgeon with hepatobiliary expertise and/or proceed with staging.
[c] The optimal diagnostic method is core needle biopsy.
[d] Principles of Surgery and Pathology (GALL-A).
[e] For patients with mismatch repair deficent (dMMR)/microsatellite instability-high (MSI-H) tumors or a family history suggestive of BRCA1/2 mutations, consider germline testing and/or referral to a genetic counselor.
[f] Principles of Molecular Testing (BIL-B).
[g] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[h] Principles of Systemic Therapy (BIL-C).
[i] Principles of Radiation Therapy (BIL-D).
[j] See NCCN Guidelines for Palliative Care.

**Other Clinical Presentations**
GALL-3, GALL-4, and GALL-5

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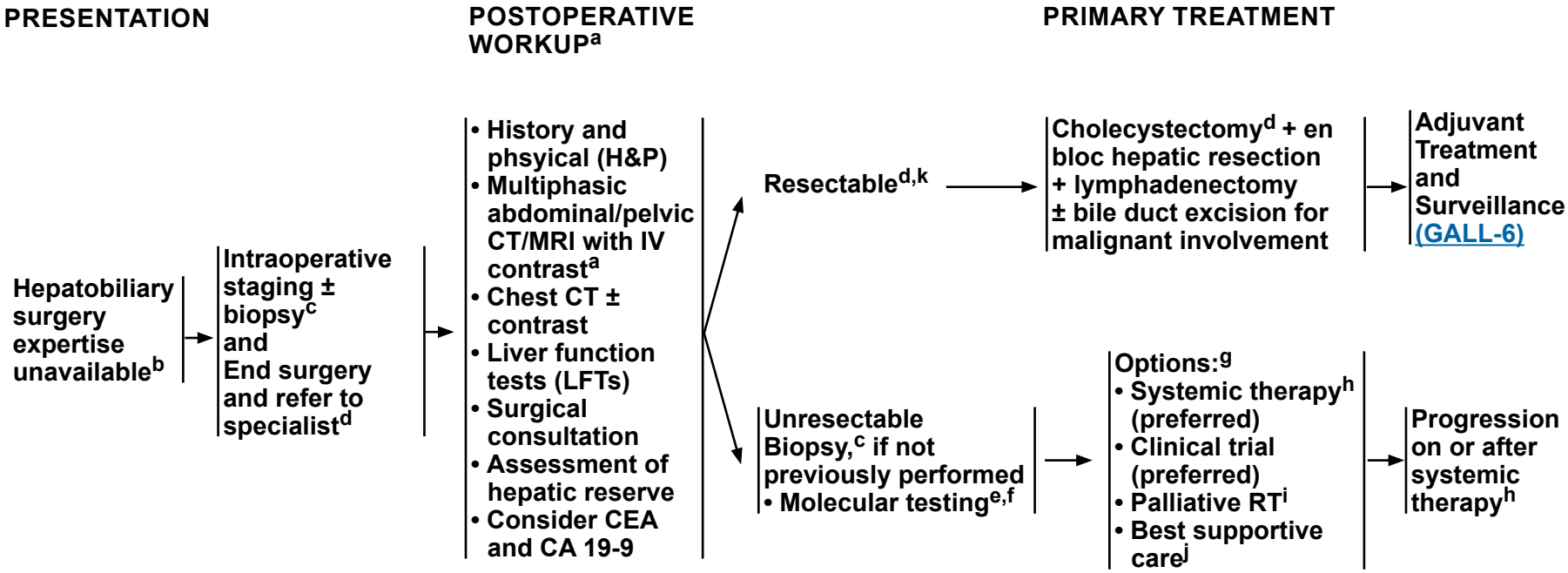


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[i] Principles of Radiation Therapy (BIL-D).
[j] See NCCN Guidelines for Palliative Care.
[k] For locoregionally advanced disease, consider neoadjuvant chemotherapy to rule out rapid progression and avoid futile surgery. There are limited clinical trial data to define a standard regimen or definitive benefit. See Principles of Systemic Therapy (BIL-C).

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# Gallbladder Cancer

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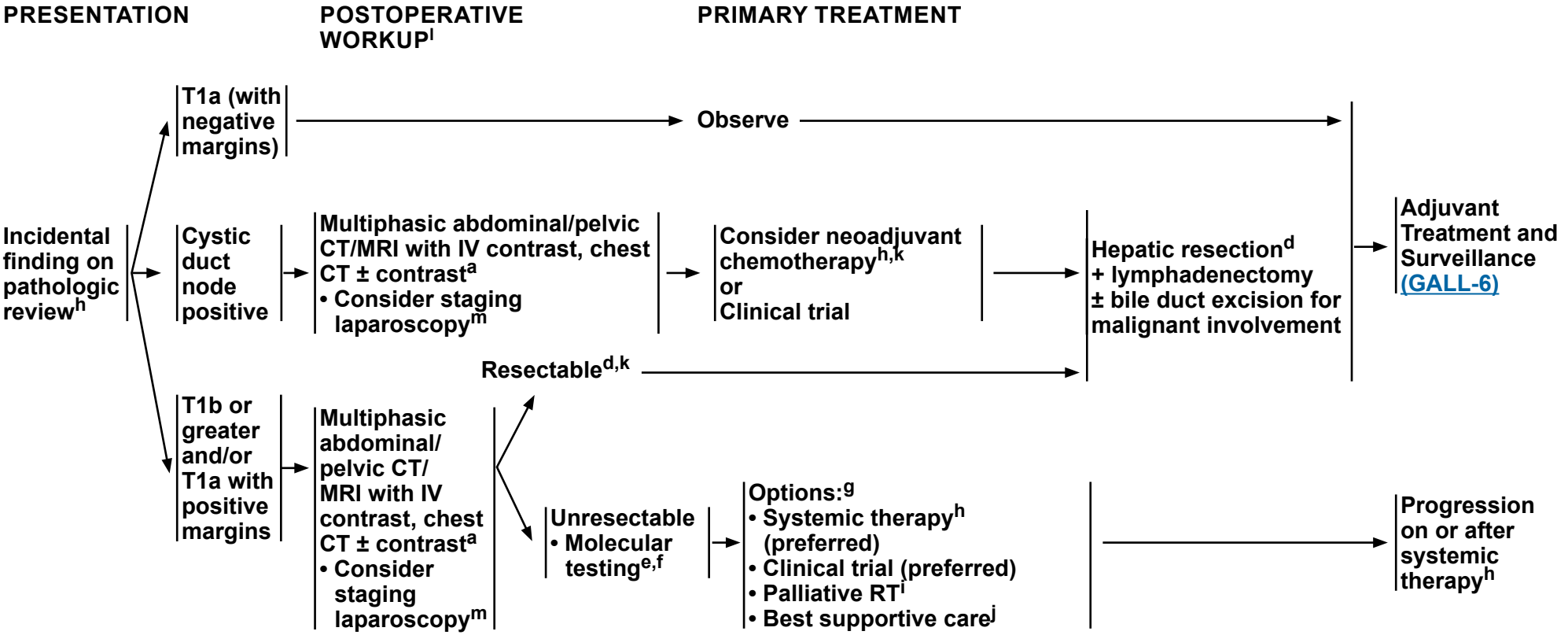


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[j] See NCCN Guidelines for Palliative Care.
[k] For locoregionally advanced disease, consider neoadjuvant chemotherapy to rule out rapid progression and avoid futile surgery. There are limited clinical trial data to define a standard regimen or definitive benefit. See Principles of Systemic Therapy (BIL-C).
[l] Consider multidisciplinary review.
[m] Butte JM, et al. HPB (Oxford) 2011;13:463-472.

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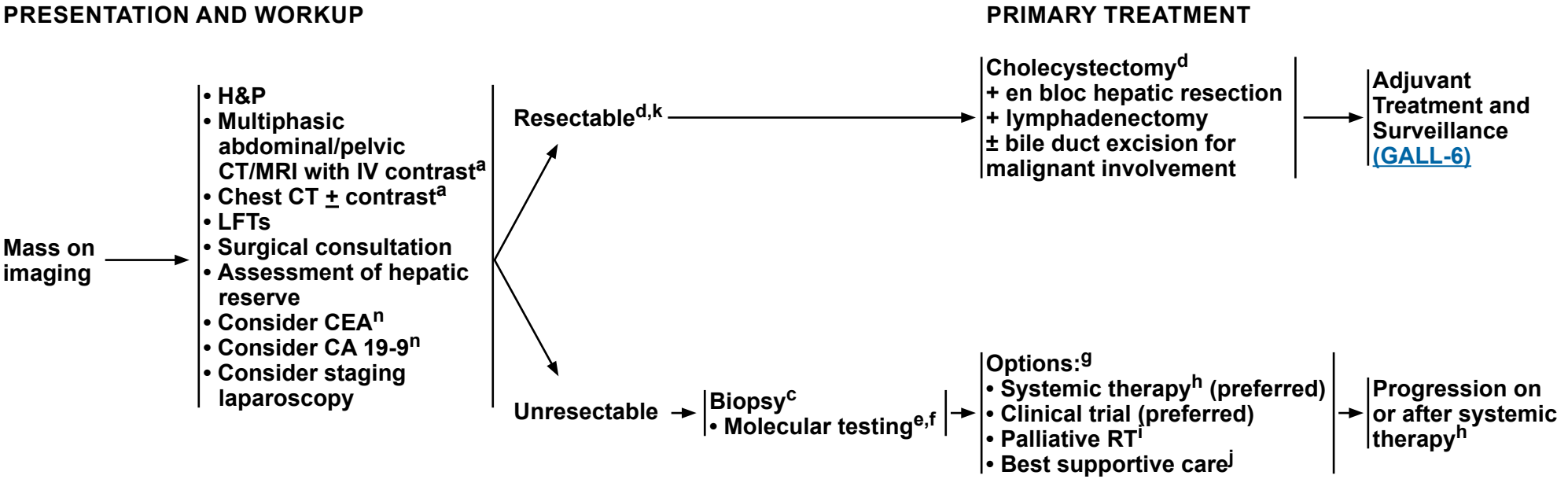
**Other Clinical Presentations**
**GALL-4 and GALL-5**

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[k] For locoregionally advanced disease, consider neoadjuvant chemotherapy to rule out rapid progression and avoid futile surgery. There are limited clinical trial data to define a standard regimen or definitive benefit. See Principles of Systemic Therapy (BIL-C).
[n] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.

**Other Clinical Presentations**
GALL-1, GALL-3, and GALL-5

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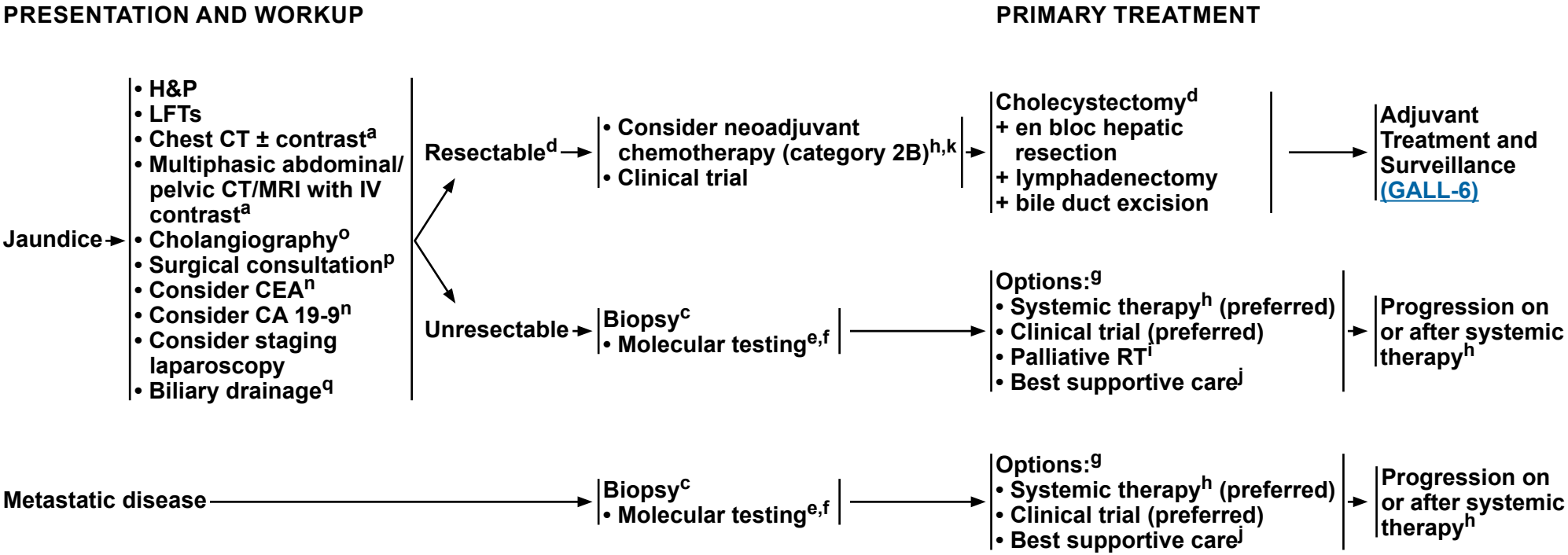


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[g] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
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[i] Principles of Radiation Therapy (BIL-D).
[j] See NCCN Guidelines for Palliative Care.
[k] For locoregionally advanced disease, consider neoadjuvant chemotherapy to rule out rapid progression and avoid futile surgery. There are limited clinical trial data to define a standard regimen or definitive benefit. See Principles of Systemic Therapy (BIL-C).
[n] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[o] Magnetic resonance cholangiopancreatography (MRCP) is preferred. Endoscopic retrograde cholangiopancreatography/percutaneous transhepatic cholangiography (ERCP/PTC) are used more for therapeutic intervention.
[p] Consult with a multidisciplinary team.
[q] Consider biliary drainage for patients with jaundice prior to resection and systemic therapy. Consider baseline CA 19-9 after biliary decompression.

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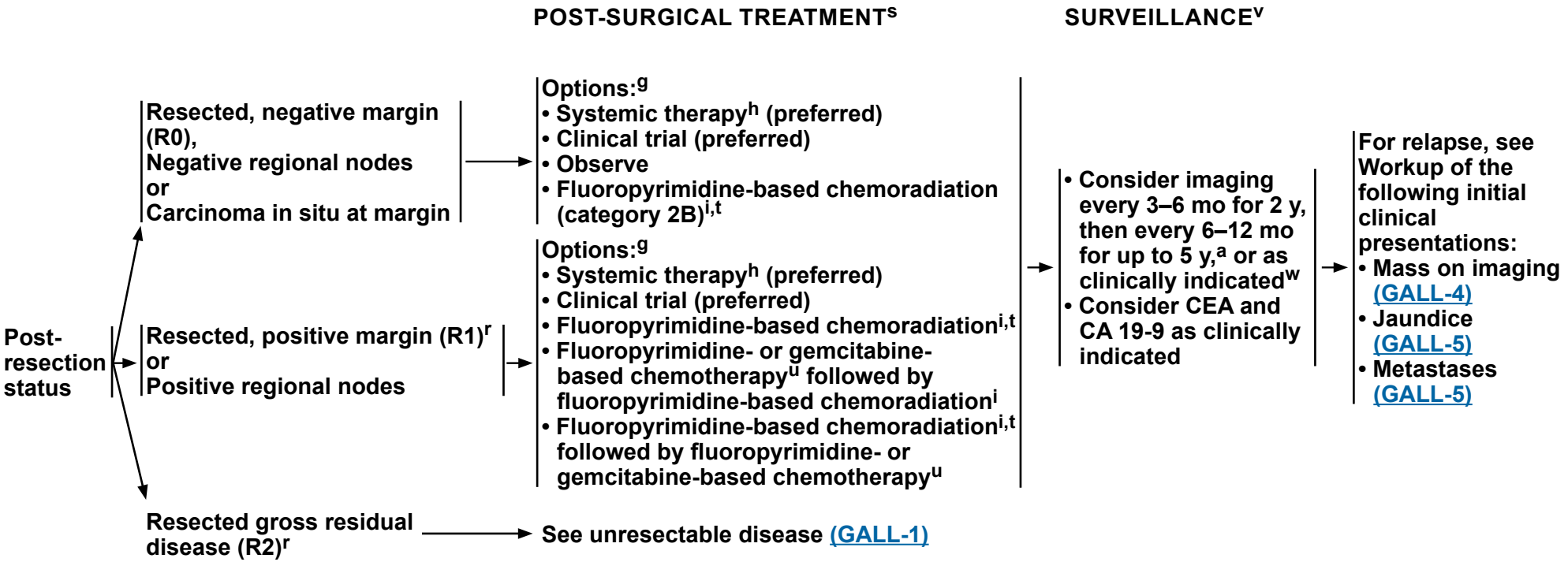
**Other Clinical Presentations GALL-3 and GALL-4**




[a] Principles of Imaging (BIL-A).
[g] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[h] Principles of Systemic Therapy (BIL-C).
[i] Principles of Radiation Therapy (BIL-D).
[r] Management of disease in patients with R1 or R2 resections should be evaluated by a multidisciplinary team.
[s] 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, et al. J Clin Oncol 2012;30:1934-1940).
[t] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[u] For a list of gemcitabine-based regimens and fluoropyrimidine-based regimens to be used before or after chemoradiation, see Adjuvant Chemotherapy (BIL-C, 1 of 5).
[v] There are no data to support a specific surveillance schedule or tests for monitoring. Physicians should discuss appropriate follow-up schedules/imaging with patients.
[w] Based on surveillance schedule used in the phase III BILCAP trial. Primrose JN, et al. Lancet Oncol 2019;20:663-673.

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## PRINCIPLES OF SURGERY AND PATHOLOGY

**Incidental Finding of Suspicious Mass During Surgery:**

- **If expertise is unavailable, document all relevant findings and refer the patient to a center with available expertise. If there is a suspicious mass, a biopsy is not necessary as this can result in peritoneal dissemination.**
- **If expertise is available and there is convincing clinical evidence of cancer, a definitive resection can be performed as written below. If the diagnosis is not clear, frozen section biopsies can be considered in selected cases before proceeding with definitive resection. If malignancy is suspected or confirmed after cholecystectomy has been initiated and expertise is available, then definitive resection should be undertaken.**
- **If malignancy is suspected before cholecystectomy has begun and there is a question of resectability (ie, locally advanced, possible metastatic disease, other), then definitive resection can be postponed, regardless of available expertise, until complete staging and evaluation has been performed. Document all findings and consider biopsy[a] if chemotherapy is anticipated.**
- **The principles of resection are the same as below consisting of radical cholecystectomy including segments IV B and V and lymphadenectomy and extended hepatic or biliary resection as necessary to obtain a negative margin.**

**Incidental Finding on Pathologic Review:**

- **Consider pathologic re-review by a hepatobiliary pathology expert and/or speak to surgeon to check for completeness of cholecystectomy, signs of disseminated disease, location of tumor, and any other pertinent information. Review the pathology report for T stage, cystic duct margin status, and other margins.**
- **Diagnostic laparoscopy can be performed but is of relatively low yield. Higher yields may be seen in patients with T3 or higher tumors, poorly differentiated tumors, or with a margin-positive cholecystectomy. Diagnostic laparoscopy should also be considered in patients with any suspicion of metastatic disease on imaging that is not amenable to percutaneous biopsy.[1]**
- **Repeat cross-sectional imaging of the chest, abdomen, and pelvis should be performed prior to definitive resection.**
- **Initial exploration should rule out distant lymph node metastases in the celiac axis or aorto-caval groove as these contraindicate further resection.**
- **Hepatic resection should be performed to obtain clear margins, which usually consists of segments IV B and V. Extended resections beyond segments IV B and V may be needed in some patients to obtain negative margins.**
- **Lymphadenectomy should be performed to clear all lymph nodes in the porta hepatis.**
- **Resection of the bile duct may be needed to obtain negative margins. Routine resection of the bile duct for lymphadenectomy has been shown to increase morbidity without convincing evidence for improved survival.[2,3]**
- **Port site resection has not been shown to be effective, as the presence of a port site implant is a surrogate marker of underlying disseminated disease and has not been shown to improve outcomes.[4]**

Footnote

[a] The optimal diagnostic method is core needle biopsy.

References

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.

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## PRINCIPLES OF SURGERY AND PATHOLOGY

**Mass on Imaging: Patients Presenting with Gallbladder Mass/Disease Suspicious for Gallbladder Cancer**

- **Staging should be carried out with multiphasic cross-sectional imaging of the chest, abdomen, and pelvis.**
- **If there is a suspicious mass, a biopsy is not necessary and a definitive resection should be carried out.**
- **Diagnostic laparoscopy is recommended prior to definitive resection.**
- **In selected cases where the diagnosis is not clear it may be reasonable to perform a cholecystectomy (including intraoperative frozen section) followed by the definitive resection during the same setting if pathology confirms cancer.**
- **The resection is carried out as per the principles described above.**

**Gallbladder Cancer and Jaundice**

- **The presence of jaundice in gallbladder cancer usually portends a poor prognosis.[5-7] These patients need careful surgical evaluation.**
- **Although a relative contraindication, in select patients curative intent resection can be attempted for resectable disease in centers with available expertise.**

References

[5] Hawkins WG, DeMatteo RP, Jarnagin WR, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol 2004;11:310-315.

[6] Regimbeau JM, Fuks D, Bachellier P, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC -GBC-2009 study group. Eur J Surg Oncol 2011;37:505-512.

[7] Nishio H, Ebata T, Yokoyama Y, et al. Gallbladder cancer involving the extrahepatic bile duct is worthy of resection. Ann Surg 2011;253:953-960.

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# NCCN Guidelines Version 2.2023
# Intrahepatic Cholangiocarcinoma

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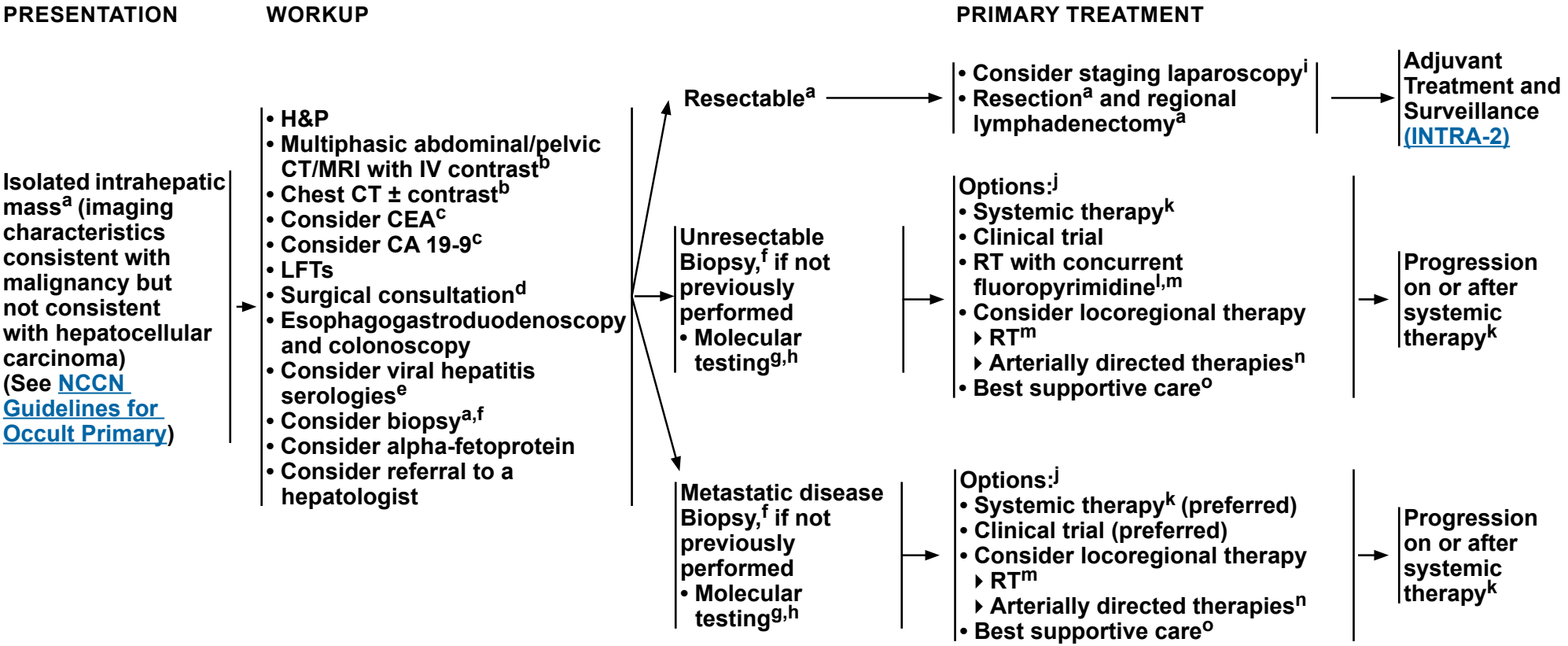


[a] Principles of Surgery (INTRA-A).
[b] Principles of Imaging (BIL-A).
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Consult with multidisciplinary team.
[e] ASCO guidelines for management of viral hepatitis B virus in patients with cancer/receiving chemotherapy: https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2020-HBV-PCO-Algorithm.pdf
[f] The optimal diagnostic method is core needle biopsy.
[g] For patients with dMMR/MSI-H tumors or a family history suggestive of *BRCA1/2* mutations, consider germline testing and/or referral to a genetic counselor.
[h] Principles of Molecular Testing (BIL-B).
[i] Laparoscopy may be done in conjunction with surgery if no distant metastases are found.
[j] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[k] Principles of Systemic Therapy (BIL-C).
[l] There are limited clinical trial data to define a standard regimen or definitive benefit. Participation in clinical trials is encouraged (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[m] Principles of Radiation Therapy (BIL-D).
[n] Intra-arterial chemotherapy (with or without systemic chemotherapy) may be used in a clinical trial or at experienced centers in carefully selected cases.
[o] See NCCN Guidelines for Palliative Care.

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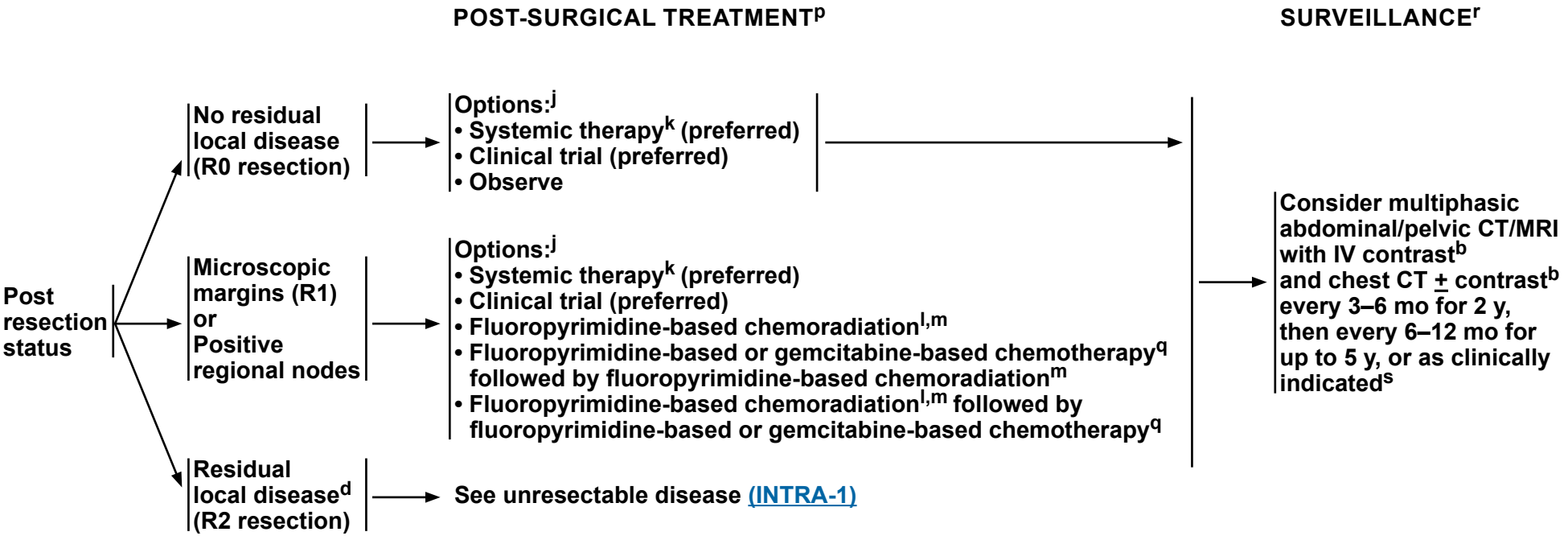


[b] Principles of Imaging (BIL-A).
[d] Consult with multidisciplinary team.
[j] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[k] Principles of Systemic Therapy (BIL-C).
[l] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[m] Principles of Radiation Therapy (BIL-D).
[p] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with BTC, especially in patients with lymph node-positive disease (Horgan AM, et al. J Clin Oncol 2012;30:1934-1940).
[q] For a list of gemcitabine-based regimens and fluoropyrimidine-based regimens to be used before or after chemoradiation, see Adjuvant Chemotherapy (BIL-C, 1 of 5).
[r] There are no data to support a specific surveillance schedule or tests for monitoring. Physicians should discuss appropriate follow-up schedules/imaging with patients.
[s] Based on surveillance schedule used in the phase III BILCAP trial. Primrose JN, et al. Lancet Oncol 2019;20:663-673.

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## PRINCIPLES OF SURGERY[1,2]

**General Principles**

- **A preoperative biopsy is not always necessary before proceeding with a definitive, potentially curative resection. A suspicious mass on imaging in the proper clinical setting should be treated as malignant.**
- **Diagnostic laparoscopy to rule out unresectable disseminated disease should be considered.**
- **Initial exploration should assess for multifocal hepatic disease, lymph node metastases, and distant metastases. Lymph node metastases beyond the porta hepatis and distant metastatic disease contraindicate resection.**
- **Hepatic resection with negative margins is the goal of surgical therapy. While major resections are often necessary, wedge resections and segmental resections are all appropriate given that a negative margin can be achieved.**
- **A regional lymphadenectomy of the porta hepatis is carried out.**
- **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.**
- **Minimally invasive approaches in experienced hands have been proven to be safe and effective.**

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

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# NCCN Guidelines Version 2.2023
# Extrahepatic Cholangiocarcinoma

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## PRESENTATION AND WORKUP

- Pain
- Jaundice
- Abnormal LFTs
- Obstruction or abnormality on imaging

→

- H&P
- Multiphasic abdominal/pelvic CT/MRI (assess for vascular invasion) with IV contrast[a]
- Chest CT ± contrast[a]
- Cholangiography[b]
- Consider CEA[c]
- Consider CA 19-9[c]
- LFTs
- Consider endoscopic ultrasound (EUS) after surgical consultation
- Consider serum IgG4 to rule out autoimmune cholangitis[d]

## PRIMARY TREATMENT

**Resectable[e]**

- Surgical exploration[g]
- Consider laparoscopic staging
- Consider preoperative biliary drainage
- Multidisciplinary review

→ Resectable[e] → Resection[e] → Adjuvant Treatment and Surveillance (EXTRA-2)

→ Unresectable, see below

**Unresectable[f]**

- Biliary drainage,[h] if indicated
- Biopsy[f,i] (only after determining transplant status)
  - Molecular testing[j,k]
- Consider referral to transplant center

→ Options:[l]
- Systemic therapy[m]
- Clinical trial
- RT with concurrent fluoropyrimidine[n,o]
- Palliative RT[o]
- Best supportive care[p]

→ Progression on or after systemic therapy[m]

**Metastatic disease**

- Biliary drainage,[h] if indicated
- Biopsy[i]
  - Molecular testing[j,k]

→ Options:[l]
- Systemic therapy[m]
- Clinical trial
- Best supportive care[p]

→ Progression on or after systemic therapy[m]

[a] Principles of Imaging (BIL-A).
[b] MRCP is preferred. ERCP/PTC are used more for therapeutic intervention.
[c] CEA and CA 19-9 are baseline tests and should not be done to confirm diagnosis.
[d] Patients with IgG-4–related cholangiopathy should be referred to an expert center.
[e] Principles of Surgery (EXTRA-A).
[f] Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy. Unresectable perihilar or hilar cholangiocarcinomas (CCAs) that measure ≤3 cm in radial diameter, with the absence of intrahepatic or extrahepatic metastases and without nodal disease, as well as those with primary sclerosing cholangitis, may be considered for liver transplantation at a transplant center that has an UNOS-approved protocol for transplantation of CCA.
[g] Surgery may be performed when index of suspicion is high; biopsy is not required.
[h] Consider biliary drainage for patients with jaundice prior to instituting systemic therapy. Consider baseline CA 19-9 after biliary decompression.
[i] The optimal diagnostic method is core needle biopsy.
[j] For patients with dMMR/MSI-H tumors or a family history suggestive of *BRCA1/2* mutations, consider germline testing and/or referral to a genetic counselor.
[k] Principles of Molecular Testing (BIL-B).
[l] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
[m] Principles of Systemic Therapy (BIL-C).
[n] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[o] Principles of Radiation Therapy (BIL-D).
[p] See NCCN Guidelines for Palliative Care.

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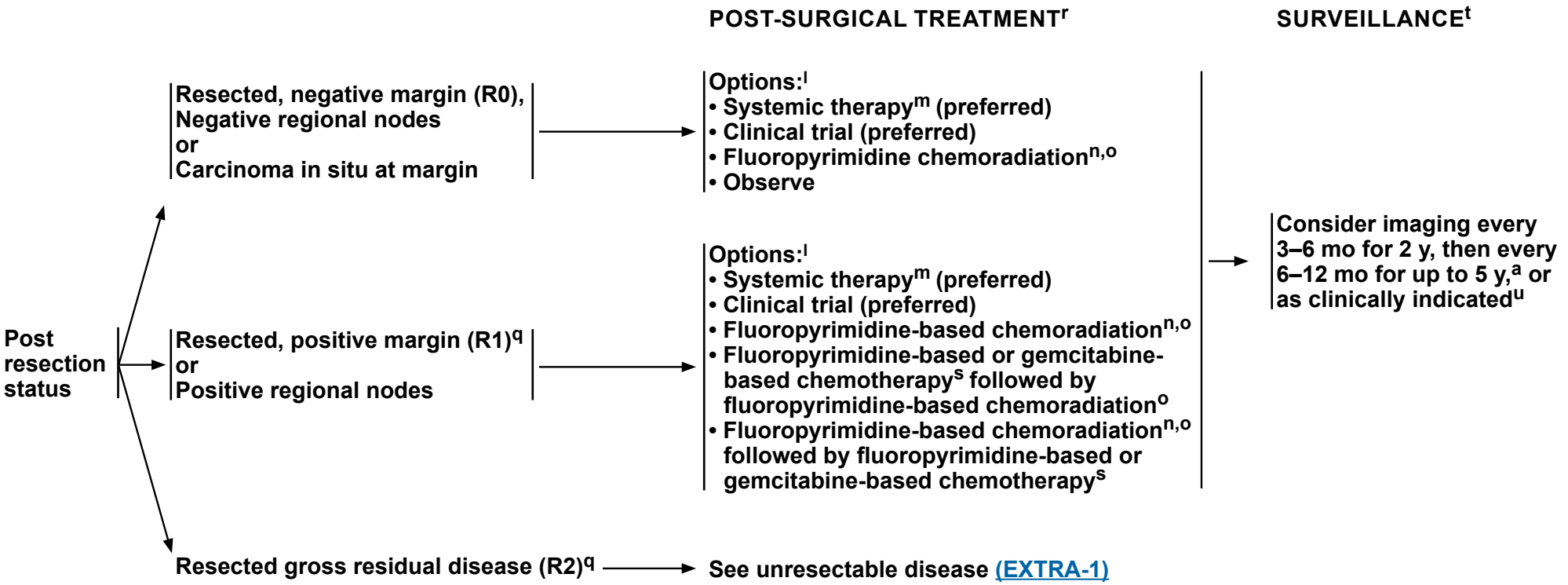


[a] Principles of Imaging (BIL-A).
[l] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease and institutional capabilities.
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[n] There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged (Macdonald OK, et al. Surg Oncol Clin N Am 2002;11:941-954).
[o] Principles of Radiation Therapy (BIL-D).
[q] Management of disease in patients with R1 or R2 resections should be evaluated by a multidisciplinary team.
[r] Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with BTC, especially in patients with lymph node-positive disease (Horgan AM, et al. J Clin Oncol 2012;30:1934-1940).
[s] For a list of gemcitabine-based regimens and fluoropyrimidine-based regimens to be used before or after chemoradiation, see Adjuvant Chemotherapy (BIL-C, 1 of 5).
[t] There are no data to support a specific surveillance schedule or tests for monitoring. Physicians should discuss appropriate follow-up schedules/imaging with patients.
[u] Based on surveillance schedule used in the phase III BILCAP trial. Primrose JN, et al. Lancet Oncol 2019;20:663-673.

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## PRINCIPLES OF SURGERY

### General Principles

- **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.**
- **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 should be considered.**
- **Occasionally a bile duct tumor will involve the biliary tree over a long distance such that a hepatic resection and pancreaticoduodenectomy will be necessary. These are relatively morbid procedures and should only be carried out in very healthy patients without significant comorbidity. Nonetheless, these can be potentially curative procedures and should be considered in the proper clinical setting. Combined liver and pancreatic resections performed to clear distant nodal disease are not recommended.**

### Hilar Cholangiocarcinoma

- **Detailed descriptions of imaging assessment of resectability are beyond the scope of this outline. The basic principle is that the tumor will need to be resected along with the involved biliary tree and the involved hemi-liver with a reasonable chance of a margin-negative resection. The contralateral liver requires intact arterial and portal inflow as well as biliary drainage.[1-3]**
- **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. While not necessary in all cases, the use of preoperative biliary drainage of the FLR and contralateral portal vein embolization should be considered in cases of a small FLR.[4,5]**
- **Initial exploration rules out distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis as these findings contraindicate resection. Further exploration must confirm local resectability.**
- **Since hilar tumors, by definition, abut or invade the central portion of the liver they require major hepatic resections on the involved side to encompass the biliary confluence and generally require a caudate resection.**
- **Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection and require expertise in these procedures.**
- **Biliary reconstruction is generally through a Roux-en-Y hepaticojejunostomy.**
- **A regional lymphadenectomy of the porta hepatis is carried out.**
- **Frozen section assessment of proximal and distal bile duct margins is recommended if further resection can be carried out.**

### Distal Cholangiocarcinoma

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

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

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## PRINCIPLES OF IMAGING[1-4]

### General Principles

- **CT of the chest with or without contrast and multiphasic contrast-enhanced CT or MRI of the abdomen and pelvis are recommended for follow-up imaging.**
- **PET/CT has limited sensitivity but high specificity and may be considered when there is an equivocal finding.[5] The routine use of PET/CT in the preoperative setting has not been established in prospective trials.**

### Gallbladder Cancer

- **Detection of early-stage gallbladder cancer remains difficult, and is commonly discovered incidentally at surgery or pathologic examination of the gallbladder.**
- **If gallbladder cancer is suspected preoperatively, multidetector multiphase CT of the abdomen (and pelvis) or contrast-enhanced MRI with magnetic resonance cholangiopancreatography (MRCP) of the abdomen (and pelvis) and chest CT with or without contrast should be performed. MRI is preferred for evaluating masses within the gallbladder and demonstrating bile duct involvement.**
- **Because lymphatic spread is common, careful attention should be made to evaluate nodal disease, specifically the porta hepatis and left gastric and aorto-caval basins.**

### Intrahepatic[6] and Extrahepatic Cholangiocarcinoma

- **Surgical management is based on the location and extent of the tumor.**
- **Preoperative imaging for accurate staging of extrahepatic cholangiocarcinoma (CCA) should be done with multidetector multiphasic abdominal/pelvic CT or MRI. Contrast-enhanced MRI with MRCP is preferred for evaluating the extent of biliary tract involvement. Imaging with multiphasic CT or MRI with thin cuts, or multiphase CT or MRI of the liver and biliary tree should specifically address the anatomy of the biliary tree, hepatic arteries, and portal veins and their relationship to the tumor.[7]**
- **Chest CT with or without contrast is recommended for staging.**
- **When biliary duct involvement is suspected, it is very important to obtain high-quality biliary protocol imaging (preferably CT) to evaluate the extent of tumor prior to stenting. Reactive changes from stenting could potentially compromise the ability to delineate the complete extent of biliary tract involvement.**
- **EUS or endoscopic retrograde cholangiopancreatography (ERCP) may be helpful in the setting of bile duct dilation if no mass is seen on CT or MRI. EUS or ERCP can also be used to establish tissue diagnosis and provide access to relieve biliary obstruction.**
- **CT of the chest with or without contrast and CT or MRI of the abdomen and pelvis with contrast may be used for follow-up.**
- **Delayed phase imaging is preferred when the diagnosis of intrahepatic CCA is suspected or confirmed.**

[1] Srinivasa S, McEntee B, Koea JB. The role of PET scans in the management of cholangiocarcinoma and gallbladder cancer: a systematic review for surgeons. Int J Diagnostic Imaging 2015;2.

[2] Corvera CU, Blumgart LH, Akhurst T, et al. 18F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. J Am Coll Surg 2008;206:57-65.

[3] Brandi G, Venturi M, Pantaleo MA, Ercolani G, GICO. Cholangiocarcinoma: Current opinion on clinical practice diagnostic and therapeutic algorithms: A review of the literature and a long-standing experience of a referral center. Dig Liver Dis 2016;48:231-241.

[4] Navaneethan U, Njei B, Venkatesh PG, et al. Endoscopic ultrasound in the diagnosis of cholangiocarcinoma as the etiology of biliary strictures: a systematic review and meta-analysis. Gastroenterol Rep (Oxf) 2015;3:209-215.

[5] Lamarca A, Barriuso J, Chander A, et al. 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) for patients with biliary tract cancer: Systematic review and meta-analysis. J Hepatol 2019;71:115-129.

[6] Sutton TL, Billingsley KG, Walker BS, et al. Detection of tumor multifocality in resectable intrahepatic cholangiocarcinoma: Defining the optimal pre-operative imaging modality. J Gastrointest Surg 2021;25:2250-2257.

[7] ACR-SAR-SPR practice parameter for the performance of magnetic resonance imaging (MRI) of the liver. American College of Radiology, 2020. Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/MR-Liver.pdf. Accessed 01/18/22.

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## PRINCIPLES OF MOLECULAR TESTING

- **Biliary tract cancers (BTCs) are known to harbor clinically relevant molecular alterations that are differentially expressed in gallbladder cancers, and intrahepatic and extrahepatic (perihilar and distal) CCAs. Specifically, genotyping of the tumor tissue has identified translocations in *FGFR2* and *NTRK*, mutations in the *IDH1* and *BRAF* genes, and microsatellite instability (MSI) along with other rare molecular alterations for which specific treatments are now available.[1-22]**

- **Additionally, while most biliary tract carcinomas are considered sporadic, up to 10%–15% of BTCs may be associated with an inherited cancer predisposition syndrome.[23,24] Recent studies have evaluated germline mutation testing in large cohorts of unselected patients with biliary tract carcinoma and discovered high to moderate penetrance deleterious germline mutations in roughly 9-11% of BTCs, including intrahepatic/extrahepatic CCAs and gallbladder carcinomas.[23,25] The highest prevalence was found for *BRCA2* mutation followed by *BRCA1* and to a lesser extent *MLH1*, *MSH2*, *PALB2*, *RAD51D*, *BAP1* and *ATM* mutations.[23,25,26] These findings are consistent with earlier literature suggesting an increased risk of BTC in patients with *BRCA* mutations and Lynch syndrome.[27,28]**

**Recommendations**

- **Molecular profiling in BTCs: Comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC who are candidates for systemic therapy (see Table 1 and Table 2). A comprehensive panel including the targets listed in Table 1 may optimize the chance of identifying a targetable aberration. If tissue is too scant or not available, consider repeat biopsy depending on tumor accessibility, safety, and clinical context. A cell-free DNA (cfDNA) test may also be considered for identifying gene mutations. This technique may not reliably identify gene fusions or rearrangements depending on the panel used and the specific partner gene.**

- **Germline testing in hepatobiliary cancers: Evidence remains insufficient for definitive recommendations regarding specific criteria to guide genetic risk assessment in hepatobiliary cancers or for universal germline testing in these tumors. In BTCs, genetic counseling referral and potential germline testing should be considered in patients with any of the following characteristics: young age at diagnosis; a strong personal or family history of cancer; no known risk factors for liver disease; or presence of mutations identified during tumor testing that are suspected to be possible germline alterations. For patients who do harbor a known germline mutation associated with a cancer predisposing syndrome (ie, Lynch syndrome or hereditary breast and ovarian cancer syndrome), there is currently insufficient evidence to support screening for biliary tract malignancies. Further recommendations and a detailed discussion of genetic counseling and testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**

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## PRINCIPLES OF MOLECULAR TESTING

**Table 1: Recommendations for Molecular Testing in Unresectable or Metastatic Biliary Tract Cancers[a-d]**

| Recommended Molecular Testing | Anatomic Subsite | | |
|---|---|---|---|
| | Gallbladder | Intrahepatic CCA | Extrahepatic CCA |
| ***NTRK* gene fusion** | X | X | X |
| **MSI-H/dMMR** | X | X | X |
| **TMB-H** | X | X | X |
| ***BRAF* V600E mutation** | X | X | X |
| ***FGFR2* fusion or rearrangement** | – | X | X |
| ***IDH1* mutation** | – | X | X |
| **HER2 *(ERBB2)* overexpression and/or amplification** | X | X | X |
| ***RET* gene fusion** | X | X | X |

**MSI-H: microsatellite instability-high**
**dMMR: mismatch repair deficient**
**TMB-H: tumor mutational burden-high**

[a] Consider repeat biopsy or performing cfDNA analysis if initial biopsy sample yields insufficient tumor content, depending on clinical context.
[b] If unsure about the primary anatomic site within the biliary tree, comprehensive testing is recommended, including consideration of *FGFR2* fusion or rearrangement testing and *IDH1* mutation testing in gallbladder cancer or in large tumors of uncertain anatomic origin within the biliary tree.
[c] Testing for *FGFR2* fusions or rearrangements and *IDH1* mutations should be considered in patients with unresectable or metastatic gallbladder cancer.
[d] Genetic counseling referral and germline testing should be considered in patients with any of the following characteristics: young age at diagnosis; a strong personal or family history of cancer; no known risk factors for liver disease; or presence of mutations identified during tumor testing that are suspected to be possible germline alterations.

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References

## PRINCIPLES OF MOLECULAR TESTING

**Table 2: Incidence of Therapeutic Targets in Advanced Biliary Tract Cancers**

| Aberration | Approximate Incidence[e] |
|---|---|
| ***NTRK* fusion** | **<1%** |
| **MSI-H/dMMR** | **1%–3%** |
| **TMB-H** | **<5%** |
| ***BRAF* V600E mutation** | **1%–5%** |
| ***FGFR2* fusion or rearrangement** | **9%–15% of intrahepatic CCAs and rare in other subsites** |
| ***IDH1* mutation** | **10%–20% of intrahepatic CCAs and rare in other subsites** |
| **HER2 (*ERBB2*) overexpression and/or amplification** | **5%–20% of CCAs, 15%–30% of gallbladder cancer** |
| ***RET* fusion** | **<1%** |

[e] The rarity of individual subgroups limits precise incidence and frequency estimates. Incidence estimates refer to BTCs across anatomic subsites, unless otherwise stated.

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References

## PRINCIPLES OF MOLECULAR TESTING

### *NTRK* Fusions

- **Testing Modalities and Considerations: Multi-gene next-generation sequencing (NGS) testing, preferably with a transcriptome-based approach, is the preferred assay given the rarity of *NTRK* fusions in BTCs.**

- **Recommendation: Testing for *NTRK* fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. These assessments are feasible in the context of multi-target assessment in NGS gene panels currently in clinical use and *NTRK* fusion-positive CCA have demonstrated responses in clinical trials.**

### Immunotherapy Biomarkers (MSI-H/dMMR/TMB-H, PD-L1)

- **Testing Modalities and Considerations: There are three possible tests to evaluate mismatch repair (MMR) protein deficiency or microsatellite status. First, immunohistochemical staining for the *MLH1*, *MSH2*, *MSH6*, and *PMS2* gene products establishes protein retention or loss. If all 4 proteins are retained, it is unlikely the sample will display high rates of DNA mutations in microsatellite regions. Loss of two of the four proteins (typical in MLH1/PMS2 and MSH2/MSH6 pairs) correlates with MSI or MSI-H. Second, NGS determines if there are inactivating mutations in the MMR genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Mutations associated with nonfunctional MMR proteins correlate with MSI-H status. Last, microsatellite repeats of tumor DNA are examined by polymerase chain reaction (PCR). Abnormal microsatellites in two or more regions demonstrates MSI-H status. Tumor mutational burden (TMB) can be tested with a clinically validated NGS panel but has inherent platform variation.**

- **Recommendation: Testing for MSI or MMR deficiency is recommended in patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.**

- **Testing for TMB is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA based upon clinical benefit observed across advanced solid tumors.**

- **Further recommendations for MSI/MMR testing can be found in the NCCN Guidelines for Colon Cancer.**

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## PRINCIPLES OF MOLECULAR TESTING

### *BRAF* V600E Mutations

- **Testing Modalities and cfDNA Considerations: NGS or PCR testing of tumor tissue; NGS of cfDNA can also detect tumor *BRAF* mutations.**
- **Recommendation: Testing for *BRAF* V600E mutations is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.**

### *FGFR2* Fusions/Other *FGFR* Pathway Aberrations

- **Testing Modalities and Considerations: Both NGS assays, which include the *FGFR2* gene including its intronic regions, and break apart fluorescence in situ hybridization (FISH) assays, can be used to identify patients with *FGFR2* fusions/rearrangements in tumor tissue samples.[1,29] Some fusion breakpoints may be detectable using cfDNA assays but sensitivity is lower than for tumor tissue testing.[30]**
- **Recommendation: Testing for *FGFR2* fusions or rearrangements is recommended for patients with unresectable or metastatic intrahepatic or extrahepatic CCA and should be considered for patients with unresectable or metastatic gallbladder cancer.**

### *IDH1* Mutations

- **Testing Modalities and Considerations: *IDH1* mutations in intrahepatic CCA occur most commonly at codon 132 (R132X).[9,31] Testing can be performed by tumor NGS using a multi-gene panel or by hotspot mutation testing. cfDNA testing can also detect hotspot mutations in *IDH1*.**
- **Recommendation: Testing for *IDH1* mutations is recommended for patients with unresectable or metastatic intrahepatic CCA or extrahepatic CCA and should be considered for patients with unresectable or metastatic gallbladder cancer.**

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## PRINCIPLES OF MOLECULAR TESTING

### HER2/*ERBB2* Overexpression/Amplification/Activating Mutations

- **Testing Modalities and Considerations: HER2 amplification can be detected by immunohistochemistry (IHC), FISH, or NGS techniques. NGS testing offers the ability to assess numerous molecular alterations simultaneously and has the added benefit of detecting HER2 activating mutations. NGS can be considered upfront when limited diagnostic tissue is available, though other methodologies such as IHC/FISH remain the most commonly utilized. However, the predominant limitation of HER2 or *ERBB2* testing in hepatobiliary tumors is the lack of specific guideline cutoff points or standardized algorithms to define HER2 positivity by protein expression or *ERBB2* amplification in hepatobiliary malignancies. Various cutoff values including those described for breast and gastroesophageal junction neoplasms have been used in prior and ongoing clinical trials, making direct comparisons between studies difficult. Other challenges to be considered include the significant heterogeneity that can be seen with protein overexpression in BTCs, which may affect positivity rates when IHC is performed in biopsy specimens.[32] Lastly, while most alterations are identified through overexpression or amplification, activating missense mutations have also been shown to represent a significant subset of HER2-altered tumors, which will be missed with standard IHC and FISH techniques.[13,33]**

- **Recommendation: Testing for HER2 (*ERBB2*) overexpression/amplification is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.**

### Other Biomarkers (RET/ROS1, KRAS G12C/Other KRAS, Other Tumor-Agnostic Markers)

- **In addition to the genomic aberrations reviewed above, NGS testing may uncover other potentially actionable molecular alterations that could determine eligibility for ongoing clinical trials in patients with advanced BTCs. While there is insufficient evidence to recommend universal assessment, alterations for which targeted therapies exist and have been FDA-approved in other tumor types, including *KRAS* G12C mutation,[34-36] *MET* amplification,[37-39] and *ALK*,[40] *RET*,[20] or *ROS1* fusions,[41] among others,[42] have been described with variable but overall rare frequency in biliary tract carcinomas and hepatocellular carcinoma.[43] However, limited data currently exist regarding the efficacy of targeted therapy in these situations, due to their rarity.**

- **Recommendation: Testing for *RET* fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. A comprehensive NGS panel may identify additional alterations for which targeted therapies exist and have FDA-approved treatments in other tumor types.**

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## PRINCIPLES OF SYSTEMIC THERAPY

### Neoadjuvant Therapy[a]

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| • None | • FOLFOX<br>• Capecitabine + oxaliplatin<br>• Gemcitabine + capecitabine<br>• Gemcitabine + cisplatin<br>• Durvalumab + gemcitabine + cisplatin<br>• Gemcitabine + cisplatin + albumin-bound paclitaxel (category 2B)[1] | • None |

### Adjuvant Therapy[b,2]

| Preferred Regimens | Other Recommended Regimens | Useful in Certain Circumstances |
|---|---|---|
| • Capecitabine (category 1)[c,3] | • FOLFOX<br>• Capecitabine + oxaliplatin<br>• Gemcitabine + capecitabine<br>• Gemcitabine + cisplatin<br>• Capecitabine + cisplatin (category 3)<br>• Single agents:<br>▸ 5-fluorouracil<br>▸ Gemcitabine | • None |

### Agents Used with Concurrent Radiation

- 5-fluorouracil
- Capecitabine

[a] The decision to use neoadjuvant therapy needs to be individualized and in close consultation with surgical oncologist and multidisciplinary team. A period of 2 to 6 months with reassessment every 2 to 3 months is reasonable. There are limited clinical trial data to define a standard regimen or definitive benefit. Clinical trial participation is encouraged. The listed regimens are extrapolated from the metastatic setting.

[b] Adjuvant therapy up to 6 months. Adjuvant chemotherapy or chemoradiation has been associated with survival benefit in patients with BTC, especially in patients with lymph node-positive disease.

[c] The phase III BILCAP study shows improved overall survival for adjuvant capecitabine in the per-protocol analysis, and the overall survival did not reach statistical significance in the intent-to-treat analysis. Primrose JN, Fox RP, Palmer DH, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncol 2019;20:663-673. Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. J Clin Oncol 2015;33:2617-2622.

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References

Continued

## PRINCIPLES OF SYSTEMIC THERAPY

### Primary Treatment for Unresectable and Metastatic Disease

**Preferred Regimens**

- Durvalumab + gemcitabine + cisplatin (category 1)[d,e,f,4]

**Other Recommended Regimens**

- Gemcitabine + cisplatin (category 1)[5]
- FOLFOX
- Capecitabine + oxaliplatin
- Gemcitabine + albumin-bound paclitaxel
- Gemcitabine + capecitabine
- Gemcitabine + oxaliplatin
- Gemcitabine + cisplatin + albumin-bound paclitaxel (category 2B)[1]
- Single agents:
  - 5-fluorouracil
  - Capecitabine
  - Gemcitabine

**Useful in Certain Circumstances**

- Targeted therapy (BIL-C 3 of 5)

### Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[g]

**Preferred Regimens**

- FOLFOX[6]

**Other Recommended Regimens**

- FOLFIRI (category 2B)[7]
- Regorafenib (category 2B)[8]
- Liposomal irinotecan + fluorouracil + leucovorin (category 2B)[9]
- See also: Preferred and Other Recommended Regimens for Unresectable and Metastatic Disease above

**Useful in Certain Circumstances**

- Targeted therapy (BIL-C 3 of 5)
- Nivolumab (category 2B)[e,f,10]
- Lenvatinib + pembrolizumab (category 2B)[e,f,11]

[d] Durvalumab + gemcitabine + cisplatin is also a recommended treatment option for patients who developed recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy.
[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.

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References

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## PRINCIPLES OF SYSTEMIC THERAPY
## TARGETED THERAPY

### Primary Treatment for Unresectable and Metastatic Disease

**Useful in Certain Circumstances**

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[12,13]
  - Larotrectinib[14]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,h,15,16,17]
- For TMB-H tumors:
  - Nivolumab + ipilimumab (category 2B)[e,18]
- For *RET* gene fusion-positive tumors:
  - Pralsetinib (category 2B)[19]
  - Selpercatinib for CCA (category 2B)[20]

### Subsequent-Line Therapy for Biliary Tract Cancers if Disease Progression[g]

**Useful in Certain Circumstances**

- For *NTRK* gene fusion-positive tumors:
  - Entrectinib[12,13]
  - Larotrectinib[14]
- For MSI-H/dMMR tumors:
  - Pembrolizumab[e,f,h,15,16,17]
  - Dostarlimab-gxly (category 2B)[e,f,i,21,22]
- For TMB-H tumors:
  - Nivolumab + ipilimumab[e,f,j,18]
  - Pembrolizumab[e,f,h,23]
- For *BRAF* V600E-mutated tumors
  - Dabrafenib + trametinib[24,25]
- For CCA with *FGFR2* fusions or rearrangements:
  - Futibatinib[26]
  - Pemigatinib[27]
- For CCA with *IDH1* mutations
  - Ivosidenib (category 1)[28,29]
- For HER2-positive tumors:
  - Trastuzumab[k] + pertuzumab[30]
- For *RET* gene fusion-positive tumors:
  - Selpercatinib for CCA[20]
  - Pralsetinib (category 2B)[19]

[e] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[f] For patients who have not been previously treated with a checkpoint inhibitor when used as subsequent-line therapy because there is a lack of data for use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor.
[g] Treatment selection depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.
[h] There are limited clinical trial data to support pembrolizumab in this setting. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-750.
[i] Dostarlimab-gxly is a recommended treatment option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
[j] For patients with disease refractory to standard therapies or who have no standard treatment options available.
[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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References

Continued

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## PRINCIPLES OF RADIATION THERAPY

### General Principles

- **Image-guided RT (IGRT) is strongly recommended when using RT, intensity-modulated RT (IMRT), and stereotactic body RT (SBRT) to improve treatment accuracy and reduce treatment-related toxicity.**
- **Adjuvant RT[1,2]**
  - **Postoperative RT using conventional 3D conformal RT (3D-CRT) or IMRT is an option for resected extrahepatic CCA and gallbladder cancer.[3,4] Target volumes should cover the draining regional lymph nodes: porta hepatis, celiac, superior mesenteric, gastrohepatic, and para-aortic to 45 Gy at 1.8 Gy/fraction and 50–60 Gy in 1.8–2 Gy/fraction to the tumor bed depending on margin positivity.**
- **Unresectable**
  - **All tumors irrespective of the location may be amenable to RT (3D-CRT, IMRT, or SBRT).**
  - **Conventionally fractionated radiotherapy with concurrent fluoropyrimidine-based chemotherapy[a] to standard or high dose is acceptable for intrahepatic and extrahepatic tumors.**
  - **Hypofractionation with photons[5] or protons[6] is an acceptable option for intrahepatic tumors, although treatment at centers with experience is recommended.**
  - **Palliative RT is appropriate for symptom control and/or prevention of complications from metastatic lesions, such as bone or brain.**
- **RT dosing,[7] depending on the ability to meet normal organ constraints and underlying liver function:**
  - **Conventional fractionation (postoperative or unresectable):[3]**
    - **Initial volumes to 45 Gy in 1.8 Gy per fraction**
    - **Boost to 50 to 60 Gy in 1.8–2 Gy per fraction**
  - **Hypofractionation (unresectable): 58–67.5 Gy in 15 fractions for a median biologic equivalent dose of 80.5 Gy.[5,6]**
  - **SBRT (unresectable):**
    - **30–50 Gy (typically in 3–5 fractions)**

Footnote

[a] See Principles of Systemic Therapy (BIL-C).

References

[1] Mallick S, Benson R, Haresh KP, et al. Adjuvant radiotherapy in the treatment of gallbladder carcinoma: What is the current evidence? J Egypt Natl Canc Inst 2016;28:1-6.
[2] Kim Y, Amini N, Wilson A, et al. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: A multi-institutional analysis. Ann Surg Oncol 2016;23:2998-3008.
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[5] Tao R, Krishnan S, Bhosale PR, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol 2016;34:219-226.
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[7] Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2022;12:28-51.

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

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

***Table 3.*** **Definitions for T, N, M**

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

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

| | |
|---|---|
| **M** | **Distant Metastasis** |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

***Table 4.*** **AJCC Prognostic Groups**

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

**Histologic Grade (G)**

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

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Continued

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

***Table 5.*** **Definitions for T, N, M**

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

| N | Regional Lymph Nodes |
|---|---|
| **NX** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Regional lymph node metastasis present |

| M | Distant Metastasis |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis present |

***Table 6.*** **AJCC Prognostic Groups**

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

**Histologic Grade (G)**

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

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Continued

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

***Table 7.*** **Definitions for T, N, M**

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

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

| M | Distant Metastasis |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

***Table 8.*** **AJCC Prognostic Groups**

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

**Histologic Grade (G)**

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

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Continued

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

***Table 9.*** **Definitions for T, N, M**

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

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

| M | Distant Metastasis |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

***Table 10.*** **AJCC Prognostic Groups**

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

**Histologic Grade (G)**

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

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## ABBREVIATIONS

| | |
|---|---|
| 3D-CRT | 3D conformal radiation therapy |
| BTC | biliary tract cancer |
| CCA | cholangiocarcinoma |
| CEA | carcinoembryonic antigen |
| cfDNA | cell-free DNA |
| dMMR | mismatch repair deficient |
| ERCP | endoscopic retrograde cholangiopancreatography |
| EUS | endoscopic ultrasound |
| FISH | fluorescence in situ hybridization |
| FLR | future liver remnant |
| IHC | immunohistochemistry |
| IMRT | intensity-modulated radiation therapy |
| LFT | liver function test |
| MRCP | magnetic resonance cholangiopancreatography |
| MMR | mismatch repair |
| MSI | microsatellite instability |
| MSI-H | microsatellite instability-high |
| NGS | next-generation sequencing |
| PCR | polymerase chain reaction |
| PTC | percutaneous transhepatic cholangiography |
| RT | radiation therapy |
| SBRT | stereotactic body radiation therapy |
| TMB | tumor mutational burden |
| TMB-H | tumor mutational burden-high |

| 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 indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

# NCCN Guidelines Version 2.2023
# Biliary Tract Cancers

## Discussion

This discussion corresponds to the NCCN Guidelines for Biliary Tract Cancers. Last updated: May 10th, 2023.

### Table of Contents

## Overview

Hepatobiliary cancers are highly lethal cancers including a spectrum of invasive carcinomas arising in the liver (hepatocellular carcinoma [HCC]), gall bladder, and bile ducts (intrahepatic and extrahepatic cholangiocarcinoma [CCA]). Gallbladder cancer and CCAs are collectively known as biliary tract cancers (BTCs). In 2023, it is estimated that 41,210 people in the United States will be diagnosed with liver cancer and intrahepatic bile duct cancer and an additional 12,220 people will be diagnosed with gallbladder cancer or other BTC.[1] Approximately 29,380 deaths from liver or intrahepatic bile duct cancer and 4510 deaths due to gallbladder cancer or other BTC are anticipated.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Biliary Tract Cancers are the work of the members of the NCCN Biliary Tract Cancers Guidelines Panel. The types of BTCs covered in these guidelines include: gallbladder cancer, and intrahepatic and extrahepatic CCA. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Although not explicitly stated at every decision point of the guidelines, participation in prospective clinical trials is a preferred option for the treatment of BTCs.

## Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Biliary Tract Cancers, an electronic search of the PubMed database was performed to obtain key literature in BTCs published since the previous Guidelines update, using the search terms: biliary tract cancer OR gallbladder cancer OR cholangiocarcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines as discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[2] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect

more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

## Gallbladder Cancer

Gallbladder cancer is the most common BTC. The vast majority of gallbladder cancers are adenocarcinomas.[3] Incidence steadily increases with age, females are more likely to be diagnosed with gallbladder cancer than males, and incidence and mortality rates in the United States are highest among males and females of American Indian and Alaska Native descent.[4] However, the incidence of gallbladder cancer has decreased in females but has gone up in Black individuals and those <45 years of age.[4,5] Globally, there are pockets of increased incidence in Korea; Japan; some areas of Eastern Europe and South America, especially Bolivia, Chile, and Spain; and in females in India, Pakistan, and Ecuador.[6-8] 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 CCA.[9]

### Risk Factors

Cholelithiasis with the presence of chronic inflammation is the most prevalent risk factor for gallbladder cancer, and the risk increases with stone size.[10,11] Calcification of the gallbladder wall (porcelain gallbladder), a result of chronic inflammation of the gallbladder, has also been regarded as a risk factor for gallbladder cancer, with historical estimates of cancer in up to 22% of gallbladders with calcification.[10] Some reports, however, suggest that the risk of developing gallbladder cancer in patients with gallbladder calcification is lower than anticipated, with gallbladder cancer being present in 7% to 15% of these patients.[12-14] Other risk factors include anomalous pancreaticobiliary duct junction, gallbladder polyps (>1 cm), chronic typhoid infection, primary sclerosing cholangitis, and inflammatory bowel disease.[11,15-17] Adenomyomatosis of the gallbladder is also a potential, albeit somewhat controversial, risk factor. Prophylactic cholecystectomy is probably beneficial for patients who are at high risk of developing gallbladder cancer (eg, porcelain gallbladder, polyps >1 cm).[10] Patients with a history of chronic cholecystitis or pancreaticobiliary maljunction have a greater prevalence of gallbladder cancers that are microsatellite instability-high (MSI-H).[18]

### Staging and Prognosis

In the AJCC staging system, gallbladder cancer is classified into four 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 8th edition of the AJCC staging system, T2 gallbladder carcinoma was divided into two groups: tumors on the peritoneal side (T2a) and tumors on the hepatic side (T2b).[19] This revision is supported by two retrospective studies showing that gallbladder tumors located on the hepatic side is associated with worse prognosis, compared to tumors located on the peritoneal side.[20,21] However, it is important to note that it can be difficult to determine the location of the tumor, and gallbladder cancer can spread beyond the visible tumor, contributing to difficulty in predicting tumor location. Regional lymph node involvement is now staged according to number of positive nodes, as opposed to staging based on anatomic location of involved lymph nodes.

Tumor stage is the strongest prognostic factor for patients with gallbladder cancer.[22,23] 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.[23] The median survival was 12.9 and 5.8 months for those presenting with stage IA–III and stage IV disease, respectively. It is important to note, however, that this retrospective analysis did not control well for treatment-related variables. [24]

## Diagnosis

Gallbladder cancer is often diagnosed at an advanced stage because it is often asymptomatic in its early stages and has an aggressive nature that can spread rapidly. Another factor contributing to late diagnosis of gallbladder cancer is a clinical presentation that mimics that of biliary colic or chronic cholecystitis. Hence, it is common for a diagnosis of gallbladder cancer to be an incidental finding at cholecystectomy for presumed benign gallbladder disease or, more frequently, on pathologic review following cholecystectomy for symptomatic cholelithiasis. In a retrospective review of 435 patients diagnosed and treated with curative resection at a single center from 1995 to 2005, 123 patients (47%) were diagnosed with gallbladder cancer as an incidental finding after laparoscopic cholecystectomy.[23] Other possible clinical presentations of gallbladder cancer include a suspicious mass detected on ultrasound (US) or biliary tract obstruction with jaundice or chronic right upper quadrant abdominal pain. The presence of jaundice in patients with gallbladder cancer is 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.[25] In a sample of 82 patients with gallbladder cancer who presented with jaundice, the resectability rate was low (7%), with even fewer having negative surgical margins (5%) and no disease-free survivors at 2 years.[25]

## Workup

The initial workup of patients presenting with a gallbladder mass or disease suspicious for gallbladder cancer should include liver function tests and an assessment of hepatic reserve. High-quality contrast-enhanced cross-sectional imaging (CT and/or MRI) of the chest, abdomen, and pelvis is recommended to evaluate tumor penetration through the wall of the gallbladder and the presence of nodal and distant metastases, and to detect the extent of direct tumor invasion of other organs/biliary system or major vascular invasion.[26] CT is more useful than US for the detection of lymph node involvement, adjacent organ invasion, and distant metastasis; MRI may be useful for distinguishing benign conditions from gallbladder cancer.[3] However, both techniques were unreliable in the detection of lymph node metastases that were smaller than 10 mm.[27] Although the role of PET scan has not been established in the evaluation of patients with gallbladder cancer, emerging evidence from retrospective studies indicates that it may be useful for the detection of radiologically occult regional lymph node and distant metastatic disease in patients with otherwise potentially resectable disease.[28,29,30,31] However, false positives related to an inflamed gallbladder are problematic.

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.[26]

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.[32] While CA 19-9 tends to have higher specificity (92.7% vs. 79.2% for CEA), its sensitivity tends to be lower (50% vs. 79.4% for CEA). However, these markers are not specific for gallbladder cancer and CA 19-9 could also be elevated in patients with jaundice from other causes. Therefore, the panel recommends carrying out these tests as part of a baseline assessment, and not for diagnostic purposes.

## Surgical Management

The surgical approach for the treatment of all patients with resectable gallbladder cancer is the same, with the exception that in patients with an incidental finding of gallbladder cancer on pathologic review, the gallbladder has been removed. Complete resection with negative margins remains the only potentially curative treatment for patients with gallbladder cancer.[33] The optimal resection consists of cholecystectomy with a limited hepatic resection (typically segments IVB and V) and portal lymphadenectomy to encompass the tumor with negative margins.[34] Lymphadenectomy should include lymph nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal regions without routine resection of the bile duct. Extended hepatic resections (beyond segments IV B and V) and resection of the bile duct may be necessary in some patients to obtain negative margins, depending on the stage and location of the tumor, depth of tumor invasion, proximity to adjacent organs, and expertise of the surgeon.

A simple cholecystectomy is an adequate treatment for patients with T1a tumors, with the long-term survival rate approaching 100%.[35] Cholecystectomy combined with hepatic resection and lymphadenectomy is associated with an improved survival for patients with T2 or higher tumors. There is some controversy regarding the benefit of radical resection over simple cholecystectomy for patients with T1b tumors, and there is some risk of finding residual nodal or hepatic disease when re-resecting these patients.[36-41] Some studies have demonstrated an associated improvement in cancer-specific survival for patients with T1b and T2 tumors and no improvement in survival for patients with T3 tumors.[37-39] Other reports suggest that survival benefit associated with extended resection and lymphadenectomy is seen only in patients with T2 tumors and some T3 tumors with localized hepatic invasion and limited regional node involvement.[40,41] One meta-analysis noted that regional lymphadenectomy was associated with prolonged survival in patients with T1b, T2, and T3 tumors.[42] Vega et al[43] reported an recurrence-free survival (RFS) rate of 47% at 5 years in patients with gallbladder cancer that was T1b or greater following oncologic extended resection. T3 and T4 disease were identified as independent risk factors for recurrence at 24 months post extended resection.

Empiric major hepatic resection and bile duct resection have been shown to increase morbidity without any demonstrable difference in survival.[34,44] Bile duct resection was also not associated with a higher lymph node yield.[45] A retrospective analysis of prospective data collected on 104 patients undergoing surgery for gallbladder cancer from 1990 to 2002 showed that in a multivariate analysis, higher T and N stage, poor differentiation, and common bile duct involvement were independent predictors of poor disease-specific survival.[44] Major hepatectomy and common bile duct excision significantly increased overall perioperative morbidity (53%) and were not independently associated with long-term survival.[44] Fuks et al from the AFS-GBC-2009 study group also reported that bile duct resection resulted in a postoperative morbidity rate of 60% in patients with an incidental finding of gallbladder cancer.[34] However, for these patients, it has been suggested that common duct resection should be performed at the time of re-resection for those with positive cystic duct margins due to the presence of residual disease.[46] However, occasionally the cystic duct stump can be re-resected to a negative margin.

With these data in mind, the guidelines recommend that extended hepatic resections (beyond segments IV B and V) should be performed only when necessary to obtain negative margins (R0 resection) in well-selected clinical situations as discussed above.[37,39-41] Bile duct excision should only be performed in the presence of adherent nodal disease and/or locally invasive disease or to obtain a negative cystic duct margin if necessary.[44]

Among patients with an incidental finding of gallbladder cancer, there is some evidence that a delayed resection due to referral to a tertiary cancer

center or a radical resection following an initial noncurative procedure is not associated with a survival deficit compared with immediate resection.[47,48] However, these comparisons are difficult to interpret due to selection bias. Nevertheless, in all patients with convincing clinical evidence of gallbladder cancer, the guidelines recommend that surgery can be performed by an experienced surgeon who is prepared to do a definitive resection of the tumor. If malignancy is suspected or confirmed after cholecystectomy has been initiated and expertise is available, then definitive resection should be undertaken. If expertise is unavailable, patients should be referred to a center with available expertise. If the diagnosis is not clear, frozen section biopsies can be considered in selected cases before proceeding with definitive resection. 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 with good quality imaging. If malignancy is suspected before cholecystectomy has begun and there is a question of resectability (ie, locally advanced disease, possible metastatic disease, other), then definitive resection can be postponed regardless of available expertise, until complete staging and evaluation has been performed. All findings should be documented, and biopsy considered if chemotherapy is anticipated. The optimal diagnostic method is core needle biopsy. Consultation with a pathologist with expertise in the hepatobiliary region should be considered, and careful review of the pathology report for T stage, cystic duct margin status, and other margins following surgery is crucial. If an imaging study shows a suspicious gallbladder mass, then the patient should be referred to an experienced center where they may be considered for upfront definitive resection.

### Management of Resectable Disease

All patients should undergo cross-sectional imaging (CT and/or MRI) of the chest, abdomen, and pelvis prior to surgery to evaluate local extent of disease and the presence of distant metastases. Staging laparoscopy has been shown to identify radiographically occult disseminated disease in patients with primary gallbladder cancer.[49] In a prospective study that evaluated the role of staging laparoscopy in 409 patients diagnosed with primary gallbladder cancer, Agarwal et al reported a significantly higher yield in locally advanced tumors compared with early-stage tumors (25.2% vs. 10.7%; $P = .02$); the accuracy for detecting unresectable disease and a detectable lesion in locally advanced tumors (56.0% and 94.1%, respectively) was similar to that in early-stage tumors (54.6% and 100%, respectively).[49] In this study, the use of staging laparoscopy obviated the need for laparotomy in 55.9% of patients with unresectable disease. Staging laparoscopy, however, is of relatively low yield in patients with incidental finding of gallbladder cancer, since disseminated disease is relatively uncommon, and the patients have already had an assessment of their peritoneal cavity at the time of cholecystectomy.[50] 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).[50]

In patients with a suspicious gallbladder mass discovered during surgery, a definitive resection with cholecystectomy and en bloc hepatic resection and lymphadenectomy is recommended when hepatobiliary surgery is available. In cases where a suspicious gallbladder mass is discovered during surgery, but hepatobiliary expertise is unavailable or resectability is unclear, the abdomen should be visually inspected, and all findings should be documented. Intraoperative staging, with or without biopsy, is recommended. The surgery should be ended and the patient should be referred to a specialist. Additional postoperative workup is recommended. Contraindications for resection include tumors with distant lymph node metastases beyond the porta hepatis (most commonly the celiac axis or aortocaval groove [retropancreatic]) or distant metastatic disease (ie, most commonly liver and peritoneal cavity). Additionally, some tumors are unresectable based on local invasion of the porta hepatis and its vascular and biliary structures.

Among patients with an incidental finding of gallbladder cancer on pathologic review, those with T1a lesions may be observed if the tumor margins are negative since these tumors have not penetrated the muscle layer and long-term survival approaches 100% with simple cholecystectomy.[35] In a sample of 122 patients with gallbladder cancer diagnosed incidentally, identified in a prospectively maintained database, liver involvement at re-resection (after cholecystectomy) was associated with decreased RFS and disease-specific survival for patients with T2 tumors (median RFS was 12 months vs. not reached for patients without liver involvement, *P* = .004; median was 25 months vs. not reached for patients without liver involvement, *P* = .003) but not in patients with T1b tumors.[24]

As mentioned above, hepatic resection and lymphadenectomy with or without bile duct excision (for malignant involvement) is recommended for patients with T1b or greater lesions and/or with T1a lesions with positive margins.[37,39,40] Re-resection to achieve negative margins is recommended for these patients with incidental gallbladder cancer since a significant percentage of these patients have been found to harbor residual disease within the liver and common bile duct.[23,46] Furthermore, although randomized trials are lacking, re-resection is generally associated with improved OS compared to cholecystectomy alone. Port site disease is associated with disseminated peritoneal metastases, and prophylactic port site resection is not associated with improved survival or disease recurrence in patients with incidental findings of gallbladder cancer and, thus, should not be considered during definitive resection.[51,52]

For patients with a suspicious mass detected on imaging, the guidelines recommend cholecystectomy plus en bloc hepatic resection, and lymphadenectomy, with or without bile duct excision (for malignant involvement). A biopsy is not necessary in most cases and a diagnostic laparoscopy is recommended prior to definitive resection.[49] Jaundice in patients with gallbladder cancer is considered a relative contraindication to surgery, and outcomes are generally poor in these patients; only a rare group of patients with localized node-negative disease potentially benefit from complete resection.[25,53-55] In patients with jaundice, if gallbladder cancer is suspected, surgery should only be performed if a complete resection is feasible. These patients should be carefully evaluated prior to surgery and referral to an experienced center should be considered. The guidelines recommend consideration of preoperative biliary drainage for patients with jaundice. However, caution should be exercised in patients with biliary obstruction as drainage is not always feasible and can be dangerous. Decisions regarding biliary drainage should be made by a multidisciplinary team.

Although there are limited clinical trial data to define a standard regimen or definitive benefit, the panel recommends consideration of a course of neoadjuvant chemotherapy for patients with jaundice. Gallbladder cancer that is locally advanced or has lymph node involvement is associated with a poor prognosis, but neoadjuvant chemotherapy may allow the oncologist to evaluate the biology of the tumor and identify patients who are most likely to benefit from surgical intervention. A systematic review of eight studies found that approximately one third of the 474 patients achieved an R0 resection with the use of neoadjuvant chemotherapy or chemoradiotherapy.[56] In a retrospective analysis of 74 patients with locally advanced or lymph node-positive disease who received systemic therapy, 30% of patients underwent resection.[57] Out of the 22 patients who underwent resection, 45% underwent definitive resection, with OS being significantly greater for patients who underwent definitive resection compared to those who did not (51 vs. 11 months, respectively; *P* = .003). Another study reported a response rate of 52.5% and a clinical benefit rate of 70% in 160 patients with gallbladder cancer treated with neoadjuvant chemotherapy. 41.2% of patients underwent resection with curative intent.[58] These patients had a significantly improved OS (49 vs. 7 months; *P* =

.0001) and event-free survival (25 vs. 5 months; *P* = .0001) compared to those who did not undergo resection. A phase III randomized study is underway to compare neoadjuvant chemotherapy versus neoadjuvant chemoradiation in patients with locally advanced gallbladder cancer (NCT02867865).[59]

In patients for whom there is evidence of locoregionally advanced disease (ie, nodal disease or evidence of other high-risk disease), neoadjuvant chemotherapy should be considered to rule out rapid progression and avoid futile surgery. The decision to use neoadjuvant therapy needs to be individualized and in close consultation with a surgical oncologist and a multidisciplinary team. A period of 2 to 6 months with reassessment every 2 to 3 months is reasonable. The following regimens, whose efficacy was extrapolated from clinical trials in the metastatic disease setting, may be used for gallbladder cancer in the neoadjuvant setting: FOLFOX, capecitabine/oxaliplatin, gemcitabine/capecitabine, gemcitabine/cisplatin, durvalumab/gemcitabine/cisplatin, and gemcitabine/cisplatin/albumin-bound paclitaxel (category 2B). The panel currently does not recommend neoadjuvant chemoradiation for these patients, although a prospective study including 28 patients with locally advanced gallbladder cancer showed that an R0 resection was achieved in 14 patients, with good local control (93%) and 5-year survival (47%), following treatment with gemcitabine with concurrent radiation therapy (RT).[60]

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

### Management of Unresectable or Metastatic Disease

Preoperative evaluation and a biopsy to confirm the diagnosis is recommended for patients with unresectable (includes tumors with distant lymph node metastases in the celiac axis or 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). Additional molecular testing is recommended. Primary options for these patients include: 1) systemic therapy; 2) clinical trial; or 3) best supportive care. In addition, palliative RT is included as an option for patients with unresectable disease. Systemic therapy or enrollment in a clinical trial are preferred options. See sections on *Chemotherapy* and *Chemoradiation and Radiation Therapy* for *Treatment for Advanced Biliary Tract Cancers*.

In patients with unresectable or metastatic gallbladder cancer and jaundice, biliary drainage is an appropriate palliative procedure and should be considered before instituting resection and systemic therapy if technically feasible.[53] However, caution should be exercised in patients with biliary obstruction as drainage is not always feasible and can be dangerous. Decisions regarding biliary drainage should be made by a multidisciplinary team. Biliary drainage followed by chemotherapy can result in improved quality of life. CA 19-9 testing can be considered after biliary decompression.

### Surveillance

There are no data to support a specific surveillance schedule or tests following resection of gallbladder cancer; determination of appropriate follow-up schedule/imaging should include a careful patient/physician discussion. Follow-up of patients undergoing an extended cholecystectomy for gallbladder cancer should include consideration of imaging studies every 3 to 6 months for 2 years, then annually up to 5 years or as clinically indicated. Assessment of CEA and CA 19-9 may also be considered as clinically indicated. Re-evaluation according to the initial workup should be considered in the event of disease relapse or progression.

## Cholangiocarcinomas

Cholangiocarcinomas encompass all tumors originating in the epithelium of the bile duct. More than 90% of CCAs are adenocarcinomas and are broadly divided into three histologic types based on their growth patterns: mass-forming, periductal-infiltrating, and intraductal-growing.[61] CCAs are diagnosed throughout the biliary tree and are typically classified as either intrahepatic or extrahepatic CCA. Extrahepatic CCAs are more common than intrahepatic CCAs. Analyses of SEER data from 1973 to 2012 showed that incidence of intrahepatic CCA increased dramatically, while incidence of extrahepatic CCA increased at a slower rate.[62,63] The increase in incidence of intrahepatic CCA may have been due to an improvement in the ability to accurately diagnose intrahepatic CCA, such as with imaging, molecular diagnostics, and pathology.[62] These cancers might have previously been diagnosed as cancers of unknown primary, in which incidence decreased from 1973 to 2012 [annual percentage change (APC), -1.87%].[62] Five-year OS rates for CCA improved from 1973 to 2008, likely due to improvements in treatment for this disease.[63]

Intrahepatic CCAs are located within the hepatic parenchyma and have also been called “peripheral CCAs” (Figure 1). Extrahepatic CCAs occur anywhere within the extrahepatic bile duct—from the junction of the right and left hepatic ducts to the common bile duct, including the intrapancreatic portion (Figure 1)—and are further classified into hilar or distal tumors. Hilar CCAs (also called Klatskin tumors) occur at or near the junction of the right and left hepatic ducts; distal CCAs are extrahepatic lesions arising in the extrahepatic bile ducts above the ampulla of Vater and below the confluence of the left and right bile ducts.[64] Hilar CCAs are the most common type of extrahepatic CCAs.

The NCCN Guidelines discuss the clinical management of intra- and extrahepatic CCAs including hilar CCA and the distal bile duct tumors. Tumors of the ampulla of Vater are not included in the NCCN Guidelines for Biliary Tract Cancers.

### Risk Factors

No predisposing factors are identified in most patients diagnosed with CCA,[65] although there is evidence that particular risk factors may be associated with the disease in some patients. These risk factors, like those for gallbladder cancer, are associated with the presence of chronic inflammation. Primary sclerosing cholangitis, chronic calculi of the bile duct (hepatolithiasis), choledochal cysts, and liver fluke infections are well-established risk factors for CCA. Unlike gallbladder cancer, however, cholelithiasis is not thought to be linked with CCA.[66] Inflammatory bowel disease may also be a risk factor for CCA, although this association may be confounded by primary sclerosing cholangitis.[67] Other risk factors for intrahepatic CCA, which tends to be similar to HCC, have been found to include hepatitis B virus (HBV) infection, cirrhosis, diabetes, obesity, alcohol, and tobacco.[68] A systematic review and meta-analysis reported that the strongest risk factors for both intrahepatic and extrahepatic CCA included biliary cysts and stones, cirrhosis, HBV, and hepatitis C virus.[69] This may be responsible for the increased incidence of intrahepatic CCA observed at some centers, although future studies are needed to further explore this putative association.[70] A systematic review including seven case-control studies (9102 patients and 129,111 controls) showed that non-alcoholic fatty liver disease is associated with increased incidence of both intrahepatic (pooled adjusted OR, 2.09; 95% CI, 1.49–2.91) and extrahepatic CCA (pooled adjusted OR, 2.05; 95% CI, 1.59–2.64).[71]

### Staging and Prognosis

#### *Intrahepatic Cholangiocarcinoma*

In the 6th edition of the AJCC staging system, intrahepatic CCA 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 CCA.[72] In some reports, tumor size had no effect on survival in patients undergoing complete resection.[73,74] In a SEER database analysis of 598 patients with intrahepatic CCA who had undergone surgery, Nathan et al reported that multiple lesions and vascular invasion predicted adverse prognosis following resection; lymph node status was of prognostic significance among patients without distant metastases.[73] 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 CCA.[74] The 5-year survival rate was higher for patients who lacked all three 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 a multivariate analysis.

In the revised 7th edition of the AJCC staging system, intrahepatic CCA had a new staging classification that was independent of the staging classification used for HCC.[75] This classification focused on multiple tumors, vascular invasion, and lymph node metastasis. Farges et al from the AFC-IHCC study group validated this staging classification in 163 patients with resectable intrahepatic CCA.[76] 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).

In the revised 8th edition of the AJCC staging system, T1 disease (ie, solitary tumor without vascular invasion) should now be staged according to tumor size (ie, T1a refers to a tumor that is ≤5 cm, while T1b refers to a tumor that is >5 cm).[19] T2 disease, on the other hand, is no longer divided into T2a (solitary tumor with vascular invasion) and T2b (multiple tumors with or without vascular invasion) disease.

***Extrahepatic Cholangiocarcinoma***

The 7th edition of the AJCC staging system included a separate TNM classification for hilar and distal extrahepatic CCA, based on the extent of liver involvement and distant metastatic disease.[75] In the revised 8th edition of the AJCC staging system, regional lymph node involvement is now staged according to number of positive nodes.[19] Depth of tumor invasion is an independent predictor of outcome in patients with distal as well as hilar CCAs.[77,78] In the revised 8th edition of the AJCC staging system for cancer of the distal bile duct, depth of tumor invasion has been added to the categorization of T1, T2, and T3 tumors.[19]

The modified Bismuth-Corlette staging system[79] and the Blumgart staging system[80] are used for the classification of hilar CCAs. The modified Bismuth-Corlette staging system classifies hilar CCAs into four types based on the extent of biliary involvement. However, this does not include other clinicopathologic features such as vascular encasement, lymph node involvement, distant metastases, and liver atrophy. In addition, both the AJCC and the Bismuth-Corlette staging systems are not useful for predicting resectability or survival. The Blumgart staging system is a useful preoperative staging system that predicts resectability, likelihood of metastatic disease, and survival.[80,81] In this staging system, hilar CCAs are classified into three stages (T1–T3) based on the location and extent of bile duct involvement, the presence or absence of portal venous invasion, and hepatic lobar atrophy.[80] Negative histologic margins, concomitant partial hepatectomy, and well-differentiated tumor histology were associated with improved outcome after resection; increasing T stage significantly correlated with reduced R0 resection rate, distant metastatic disease, and lower median survival.[81]

## Diagnosis

Early-stage CCA may only manifest as mild changes in serum liver function tests. Patients with intrahepatic CCA, due to their often late presentation, are more likely to present with nonspecific symptoms such as fever, weight loss, and/or abdominal pain; symptoms of biliary obstruction are uncommon because these tumors do not necessarily involve the common hepatic/bile duct. Intrahepatic CCA may be detected incidentally as an isolated intrahepatic mass on imaging.[82] In contrast, patients with extrahepatic CCA are likely to present with jaundice followed by evidence of a biliary obstruction or abnormality on subsequent imaging.

## Workup

The initial workup should include liver function tests. CEA and CA 19-9 testing can be considered for baseline assessment, although these markers are not specific for CCA; they are also associated with other malignancies and benign conditions.[83] CA 19-9 may be falsely elevated due to jaundice.[84] Viral hepatitis serologies should be considered for intrahepatic CCA. If hepatitis is diagnosed, it needs to be monitored and managed following ASCO's guidelines.[85] Since the diagnosis of HCC versus intrahepatic CCA can be difficult, alpha-fetoprotein (AFP) testing may also be considered, especially in patients with chronic liver disease. Further, there are a number of mixed HCC/intrahepatic CCA cases in which AFP may be elevated. Liver Imaging Reporting and Data System provides some guidance in distinguishing between HCC and intrahepatic CCA lesions.[86]

Early surgical consultation (prior to drainage in patients with jaundice) with a multidisciplinary team is recommended as part of the initial workup for assessment of resectability in intrahepatic and extrahepatic CCAs. The panel emphasizes that a multidisciplinary review of imaging studies involving experienced radiologists and surgeons is necessary to stage the disease and determine potential treatment options (ie, resection or other approach). Providers should only proceed with biopsy once transplant (for patients with extrahepatic CCA) or resectability status has been determined. For patients with hilar CCA who may be candidates for transplant, transperitoneal biopsy is contraindicated and will likely preclude transplantation based on current protocols.[87] The optimal diagnostic method is core needle biopsy. For patients undergoing resection, biopsy is usually not necessary.

In patients with unresectable disease, direct visualization of the bile duct with directed biopsies is the ideal technique for the workup of CCA. Multiphasic CT/MRI with IV contrast of the abdomen and pelvis to assess the involvement of the liver, major vessels, nearby lymph nodes, and distant sites is also recommended when extrahepatic CCA is suspected.[88,89] There are no pathognomonic CT/MRI features associated with intrahepatic CCA, but CT/MRI can indicate the involvement of major vessels and the presence of vascular anomalies and satellite lesions.[88] Therefore, multiphasic CT/MRI with IV contrast is used to help determine tumor resectability by characterizing the primary tumor, its relationship to nearby major vessels and the biliary tree, the presence of satellite lesions and distant metastases in the liver, and lymph node involvement.[82,88] In addition, chest CT (with or without contrast) should be performed, and staging laparoscopy may be considered in conjunction with surgery if no distant metastasis is found. The American College of Radiology has published recommendations for liver MRI.[90] Endoscopic US may be useful for distal common bile duct cancers for defining a mass or abnormal thickening, which can direct biopsies. For hilar CCA, endoscopic US should only be done after surgical consultation to prevent jeopardizing a patient's candidacy for transplantation. Esophagogastroduodenoscopy and colonoscopy are recommended as part of initial workup for patients with intrahepatic CCA since a mass diagnosed as adenocarcinoma can be metastatic disease. Pathologic workup can be suggestive of CCA but is not definitive. IgG4-associated cholangitis, which presents with biliary strictures

and obstructive jaundice, may mimic extrahepatic CCA.[91,92] Therefore, serum IgG4 should be considered in patients for whom a diagnosis of extrahepatic CCA is not clear, in order to avoid an unnecessary surgical resection.[93,94] Patients with IgG4-related cholangiopathy should be referred to an expert center.

Contrast-enhanced MRCP and/or CT as a diagnostic modality is recommended over direct cholangiography for the diagnosis of bile duct cancers.[95,96] MRCP has been shown to have a higher sensitivity, specificity, and diagnostic accuracy compared to ERCP in the diagnosis and pre-treatment staging of hilar CCAs.[97] Data also support the use of MRCP and CT as the preferred method of cholangiography for the assessment of bile duct tumors.[98] Direct cholangiography should only be performed when necessary as a diagnostic procedure in patients with unresectable disease or in patients in whom a therapeutic intervention is necessary. ERCP/PTC is not recommended for the diagnosis of extrahepatic CCA, since this is associated with complications and contamination of the biliary tree. For distal bile duct tumors in which a diagnosis is needed or where palliation is indicated, an ERCP allows for complete imaging of the bile duct and stenting of the obstruction. In addition, brush cytology of the bile duct can be obtained for pathologic evaluation. Since many of the patients with extrahepatic CCA present with jaundice, workup should include noninvasive cholangiography with cross-sectional imaging to evaluate local tumor extent.[88] Although the role of PET imaging has not been established in the evaluation of patients with CCA, 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.[28-30,99,100]

### Management of Intrahepatic Cholangiocarcinoma

Complete resection is the only potentially curative treatment for patients with resectable disease, although most patients are not candidates for surgery due to the presence of advanced disease at diagnosis. The optimal surgical margin associated with improved survival and reduced risk of recurrence in patients undergoing surgery remains uncertain, with some reports documenting R0 resection as a significant predictor of survival and recurrence,[101-106] while others suggest that margin status is not a significant predictor of outcome.[107,108] Ribero et al from the Italian Intrahepatic Cholangiocarcinoma Study Group reported that margin-negative resection was associated with significantly higher survival rates (the estimated 5-year survival rates were 39.8% vs. 4.7% for patients with a positive margin) and significantly lower recurrence rates (53.9% vs. 73.6% for those with a positive margin); however, in patients resected with negative margins, the margin width had no long-term impact on survival ($P$ = .61) or recurrence ($P$ > .05) following resection.[106] Farges et al from the AFC-IHCC-2009 study group reported that although R1 resection was the strongest independent predictor of poor outcome in pN0 patients undergoing surgery, its prognostic impact on survival was very low in pN+ patients (median survival was 18 months and 13 months, respectively, after R0 and R1 resections; $P$ = .10).[108] In this study, a margin width greater than 5 mm was an independent predictor of survival among pN0 patients with R0 resections, which is in contrast to the findings reported by Ribero et al.[106] A retrospective analysis of 535 patients with intrahepatic CCA who underwent resection showed that other factors associated with worse survival post-resection include multifocal disease (hazard ratio [HR], 1.49; 95% CI, 1.19–1.86; $P$ = .01), lymph node metastasis (HR, 2.21; 95% CI, 1.67–2.93; $P$ < .01), and vascular invasion (HR, 1.39; 95% CI, 1.10–1.75; $P$ = .006).[109]

Available evidence (although not conclusive) supports the recommendation that hepatic resection with negative margins should be the goal of surgical therapy for patients with potentially resectable disease.[110] Extensive hepatic resections are often necessary to achieve clear margins since the majority of tumors present as large masses.[106]

Initial surgical exploration should include assessment of multifocal liver disease, lymph node metastases, and distant metastases.[111] Multifocal liver disease, distant (beyond the porta hepatis) nodal metastases, and distant metastases contraindicate surgery as these generally indicate advanced incurable disease. In highly selected situations, resection can be considered. A preoperative biopsy is not always necessary prior to definitive and potentially curative resection. Although limited multifocal liver tumors (including satellite lesions) and gross lymph node metastases to the porta hepatis are considered relative contraindications to surgery, surgical approaches can be considered in selected patients. Minimally invasive approaches in experienced hands have been proven to be safe and effective.[112,113] Patient selection for surgery is facilitated by careful preoperative staging, which may include laparoscopy to identify patients with unresectable or disseminated metastatic disease.[114,115] Staging laparoscopy has been shown to identify peritoneal metastases and liver metastases with a respective yield of 36% and 67% accuracy in patients with potentially resectable intrahepatic CCA.[114] A portal lymphadenectomy helps provide accurate staging information.[116] Lymph node metastasis is an important prognostic indicator of survival.[74,106] Therefore, regional lymphadenectomy of the porta hepatis is recommended. It is important to note, however, that there are no data to support a therapeutic benefit of routine lymph node dissection in patients undergoing surgery.[117-120] One study determined that neoadjuvant chemotherapy resulted in higher OS (HR, 0.16; *P* = .01) but did not impact RFS (HR, 0.54; *P* = .27) in patients undergoing hepatic resection.[121] Another study found no difference in survival both in an unadjusted analysis (*P* = .51) and in a propensity score-matched analysis (HR, 0.78; *P* = .16).[122] However, the data suggest that patients with stage II–III intrahepatic CCA may have a survival benefit from neoadjuvant therapy (unadjusted analysis *P* = .10; propensity-score matched analysis HR, .58; *P* = .02)

The optimal adjuvant treatment strategy for patients with resected intrahepatic CCA has not been determined and there are limited clinical trial data to support a standard regimen for adjuvant treatment. Lymphovascular and perineural invasion, lymph node metastasis, and tumor size greater than or equal to 5 cm have been reported as independent predictors of recurrence and reduced OS following resection.[123-125] Since recurrence following resection is common, these tumor-specific risk factors could be considered as criteria for selection of patients for adjuvant treatment in clinical trials. See *Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers* in this discussion.

Primary treatment options for patients with unresectable or metastatic disease include: 1) systemic therapy; 2) clinical trial; or 3) consideration of locoregional therapy (RT or arterially directed therapies); or 4) best supportive care. In addition, RT with concurrent fluoropyrimidine is included as an option for patients with unresectable disease. Systemic therapy or enrollment in a clinical trial are preferred options for patients with metastatic intrahepatic CCA. See sections on *Chemotherapy* and *Chemoradiation and Radiation Therapy* for *Treatment for Advanced Biliary Tract Cancers* in this discussion.

***Locoregional Therapy***

Locoregional therapies such as radiofrequency ablation,[126,127] transarterial chemoembolization (TACE),[128-130] TACE with drug-eluting beads (DEB-TACE), or TACE drug-eluting microspheres,[129,131,132] and radioembolization (TARE) with Y-90 microspheres[130,133-138] have been shown to be safe and effective in a small retrospective series of patients with unresectable intrahepatic CCAs. The results of two independent prospective studies showed that the efficacy of TACE with irinotecan DEB was similar to that of gemcitabine and oxaliplatin (GEMOX), but was superior to that of TACE with mitomycin in terms of progression-free

survival (PFS) and OS for patients with unresectable intrahepatic CCA.[129] In a systematic review of 12 studies with 298 patients, the effects of radioembolization with Y-90 microspheres in unresectable intrahepatic CCA were assessed.[139] The overall weighted median survival for this treatment was 15.5 months, partial tumor response was seen for 28% of patients, and stable disease (SD) was seen for 54% of patients. Another systematic review and meta-analysis of 21 studies with 921 patients reported an overall disease control rate of 82.3% in patients with unresectable intrahepatic CCA treated with radioembolization with Y-90.[140] The median OS and PFS were 12.7 months and 7.8 months, respectively. Other smaller series have also reported favorable response rates and survival benefit for patients with unresectable intrahepatic CCA treated with TARE with Y-90 microspheres.[133,136,138] Due to the rarity of this disease, none of these locoregional approaches has been evaluated in randomized controlled trials (RCTs). In the phase II MISPHEC trial, investigators determined that the combination of radioembolization with Y-90 microspheres with chemotherapy (cisplatin and gemcitabine) as a first-line treatment option in 41 patients with unresectable intrahepatic CCA resulted in a 39% response rate, by RECIST criteria.[141] The median PFS and OS were 14 months and 22 months, respectively. Additionally, 22% of patients were downstaged to surgery.

Consideration of RT is a locoregional treatment option for unresectable intrahepatic CCA.[142] A single-institution study including 79 patients with unresectable intrahepatic CCA showed that higher doses of RT (3D conformal RT [3D-CRT] with photons or protons) were associated with better 3-year OS (73% vs. 38%, respectively; $P = .017$) and 3-year local control (78% vs. 45%, respectively; $P = .04$), compared with lower doses of RT.[143] Stereotactic body RT (SBRT) may also be used for patients with unresectable intrahepatic CCA.[144] A non-randomized multi-institutional trial including 39 patients with unresectable intrahepatic CCA showed that hypofractionated proton therapy resulted in a 2-year OS rate of 46.5% (median OS, 22.5 months) and a 2-year PFS rate of 25.7%.[145] Another multi-institutional trial reported a local control rate of 90.9% and an OS rate of 81.8% at 1 year for patients with intrahepatic CCA treated with hypofractionated proton beam therapy.[146] Hypofractionated photon[143] or proton therapy[145] is an acceptable option for patients with unresectable intrahepatic CCA, although treatment at centers with experience is recommended. RT dosing depends on the ability to meet normal organ constraints and underlying liver function. The dosing for hypofractionation for unresectable disease is 58 to 67.5 Gy in 15 fractions for a median biologic equivalent dose of 80.5 Gy.[143,145]

Data from prospective studies support the use of hepatic arterial infusion (HAI) chemotherapy in patients with advanced, liver-confined, and unresectable intrahepatic CCA.[147-151] In a meta-analysis including 20 studies ($N = 657$), HAI was compared to TACE, DEB-TACE, and TARE with Y-90 microspheres.[152] OS and tumor response were greatest for HAI, with a median tumor response rate of 57%, although grade III/IV toxicity was also highest, relative to the other arterially directed therapies. A retrospective analysis of 525 patients with intrahepatic CCA showed that patients who received a combined regimen of HAI and another chemotherapy agent (gemcitabine, irinotecan, or 5-FU) had greater OS, relative to patients receiving chemotherapy without HAI (30.8 vs. 18.4 months; $P < .001$).[153]

Based on the available evidence as discussed above, the panel has included locoregional therapy as a treatment option that may be considered for patients with unresectable disease or metastatic cancer without extrahepatic disease. Intra-arterial chemotherapy is recommended only in the context of a clinical trial or at experienced centers in carefully selected cases for patients with advanced disease confined to the liver.

## Management of Extrahepatic Cholangiocarcinoma

Complete resection with negative margins is the only potentially curative treatment for patients with resectable disease. The reported 5-year survival rates following complete resection are in the range of 20% to 42% and 16% to 52%, respectively, for patients with hilar and distal CCAs.[154,155]

Surgical margin status and lymph node metastases are independent predictors of survival following resection.[105,156,157] Regional lymphadenectomy of the porta hepatis (hilar CCA) or in the area of the head of the pancreas (distal CCA) are considered standard parts of curative resections.[158,159] Since these surgical procedures are associated with postoperative morbidity, they should be carried out in patients who are medically fit for a major operation. Surgery is contraindicated in patients with distant metastatic disease to the liver, peritoneum, or distant lymph nodes beyond the porta hepatis (or head of the pancreas for distal tumors).

The type of surgical procedure for a resectable tumor is based on its anatomic location in the biliary tract. Resection of the involved biliary tract and en bloc liver resection (typically a major hepatectomy involving the right or left liver with the caudate lobe) is recommended for hilar tumors. Bile duct excision with frozen section assessment of proximal and distal bile duct margins and pancreaticoduodenectomy can be attempted for mid bile duct tumors not involving the liver or pancreas. However, mid bile duct tumors that can be completely resected with an isolated bile duct resection are uncommon. A combined pancreaticoduodenectomy and hepatic resection is required, in rare instances, for a bile duct tumor with extensive biliary tract involvement. This operation, however, is associated with high morbidity and should only be considered in well-selected cases.[160,161] Combined hepatic and pancreatic resections to clear distant nodal disease (as opposed to biliary extent) are not recommended, as these are highly morbid procedures with no obvious associated survival advantage. The guidelines recommend consideration of biliary drainage prior to definitive resection for patients with jaundice prior to instituting systemic therapy. However, caution should be exercised in patients with hilar biliary obstruction as drainage is not always simple and can be associated with significant morbidity.[162] Decisions about whether preoperative biliary drainage is appropriate (and the type of drainage) should be made by a multidisciplinary team at a high-volume center.

In patients with hilar CCA, extended hepatic resection (to encompass the biliary confluence) with caudate lobectomy is recommended, since hilar tumors, by definition, abut or invade the central portion of the liver. The recommendation for extended liver resection is supported by retrospective analyses showing a higher rate of R0 resection, prolonged survival, and decreased hepatic recurrence associated with extended hepatic resections as compared to bile duct resections.[163-167] Resection and reconstruction of the portal vein and/or hepatic artery may be necessary for complete resection, especially in patients with more advanced disease. This approach requires substantial experience and appropriate surgical support for such technical operations.[168,169] For adjuvant treatment of resected hilar CCA, see the section on *Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers*.

Patient selection for surgery is facilitated by careful preoperative staging, surgical exploration, biopsy, and consideration of diagnostic laparoscopy to identify patients with unresectable or distant metastatic disease. A preoperative biopsy is not necessary if the index of suspicion is high. Laparoscopy can identify the majority of patients with occult metastatic hilar CCA, albeit with a lower yield. A review including six studies of staging laparoscopy in patients with hilar CCA showed a yield of 14% to 45% and an accuracy of 32% to 71%.[170] The decreasing yield of staging laparoscopy over time may be due to improvements in imaging techniques.[171]

While not routinely used in all patients undergoing resection, the consensus of the panel is that in patients with hilar CCA, preoperative treatments

including biliary drainage targeted to the future liver remnant (FLR) (using ERCP or PTC)[172-175] and contralateral PVE[176,177] should be considered for patients with low FLR volumes. Patients with unresectable or metastatic disease should be considered for biliary drainage using either surgical bypass (although rarely used) or ERCP or PTC, most often involving biliary stent placement.[178-181]

In patients with unresectable or metastatic disease, biopsy is recommended to confirm the diagnosis prior to the initiation of further treatment. The optimal diagnostic method is core needle biopsy. For patients with unresectable disease, biopsy is recommended only after determining transplant status. Molecular testing is recommended to potentially guide targeted treatment. Primary treatment options for these patients include: 1) systemic therapy; 2) clinical trial; or 3) best supportive care. In addition, RT with concurrent fluoropyrimidine or palliative RT are also included as options for patients with unresectable disease. Data to support particular chemoradiation and chemotherapy regimens are limited. See sections on *Chemotherapy* and *Chemoradiation and Radiation Therapy* for *Treatment of Advanced Biliary Tract Cancers*.

Liver transplantation is a potentially curative option for selected patients with lymph node-negative, non-disseminated, locally advanced hilar CCAs.[182-185] There is retrospective evidence suggesting that neoadjuvant chemoradiation followed by liver transplantation is effective for selected patients with hilar CCA.[186-188] Results from two studies suggest that the combination of liver transplantation and neoadjuvant and/or adjuvant chemoradiation is associated with higher RFS than a potentially curative resection.[189,190] However, in one of these studies, there were substantial differences in the characteristics of patients in the two treatment groups.[189] It is important to note that many of these reports include patients with primary sclerosing cholangitis, and some have not had a definitive histologic cancer diagnosis. Liver transplantation should be considered only for highly selected patients (ie, tumor ≤3 cm in radial diameter, no intrahepatic or extrahepatic metastases, no nodal disease) with either unresectable disease with otherwise normal biliary and hepatic function or underlying chronic liver disease precluding surgery. The panel encourages continuation of clinical research in this area, and referral of patients with unresectable disease to a transplant center with a United Network for Organ Sharing-approved protocol for transplant of CCA should be considered.

Photodynamic therapy (PDT) is an ablative therapy that involves intravenous injection of a photosensitizing drug followed by selective irradiation with light of a specific wavelength to initiate localized drug activation, and has been used for palliation in patients with extrahepatic CCA. The combination of PDT with biliary stenting was reported to be associated with prolonged OS in patients with unresectable CCA in two small RCTs.[191,192]

### Surveillance

There are no data to support a specific surveillance schedule or tests in patients undergoing resection of CCA; 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 CCA should include consideration of imaging studies every 3 to 6 months for 2 years, then annually for up to 5 years. Re-evaluation according to the initial workup should be considered in the event of disease progression.

## Adjuvant Chemotherapy and Chemoradiation for Biliary Tract Cancers

Recurrence following surgery is a primary limitation for cure in patients with BTCs and provides an important justification for the use of adjuvant therapy, which can be given for up to 6 months. In a sample of 80 patients

with extrahepatic CCA who underwent resection, 48.8% died of disease by 28 months, while 11.3% died of other causes.[80] The role of adjuvant chemotherapy or chemoradiation therapy in patients with resected BTCs is poorly defined, with a lack of data from phase III RCTs.[193,194] Due to the low incidence of BTCs, the efficacy and safety of adjuvant chemotherapy or chemoradiation therapy in these patients have been evaluated mostly in retrospective studies that have included only a small number of patients. Further, these studies often combined patients with gallbladder and bile duct cancers (with a few exceptions), which is problematic since the biology of these tumors is completely different. Despite the challenges associated with the accrual of large numbers of patients with BTC for randomized phase III trials, it is widely recognized that efforts should be made to conduct such studies in which the individual disease entities are evaluated separately.

Data supporting adjuvant chemotherapy in patients with resected BTC have come from two randomized phase III trials. In the phase III BILCAP study, 447 patients with completely resected CCA or gallbladder cancer were randomized to receive either adjuvant capecitabine or observation.[195] RFS was significantly greater for patients in the capecitabine arm in both the intent-to-treat analysis (24.4 vs. 17.5 months; HR, 0.75; 95% CI, 0.58–0.98; $P$ = .033) and in the per-protocol analysis ($n$ = 430; HR, 0.70; 95% CI, 0.54–0.92; $P$ = .009). Median OS was 51.1 months for the capecitabine arm and 36.4 months for the observation arm. This difference was statistically significant in the per-protocol analysis (HR, 0.75; 95% CI, 0.58–0.97; $P$ = .028) but not in the intent-to-treat analysis. Data from a long-term analysis in the intent-to-treat population have corroborated these findings, with a median OS of 49.6 months for the capecitabine arm and 36.1 months for the observation arm (adjusted HR, 0.84; 95% CI, 0.67–1.06).[196] A hazard ratio of 0.74 (95% CI, 0.59–0.94) was reported in the protocol-specified sensitivity analysis.

In the second phase III randomized trial, 508 patients with resected pancreaticobiliary cancer (139 patients had CCA and 140 patients had gallbladder cancer) were randomly assigned to adjuvant chemotherapy with fluorouracil and mitomycin C or to a control arm.[197] Results from unplanned subgroup analyses showed a significantly better 5-year disease-free survival for patients with gallbladder cancer treated with chemotherapy (20.3% compared to 11.6% in the control group; $P$ = .021), although no significant differences between the two treatment arms were observed for all patients with biliary duct cancers. Results from this trial support the suggestion that patients with gallbladder cancer undergoing resection may derive survival benefit with adjuvant chemotherapy.

A randomized phase III trial from Japan investigated whether S-1, an oral fluoropyrimidine derivative given as adjuvant therapy, benefited patients with BTCs who underwent R0/R1 resection.[198] Compared to patients treated with surgery alone, patients treated with adjuvant S-1 had significantly improved outcomes, (OS HR, 0.69; 95% CI, 0.51–0.94; one-sided $P$ = .008); RFS HR, 0.80; 95% CI, 0.61–1.04).

Negative results have been found for two gemcitabine-based regimens in two randomized phase III trials. In the phase III PRODIGE 12-ACCORD 18 trial, 196 patients with R0 or R1 resected BTC were randomized to receive GEMOX or surveillance alone.[199] No statistically significant differences were found between the study arms for RFS and OS. Negative results for survival outcomes were also found in a phase III trial from Japan evaluating the efficacy of gemcitabine monotherapy (compared to observation) in 226 patients with resected extrahepatic CCA.[200]

Retrospective studies that have combined patients with gallbladder cancer and CCAs provide conflicting evidence regarding the role of adjuvant therapy.[9,201,202] It should be noted that the majority of recurrences after resection of gallbladder cancer involve distant sites, supporting the idea of developing effective adjuvant systemic therapies.[9]

In a systematic review and meta-analysis of 6712 patients with BTCs, Horgan et al reported an associated improvement in OS (although nonsignificant) with adjuvant therapy compared with surgery alone, with no difference between patients with gallbladder cancer and bile duct cancers.[203] Chemotherapy or chemoradiation therapy was associated with statistically greater benefit than RT alone, with the greatest benefit observed in patients with lymph node-positive disease and macroscopic residual disease (R1 resection). Another systematic review and meta-analysis of 42,917 patients found a significantly higher OS with adjuvant therapy after surgery compared with surgery alone.[204] Ren et al reported a higher 5-year OS with adjuvant radiotherapy post surgery in patients with gallbladder cancer or extrahepatic CCA in a meta-analysis of 21 clinical trials.

In studies that included only patients with gallbladder cancer, a meta-analysis including 10 retrospective studies with 3191 patients showed that adjuvant chemotherapy was associated with improved OS, compared to resection alone (HR, 0.42; 95% CI, 0.22–0.80).[205] Subgroup analyses showed that the patients who are most likely to benefit from adjuvant therapy include those with a positive margin, those with nodal disease, and those with at least stage II disease. Retrospective studies have concluded that adjuvant chemotherapy or chemoradiation following R0 resection might improve OS in selected patients with T2 or T3 tumors and lymph node-positive gallbladder cancer.[206-209]

Retrospective studies that included only patients with resected extrahepatic CCA suggest that adjuvant chemoradiation may improve local control and survival, although distant metastases was the most common pattern of failure.[210-213] 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).[212,214,215]

Most of the collective experience of chemoradiation in BTCs involves concurrent chemoradiation and fluorouracil. The phase II SWOG S0809 trial, which enrolled patients with extrahepatic CCA or gallbladder cancer ($N$ = 79), provided prospective data on adjuvant chemotherapy/chemoradiation (ie, capecitabine/gemcitabine followed by concurrent capecitabine and RT). Two-year OS was 65%, and median survival was 35 months. A majority of patients enrolled in the trial (86%) completed therapy, and the regimen was generally tolerable. Confirmatory phase III trial data are needed. Concurrent chemoradiation with capecitabine has been used in other studies.[212,216] Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.[217]

Among patients with cancer of the gallbladder or extrahepatic bile duct, those who have undergone an R0 resection and who have negative regional nodes or those with carcinoma in situ at margin may be followed with systemic therapy (preferred), clinical trial (preferred), observation alone, or fluoropyrimidine-based chemoradiation (category 2B for patients with gallbladder cancer). Patients with intrahepatic CCA who have undergone an R0 resection may be followed with systemic therapy (preferred), clinical trial (preferred), or observation.

Recommended chemotherapy regimens include gemcitabine monotherapy or combined with cisplatin or capecitabine; capecitabine monotherapy (category 1) or combined with cisplatin (category 3) or oxaliplatin; 5-fluououracil monotherapy; and FOLFOX. Capecitabine monotherapy is preferred among these options. All other options are included as other recommended regimens. Besides capecitabine monotherapy, whose use in this setting is supported by the phase III BILCAP study,[195] data to support particular chemotherapy regimens for adjuvant treatment of resected BTC are limited due to lack of clinical trial data and are based on the extrapolation of data from studies of patients with advanced disease.

Additionally, some of the recommendations are based on practice patterns at NCCN Member Institutions and retrospective studies from single-center experiences. Besides gemcitabine monotherapy not being recommended for patients with resected extrahepatic CCA (based on the negative results of a phase III Japanese trial[200]), the recommendations in the NCCN Guidelines on the use of adjuvant chemotherapy are not specific to the particular type of BTC, due to the limited data and the heterogeneity of patient populations included in many of the published studies. Based on the negative results of the randomized phase III PRODIGE 12-ACCORD 18 trial,[199] gemcitabine/oxaliplatin was removed as a recommended regimen for resected BTC in 2019.

Patients with gallbladder cancer or extrahepatic CCA with resected, positive margins (R1) or gross residual local disease (R2) or those with intrahepatic CCA with residual local disease (R2) after resection should be evaluated by a multidisciplinary team to review the available treatment options on a case-by-case basis. Evaluation and treatment of gross residual disease (R2) should be consistent with evaluation and treatment for unresectable disease. For patients with R1 margins or positive regional nodes, the optimal treatment strategy has not been established but options are systemic therapy (preferred), clinical trial (preferred), or fluoropyrimidine-based chemoradiation, with or without fluoropyrimidine-based or gemcitabine-based chemotherapy. Fluoropyrimidine or gemcitabine-based chemotherapy may be followed by fluoropyrimidine-based chemoradiation, or vice versa. There are limited data to support a specific chemoradiation regimen or definitive benefit. If radiotherapy is used, then RT using 3D-CRT and intensity-modulated RT are options.[218,219] Dosing schedules may depend on margin positivity and may include up to 45 Gy at 1.8 Gy/fraction or 50 to 60 Gy at 1.8 to 2.0 Gy/fraction (to allow for an integrated boost) to the tumor bed.[194,220] RT dosing[221] is dependent on the ability to meet normal organ constraints and underlying liver function. Conventional fractionation in the postoperative or unresectable settings should follow the schedule described above. The dosing schedule for SBRT for unresectable disease is 30 to 50 Gy, typically done in 3 to 5 fractions.

## Treatment for Advanced Biliary Tract Cancers

The prognosis of patients with advanced BTCs is poor and the median survival for those undergoing supportive care alone is short.[222] Treatment options for advanced BTCs may include systemic therapy, enrollment in a clinical trial, palliative RT, RT with concurrent fluoropyrimidine, consideration of locoregional therapy (RT or arterially directed therapies), and best supportive care, depending on the disease stage and specific disease subtype. Selection of subsequent-line systemic therapy for progressive disease depends on clinical factors including previous treatment regimen/agent, somatic molecular testing results, and extent of liver dysfunction.

### Immunotherapy Plus Chemotherapy

The phase III TOPAZ-1 trial, which randomized 685 patients with unresectable or metastatic BTC with no prior treatment 1:1, demonstrated that treatment with durvalumab in combination with gemcitabine plus cisplatin significantly improved OS (HR, 0.80; 95% CI, 0.66–0.97; $P$ = .021) and PFS (HR, 0.75; 95% CI, 0.63–0.89; $P$ = .001) compared to placebo in combination with gemcitabine plus cisplatin.[223] The objective response rate (ORR) was 26.7% in the former group and 18.7% in the latter one. 75.7% of patients treated with durvalumab in combination with gemcitabine and cisplatin experienced a grade 3 or 4 adverse event compared to 77.8% of patients treated with placebo in combination with gemcitabine and cisplatin.

The panel has included combination therapy with durvalumab, gemcitabine, and cisplatin, as a category 1 preferred recommendation for the first-line systemic treatment of unresectable or metastatic BTCs. Durvalumab in combination with gemcitabine and cisplatin is also a recommended

treatment option for patients who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after completion of adjuvant therapy. This combination is a category 1 subsequent-line systemic therapy option (other recommended regimen) for progressive disease.

**Chemotherapy**

The survival benefit of chemotherapy (fluorouracil, leucovorin, and etoposide) over best supportive care for patients with advanced BTCs was initially suggested in a phase III trial of 90 patients with advanced pancreatic and BTCs, 37 of whom had advanced BTCs.[224] In a single-center randomized study of 81 patients with unresectable gallbladder cancer, Sharma et al reported that modified GEMOX improved PFS and OS compared to best supportive care or fluorouracil.[225] Median OS was 4.5, 4.6, and 9.5 months, respectively, for the best supportive care, fluorouracil, and modified GEMOX arms ($P$ = .039). The corresponding PFS was 2.8, 3.5, and 8.5 months ($P$ < .001).

Several phase II studies have also demonstrated the efficacy of chemotherapy for the treatment of patients with advanced BTCs.[226,227] The results of a pooled analysis of 104 trials that have included 2810 patients with advanced BTCs showed that response rates and tumor control were higher for the subgroup of patients receiving a combination of gemcitabine and platinum-based agents.[228] In a retrospective study of 304 patients with unresectable BTCs who were treated with gemcitabine alone, a cisplatin-based regimen, or a fluoropyrimidine-based regimen, patients receiving gemcitabine were shown to have a lower risk of death.[229] Most importantly, the support for the use of gemcitabine-based or fluoropyrimidine-based chemotherapy for patients with advanced BTCs comes from four randomized studies.[230-233] A phase II study comparing mFOLFIRINOX to gemcitabine plus cisplatin in patients with locally advanced or metastatic BTCs did not achieve its primary endpoint of PFS at 6 months in the modified intention-to-treat population.[234]

The randomized, controlled, phase III ABC-02 study, which enrolled 410 patients with locally advanced or metastatic CCA, gallbladder cancer, or ampullary cancer, demonstrated that the combination of gemcitabine and cisplatin improved OS and PFS by 30% over gemcitabine alone.[232] Median OS was 11.7 months and 8.1 months (HR, 0.64; 95% CI, 0.52–0.80; $P$ < .001), and median PFS was 8.0 months versus 5.0 months (HR, 0.63; 95% CI, 0.51–0.77; $P$ < .001), both in favor of the combination arm. Although the rate of neutropenia was higher in the group receiving gemcitabine and cisplatin, there was no significant difference in the rate of neutropenia-associated infections between the two arms. Okusaka et al also reported similar findings in a phase II randomized study of 84 patients with advanced BTCs.[233] Combined analyses from both of these trials ($n$ = 227) showed that derived neutrophil-to-lymphocyte ratio assessed at baseline was associated with greater long-term survival in those randomized to receive gemcitabine/cisplatin ($P$ < .01).[235] 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 BTCs.

Results from the randomized phase III ABC-06 study showed that compared to active symptom control alone, active symptom control combined with FOLFOX in patients previously treated with combined cisplatin and gemcitabine improved median OS (6.2 vs. 5.3 months; adjusted HR, 0.69; $P$ = .031).[236] Second-line treatment with fluorouracil and irinotecan (FOLFIRI) also provided some benefits to patients.[237] A randomized phase II trial comparing mFOLFOX with mFOLFIRI in patients with locally advanced or metastatic BTCs previously treated with gemcitabine and cisplatin reported similar efficacy between the two regimens.[238] The median OS and PFS were 6.3 months (95% CI, 4.4–8.2

months) and 2.8 months (95% CI, 2.3–3.3 months), respectively, in the mFOLFOX group and 5.7 months (95% CI, 4.7–6.7%; *P* =.677) and 2.1 months (95% CI, 1.1–3.1 months; *P* = .974) in the mFOLIFIRI group, respectively. An ORR of 5.9% and 4.0% (*P* = .663) was achieved in the mFOLFOX and mFOLFIRI groups, respectively, and the disease control rate was 66.7% and 64.0% (*P* = .778), respectively. Different adverse events were reported in the two groups.

The phase IIb NIFTY trial showed that treatment with liposomal irinotecan with fluorouracil and leucovorin in patients with confirmed metastatic BTC with disease progression on gemcitabine and cisplatin significantly improved median PFS (7.1 months; 95% CI, 3.6–8.8 months) compared to treatment with fluorouracil and leucovorin (1.4 months; 95% CI, 1.2–1.5 months; HR, 0.56; 95% CI, 0.39–0.81; *P* = .0019).[239] In an updated analysis, the median PFS, as assessed by masked independent central review, was 4.2 months for patients treated with the former compared to 1.7 months (HR, 0.61; *P* = .004) for patients treated with fluorouracil and leucovorin.[240] FOLFIRI, as well as the combination of liposomal irinotecan with fluorouracil and leucovorin, are category 2B subsequent-line systemic therapy options (other recommended regimen) for unresectable or metastatic progressive disease.

Examples of other gemcitabine-based or fluoropyrimidine (fluorouracil or capecitabine)-based regimens with demonstrated activity in phase II trials include: gemcitabine and cisplatin or oxaliplatin[241-249]; gemcitabine and fluoropyrimidine[250-254]; gemcitabine and albumin-bound paclitaxel (for CCA)[255]; gemcitabine, cisplatin, and albumin-bound paclitaxel[256]; gemcitabine and cetuximab[257]; and fluoropyrimidine and oxaliplatin or cisplatin.[258-261] In the phase II trial examining the combination of gemcitabine-cisplatin with albumin-bound paclitaxel, the disease status of 20% of patients went from unresectable to resectable.[256] A phase III study showed that the combination of capecitabine and oxaliplatin was non-inferior to the GEMOX combination in terms of the 6-month PFS.[262] Triple-drug chemotherapy regimens have also been shown to be effective in patients with advanced BTCs, albeit in a very small number of patients.[263-265] 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 BTCs, although the trial was underpowered to detect such a difference.[263] In a phase II trial, the combination of panitumumab, a monoclonal anti-EGFR antibody, with gemcitabine and irinotecan showed encouraging efficacy with good tolerability in patients with advanced CCA, with a 5-month PFS rate of 69%.[266] The median PFS and OS were 9.7 months and 12.9 months, respectively.

The effects of other gemcitabine combination therapies have been examined in phase II trials. In a randomized phase II study of 51 patients, Kornek et al established the efficacy and tolerance of mitomycin in combination with gemcitabine or capecitabine in previously untreated patients with advanced BTCs.[230] Mitomycin and capecitabine were associated with superior complete response (CR) 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 ORRs (19% and 7.1%, respectively) and OS (8 and 5 months, respectively), but the PFS was similar in both treatment arms (3.3 months).[231] In a randomized phase II trial, the combination of gemcitabine and sorafenib was compared to gemcitabine with a placebo in 102 patients with unresectable or metastatic BTC.[267] There were no significant between-group differences for OS and PFS rates, but patients who developed liver metastases following resection survived longer if they received sorafenib, relative to patients who received the placebo (*P* = .019). The gemcitabine/sorafenib combination was well-tolerated. Data from the randomized phase II NIFE trial, published in an

abstract, showed that in the intention-to-treat population, 51% of patients receiving nanoliposomal irinotecan in combination with 5-FU and leucovorin achieved PFS at 4 months.[268] The median OS and PFS were not improved in patients with intrahepatic CCA but the authors noted a clear benefit in extrahepatic CCA. Data from phase III trials are needed.

Based on the experiences from phase II or phase III studies, the following gemcitabine-based and fluoropyrimidine-based combination chemotherapy regimens are included as other recommended options for the treatment of patients with advanced biliary tract cancer: gemcitabine with cisplatin (category 1), gemcitabine with oxaliplatin or capecitabine; capecitabine with oxaliplatin; FOLFOX; gemcitabine combined with albumin-bound paclitaxel; gemcitabine combined with cisplatin and albumin-bound paclitaxel (category 2B); and single-agent fluorouracil, capecitabine, and gemcitabine. The combination of gemcitabine and fluorouracil is not included due to the increased toxicity and decreased efficacy observed with this regimen[250] when compared with results of studies of the gemcitabine and capecitabine regimen in the setting of advanced BTC.

In a systematic review including 23 studies (14 phase II clinical trials and 9 retrospective studies) with 761 patients with advanced BTC, the efficacy of second-line chemotherapy was examined.[269]

### Chemoradiation and Radiation Therapy

Chemoradiation in the setting of advanced BTCs can provide control of symptoms due to local tumor effects and may prolong OS. However, there are limited clinical trial data to define a standard regimen or definitive benefit. In a retrospective analysis of 37 patients treated with chemoradiation for unresectable extrahepatic CCA, the actuarial OS rates at 1 and 2 years were 59% and 22%, respectively, although effective local control was observed in the majority of patients during this time period (actuarial local control rates of 90% and 71% at 1 and 2 years, respectively).[270] The most extensively investigated chemotherapeutic agent for use in concurrent chemoradiation in the treatment of BTCs has been fluorouracil,[271,272] although capecitabine has been substituted for fluorouracil in some studies.[216] The panel recommends that concurrent chemoradiation (RT guided by imaging) should be limited to either fluorouracil or capecitabine, and that such treatment should be restricted to patients without evidence of metastatic disease. Concurrent chemoradiation with gemcitabine is not recommended due to the limited experience and toxicity associated with this treatment.

Evidence supports the consideration of RT for treatment of unresectable and metastatic intrahepatic CCA,[143-145,273] but there is little evidence to support this treatment option for gallbladder cancer and extrahepatic CCA without concurrent chemotherapy and in patients with unresected disease.[274,275]

### Targeted Therapy

BTCs are known to harbor clinically relevant molecular alterations that are differentially expressed in gallbladder cancer and intrahepatic and extrahepatic CCAs. Given emerging evidence regarding actionable targets for treating BTCs, comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC who are candidates for systemic therapy (see *Principles of Molecular Testing* in the algorithm for additional information regarding testing modalities and considerations). While most BTCs are considered sporadic, up to 10% to 15% of BTCs may be associated with an inherited cancer predisposition syndrome.[276,277] As evidence remains insufficient for definitive recommendations regarding specific criteria to guide genetic risk assessment in hepatobiliary cancers or for universal germline testing, genetic counselling referral and potential germline testing should be considered in patients with BTCs with any of the following: young age at diagnosis; a strong personal or family history of cancer; no known risk factors for liver disease; or the presence of

mutations identified during tumor testing which are suspected to be possible germline alterations. For patients who do harbor a known germline mutation associated with a cancer predisposing syndrome (ie, Lynch syndrome or hereditary breast and ovarian cancer syndrome), there is currently insufficient evidence to support screening for biliary tract malignancies.

***NTRK Fusions***

NTRK is a membrane-bound receptor that autophosphorylates and activates downstream pathways that drive oncogenesis. *NTRK1/NTRK2/NTRK3* fusions are estimated to occur at <1% prevalence in BTCs.[278,279] The rarity of individual subgroups limits precise incidence and frequency estimates. Two NTRK inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for a tumor agnostic indication in *NTRK* fusion-positive solid tumors: larotrectinib[280] in 2018 and entrectinib[281] in 2019. Studies have demonstrated response rates in the 57% to 75% range in pre-treated *NTRK* fusion-positive tumors.[279-281] These studies have included small numbers of patients with CCA and demonstrated evidence of clinical benefit. A few *NTRK* inhibitors such as entrectinib and larotrectinib have shown efficacy against *NTRK* fusion-positive solid tumors.[280-282] Entrectinib and larotrectinib are useful in certain circumstances first-line or subsequent-line (for progressive disease) systemic therapy options for unresectable or metastatic *NTRK* gene fusion-positive tumors.

Testing for *NTRK* fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. These assessments are feasible in the context of multi-target assessment in NGS gene panels currently in clinical use and *NTRK* fusion-positive CCAs have demonstrated responses in clinical trials.

***Immunotherapy Biomarkers (MSI-H/dMMR/TMB-H/PD-L1)***

Mismatch repair (MMR) deficiency results from tumor mutations in *MLH1, MSH2, MSH6,* and *PMS2,* which are genes encoding proteins that regulate DNA repair. MMR deficiency results in a unique genetic signature characterized by high rates of mutations, particularly in repetitive DNA sequences called microsatellites that occur throughout the genome. This signature is referred to as microsatellite instability (MSI) or MSI-H. MSI-H or mismatch repair deficient (dMMR) status is rare in BTCs.[283-287]

Tumor mutational burden (TMB) is defined as the total number of somatic mutations per coding area of a tumor's genome. Higher rates of tumor mutation may result in increased production of immunogenic mutant proteins or neoantigens.[285,287-291] The incidence of TMB-high (TMB-H) has been shown to be <5% across studies.[292]

The programmed cell death ligand 1 (PD-L1) system functions to inhibit T cell functions. PD-L1 protein expression on malignant or inflammatory associated tumor cells generally indicates active tumor immunity suppressed by the programmed cell death protein 1 (PD-1)/PD-L1 system. In BTCs, PD-L1 high status ranges from around 45% to 65% for combined tumor plus immune cell PD-L1 expression ≥1%, and 10% to 70% for tumor cell PD-L1 expression ≥1%.[285,287]

MSI-H or MMR deficiency are predictive of substantially higher rates of durable, objective response to immune checkpoint inhibition in patients across a range of solid tumor types in studies that have included patients with BTCs.[283-285,293] In the KEYNOTE-158 trial, 233 patients with MSI-H or dMMR non-colorectal solid tumor types after failure of standard therapy, including 22 patients with CCA, demonstrated an objective radiographic response rate of 34.3% (95% CI, 28.3–40.8%) with median PFS of 4.1 months (95% CI, 2.4–4.9 months) and median OS of 23.5 months (95%

CI, 13.5 months–not reached).[284] Grade 3 to 5 treatment-related adverse events were observed in 14.6% of patients. Analyses of a CCA subgroup revealed an ORR of 40.9% (95% CI, 20.7–63.6%) with a median PFS and OS of 4.2 months (95% CI, 2.1 months–not reached) and 24.3 months (95% CI, 6.5 months–not reached), respectively. The results from an updated analysis showed that out of 351 patients with advanced MSI-H/dMMR noncolorectal solid tumors who received prior treatment, 30.8% (95% CI, 25.8–36.2% achieved an overall response.[293] The median PFS, median OS, and median DOR were 3.5 months (95% CI, 2.3–4.2 months), 20.1 months (95% CI, 14.1–27.1 months), and 47.5 months (95% CI, 2.1+ months to 51.1+ months), respectively. 12% of patients experienced a grade 3–5 treatment-related adverse event. In the CCA/biliary tract subgroup, the ORR was the same as previously reported. The median PFS was 4.2 months (95% CI, 2.1–24.9 months) and the median OS was 19.4 months (95% CI, 6.5 months–not reached). These findings contributed to the FDA approval of pembrolizumab for patients with unresectable or metastatic MSI-H or dMMR solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options, agnostic to tumor histology.

In the KEYNOTE-158 trial, 102 of 805 evaluable patients were found to have tumors with TMB-H status, defined as ≥10 mutations/megabase of DNA based upon the platform used; objective radiographic responses occurred in 29% of patients (95% CI, 21–39%) by comparison with only 6% of patients (95% CI, 5–8%) in the non-TMB-H group.[288] These findings led to a histology-agnostic FDA approval of pembrolizumab for patients with TMB-H advanced solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Though none of the 63 biliary cancer patients in the KEYNOTE-158 TMB cohort were found to harbor TMB-H tumors, other studies have shown that approximately 4% of advanced BTCs have TMB-H tumors, supporting testing for TMB in this population.[287,289]

Pembrolizumab is a useful in certain circumstances first-line or subsequent-line (for progressive disease and with no prior treatment with a checkpoint inhibitor) systemic therapy option for unresectable or metastatic MSI-H, dMMR, or TMB-H (for subsequent-line therapy) BTCs, though the panel cautions that data to support this recommendation are limited, particularly in the first-line setting.[294]

Dostarlimab-gxly, another anti-PD-1 antibody, was assessed in an open-label phase I study with 2 cohorts.[295] One cohort had 103 patients with advanced or recurrent MSI-H/dMMR endometrial cancer and another had 106 patients with advanced or recurrent MSI-H/dMMR or POLE-hypermutated non-endometrial solid tumors (comprising mostly gastrointestinal tumors [93.4%] with 65.1% colorectal tumors). An interim analysis, published in an abstract, revealed an ORR of 41.6% (95% CI, 34.9–48.6%), per RECIST v1.1. The ORR for the cohort with non-endometrial cancer was 38.7% (95% CI, 29.4–48.6%). The median duration of response (DOR) was not reached (median follow-up of 16.3 months for the cohort with endometrial cancer and 12.4 months for the cohort with non-endometrial cancer). The most frequent grade 3 or higher treatment-related adverse events were anemia (2.2%), elevated lipase (1.9%), elevated alanine aminotransferase (1.1%), and diarrhea (1.1%). Another published abstract demonstrated that among the cohort with non-endometrial cancer, patients with colorectal cancer had an ORR of 36.2% (95% CI, 25.0–48.7%).[296] The cohort also included one patient with gallbladder cancer and 1 with biliary neoplasm. Both patients had a CR. Dostarlimab-gxly is a category 2B useful in certain circumstances subsequent-line systemic therapy option for patients with MSI-H/dMMR recurrent or advanced tumors that have progressed on or following prior

treatment, who have no satisfactory alternative treatment options, and who have not been previously treated with a checkpoint inhibitor.

The phase II CheckMate 848 trial randomized patients with advanced or metastatic TMB-H solid tumors) with no prior immunotherapy and who had disease refractory to standard local therapies 2:1 to receive the combination of nivolumab and ipilimumab or nivolumab monotherapy.[297] Published in an abstract, the data revealed an ORR of 35.3% (95% CI, 24.1–47.8%), a median OS of 14.5 months (95% CI, 7.7 months–not evaluable), and a median PFS of 4.1 months (95% CI, 2.8–11.3 months) in patients with tissue TMB-H tumors. Nivolumab plus ipilimumab is a useful in certain circumstances first-line (category 2B) or subsequent-line (for progressive disease and with no prior treatment with a checkpoint inhibitor) systemic therapy option for patients with unresectable or metastatic TMB-H tumors. In the subsequent-line setting, the recommendation is for patients with disease refractory to standard therapies or who have no standard treatment options available.

Testing for MSI or MMR deficiency is recommended in patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. Further recommendations for MSI/MMR testing can be found in the NCCN Guidelines for Colon Cancer. Testing for TMB is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA based upon clinical benefit observed across advanced solid tumors.

In advanced BTCs, tumor or tumor plus immune cell PD-L1 expression has shown trends towards higher rates of objective radiographic response in single-arm phase 2 studies of pembrolizumab or nivolumab as monotherapy, though rates of objective radiographic response are low overall and data from these small, uncontrolled studies are insufficient to warrant a recommendation for testing.[285,298]

In a phase II trial with 46 evaluable patients with advanced BTCs, an ORR of 22% and a disease control rate of 59% were obtained, upon investigator assessment, with the use of nivolumab, another anti-PD1 drug.[298] With blinded independent central review, the ORR was 11% and the disease control rate was 50%. In the intention-to-treat cohort, the median PFS and median OS were 3.7 months (95% CI, 2.3–5.7 months) and 14.2 months (95% CI, 6.0 months–not reached), respectively. Nivolumab is category 2B useful in certain circumstances subsequent-line systemic therapy option for patients with unresectable or metastatic progressive disease who have not been previously treated with a checkpoint inhibitor.

***BRAF V600E Mutations***

Mutation in the *BRAF* gene may lead to constitutive activation of the MAPK pathway. The most common *BRAF* mutation is type 1 alteration, which results in a single amino acid substitution for glutamic acid at residue 600 (V600E). *BRAF* mutations have been reported in around 1% to 5% of BTCs.[279,299-302] The rarity of individual subgroups limits precise incidence and frequency estimates. The phase II, open-label, single-arm, multicenter, Rare Oncology Agnostic Research (ROAR) basket trial enrolled 43 patients with *BRAF* V600E-mutated CCA, who had previously received systemic therapy.[299] The primary endpoint of overall response was achieved by 22 patients (ORR, 51%; 95% CI, 36–67%). Median PFS and OS were 9 months (95% CI, 5–10 months) and 14 months (95% CI, 10–33 months), respectively. Results from the Subprotocol H trial, which enrolled patients with solid tumors (except for melanoma, thyroid, colorectal cancer, and later non-small cell lung cancer) with a BRAF *V600E* mutation, revealed an ORR of 38% (90% CI, 22.9–54.9%; $P < .0001$) and a PFS of 11.4 months (90% CI, 8.4–16.3 months) in 29 patients.[303] Dabrafenib plus trametinib received accelerated approval for *BRAF* V600E advanced solid tumors. The oral combination of dabrafenib and trametinib is a useful in certain circumstances subsequent-line systemic therapy option for unresectable or metastatic progressive disease with *BRAF*-V600E mutations.

Testing for *BRAF* V600E mutations is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.

***FGFR2 Fusions/Other FGFR Pathway Aberrations***

FGFR2 is a member of the *FGFR* family of receptor tyrosine kinases that activate a variety of downstream signaling cascades leading to cell proliferation and tumorigenesis. *FGFR2* fusions occur at ~9% to 15% prevalence in intrahepatic CCAs and are rare in other subsites.[292,304,305] Selective FGFR inhibitors have received accelerated approval from the FDA for the treatment of pre-treated *FGFR2*-fusion CCA. Results from the phase II FOENIX-CA2 trial demonstrated an ORR of 42% (95% CI, 32–52%) with futibatinib in patients with previously unresectable or metastatic intrahepatic CCA with *FGFR2* fusions/rearrangements.[306] The median OS, median PFS, median DOR, and disease control rate were 21.7 months, 9.0 months, 9.7 months, and 83%, respectively. An ongoing randomized phase III study is testing futibatinib in the first-line versus gemcitabine/cisplatin (NCT04093362). Studies are also ongoing to determine the activity of individual FGFR inhibitors for specific *FGFR* kinase domain activating mutations or other *FGFR* aberrations.

Pemigatinib's approval in 2020 was based on the FIGHT-202 study, an open-label study including 107 patients with advanced, pre-treated *FGFR2*-fusion-positive or *FGFR2*-rearranged CCA.[307,308] The ORR was 35.5% (95% CI, 26.5–45.4%), with a median PFS of 6.9 months (95% CI, 6.2–9.6 months) and median DOR of 7.5 months (95% CI, 5.7–14.5 months).[308]

Interim results from the phase II FIDES-01 study were reported in a published abstract.[309] Treatment with derazantinib, an FGFR 1-3 inhibitor, resulted in an ORR of 8.7%, as determined by the investigator, a median PFS of 7.3 months (95% CI, 3.5–16.7 months), and a disease control rate of 73.9% (95% CI, 51.6–89.8%) in patients with advanced intrahepatic CCA with *FGFR2* mutations or amplifications who received prior chemotherapy treatment.

Futibatinib and pemigatinib are useful in certain circumstances subsequent-line systemic therapy options for unresectable or metastatic progressive CCA with *FGFR2* fusions or rearrangements.

Testing for *FGFR2* fusions or rearrangements is recommended for patients with unresectable or metastatic intrahepatic or extrahepatic CCA and should be considered for patients with unresectable or metastatic gallbladder cancer.

***IDH1 Mutations***

The IDH-1 enzyme catalyzes the conversion of alpha-ketoglutarate to D-2-hydroxyglutarate (2-HG), a metabolite that impacts chromatin regulation and cellular differentiation. Activating mutations in the *IDH1* gene lead to high levels of 2-HG accumulation and impairment of normal differentiation, accumulation of hepatic progenitor cells, and malignant transformation to intrahepatic CCA.[310] *IDH1* mutations have been reported in approximately 10% to 20% of intrahepatic CCAs.[304,311,312] The rarity of individual subgroups limits precise incidence and frequency estimates. In a randomized phase III study with 185 patients with *IDH1*-mutated CCA that progressed on standard chemotherapy, ivosidenib resulted in prolongation of PFS over placebo, with a median PFS of 2.7 versus 1.4 months (HR, 0.37; $P < .0001$).[313] Patients with ivosidenib had significantly less decline in physical functioning scores than those treated with placebo. In the intention-to-treat population, the median OS for the ivosidenib and placebo arms were 10.3 months (95% CI, 7.8–12.4 months; HR, 0.79 [95% CI, 0.56–1.12]; $P = .09$) and 7.5 months (95% CI, 4.8–11.1 months), respectively.[314] After taking into account 43 patients who crossed from the placebo arm to the ivosidenib arm, the median OS for the placebo arm was 5.1 months (95% CI, 3.8–7.6 months; HR, .49 [95% CI, 0.34–0.70]; $P < .001$). Ascites was the most frequently reported grade 3 or higher

treatment-emergent adverse event in both groups. Ivosidenib has been approved by the FDA for previously treated, locally advanced or metastatic CCA harboring *IDH1* mutations. Ivosidenib is a category 1 useful in certain circumstances subsequent-line systemic therapy option for unresectable or metastatic progressive CCA with *IDH1* mutations. Clinical trials of next-generation IDH1 inhibitors are ongoing.

Testing for *IDH1* mutations is recommended for patients with unresectable or metastatic intrahepatic CCA or extrahepatic CCA and should be considered for patients with unresectable or metastatic gallbladder cancer.

***HER2/ERBB2 Overexpression/Amplification/Activating Mutations***

HER2 (*ERBB2*) is a member of the *ErbB/EGFR* family of receptor tyrosine kinases that functions as both a homodimer and heterodimer with other family members to activate a variety of downstream signaling cascades leading to cell proliferation and tumorigenesis. HER2 overexpression or pathway activation is present in around 5% to 20% of CCAs, and 15% to 30% of gallbladder cancer.[305,312,315-321] The rarity of individual subgroups limits precise incidence and frequency estimates. Early clinical trials of HER2-targeted therapy in BTCs failed to show efficacy[322,323] but these studies were unselected for HER2 overexpression/amplification or mutation. However, small case series and biomarker-selected trials including patients with BTCs have suggested efficacy of HER2-directed therapies. Javle et al[324] retrospectively reported 8 patients with advanced gallbladder carcinoma harboring HER2 overexpression or amplification treated with trastuzumab (alone or in combination with pertuzumab or chemotherapy); all patients experienced disease stability (3), partial response (PR) (4), or CR (1).

Two additional phase II studies and a phase one study have reported promising results of HER2-targeted therapy in BTCs.[325-327] In the SUMMIT trial, a basket trial including patients with tumors with HER2 or HER3 mutations treated with neratinib, 9 BTCs with HER2 mutations were included, of which two patients experienced PR.[326] The MyPathway study included 39 patients with HER2 amplified and/or overexpressed previously treated, metastatic BTCs.[328] Patients received pertuzumab plus trastuzumab, and 9 patients achieved a PR (ORR, 23%; 95% CI, 11–39%) with an additional 11 patients showing SD for more than 4 months. Additionally, a prospective pilot study of a trastuzumab biosimilar (trastuzumab-pkrb) in combination with chemotherapy (gemcitabine plus cisplatin) included 4 patients with biliary tract carcinoma and identified a PR in 2 patients and SD in 2 patients.[329]

The results of the phase II HERB trial from Japan, published in an abstract, showed that out of 22 evaluable patients with HER2-positive BTCs refractory or intolerant to a gemcitabine-based regimen, 36.4% (95% CI, 19.6–56.1%) achieved a significantly improved-ORR ($P$ = .01) following treatment with trastuzumab deruxtecan, a HER2 targeted therapy.[330] The median OS, PFS, and disease control rate were 7.1 months (95% CI, 4.7–14.6%), 4.4 months (95% CI, 2.8–8.3%), and 81.8% (95% CI, 59.7–94.8%), respectively. Encouraging data were also reported in patients with HER2-low disease (ORR, 12.5%; median OS, 8.9 months; median PFS, 4.2 months; disease control rate, 75.0%). Due to the limited available data, there are currently no HER2-targeted therapies that have been FDA approved for BTCs. Nevertheless, multiple ongoing phase II clinical trials are studying HER2 inhibitors in various combinations. The combination of trastuzumab and pertuzumab is a useful in certain circumstances subsequent-line systemic therapy option for unresectable or metastatic progressive disease with HER2-positive tumors.

Testing for HER2 (*ERBB2*) overexpression/amplification is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA.

***Other Biomarkers (RET/ROS1, KRAS G12C/Other KRAS, Other Tumor-Agnostic Markers)***

In addition to the genomic alterations described in the previous sections, NGS testing may uncover other potentially actionable molecular alterations that could help determine eligibility for ongoing clinical trials in patients with advanced BTCs. While there is insufficient evidence to recommend universal assessment, alterations for which targeted therapies exist and have been FDA-approved in other tumor types, including *KRAS* G12C mutation,[331-333] *MET* amplification,[334-336] *ALK*,[337] *RET*,[338] or *ROS1* fusions,[339] among others,[340] have been described with variable but overall rare frequency in biliary tract carcinomas and HCC.[341] However, limited data currently exist regarding the efficacy of targeted therapy in these situations, due to their rarity. In the phase I/II ARROW study, pralsetinib, a selective RET inhibitor, demonstrated an ORR of 57% (95% CI, 35–77%) in patients with *RET* fusion-positive tumors other than non-small cell lung cancer and thyroid cancer and who received prior treatment or were ineligible for standard therapies.[338] The median OS, median PFS, and median DOR were 14 months, 7 months, and 12 months, respectively. A response was observed in two out of three patients who had CCA. However, *RET* mutations in CCA are rare.[342] Pralsetinib is a category 2B useful in certain circumstances first-line or subsequent-line (for progressive disease) systemic therapy option for unresectable or metastatic disease with *RET* gene fusion-positive tumors.

Selpercatinib, a selective RET kinase inhibitor, was investigated in the phase 1/2 LIBRETTO-001 clinical trial in patients with *RET* fusion-positive tumors.[343] Of 41 patients evaluable for efficacy and with tumors other than lung or thyroid, the ORR, as assessed by an independent review committee, was 43.9% (95% CI, 28.5–60.3%). An objective response was obtained in the one patient who had CCA. Selpercatinib is a useful in certain circumstances first-line (category 2B) or subsequent-line (for progressive disease) systemic therapy option for unresectable or metastatic intrahepatic or extrahepatic CCA with *RET* gene fusion-positive tumors.

Testing for *RET* fusions is recommended for patients with unresectable or metastatic gallbladder cancer, intrahepatic CCA, or extrahepatic CCA. A comprehensive NGS panel may identify additional alterations for which targeted therapies exist and have FDA-approved treatments in other tumor types.

***Other Targeted Therapies***

In a phase II trial, regorafenib was found to have a disease control rate of 56% and could thus be useful in patients with disease refractory to chemotherapy.[344] Another phase II trial reported an ORR of 9.1% and a disease control rate of 64%.[345] In the phase II REACHIN trial, patients with BTCs were randomized to receive best supportive care along with either regorafenib or placebo.[346] The median PFS for patients in the regorafenib arm was 3.0 months compared to 1.5 months for those in the placebo arm. The median OS was 5.3 months for the regorafenib group compared to 5.1 months for the placebo group. Regorafenib is a category 2B subsequent-line systemic therapy option (other recommended regimen) for unresectable or metastatic progressive disease.

Initial results from the phase II LEAP-005 trial, published in an abstract that examined the combination of lenvatinib with pembrolizumab as a subsequent therapy for patients with advanced biliary tract disease, demonstrated an ORR of 9.7% (95% CI, 2.0–25.8%), with a median PFS of 6.1 months.[347] The combination of lenvatinib and pembrolizumab is a category 2B useful in certain circumstances subsequent-line systemic therapy option for patients with unresectable or metastatic progressive disease who have not been previously treated with a checkpoint inhibitor.

## Summary

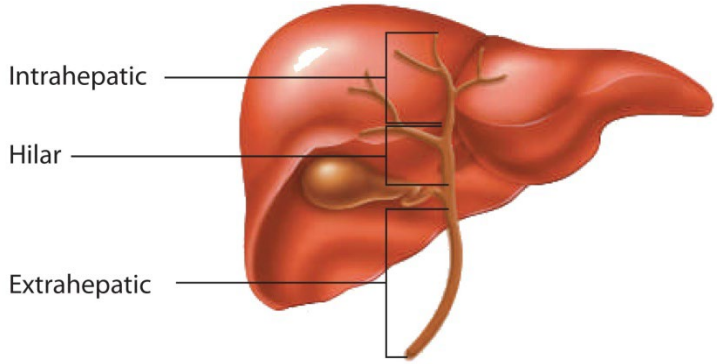
BTCs are associated with a poor prognosis and patients with BTCs commonly present with advanced disease. In the past few years, several advances have been made in the therapeutic approaches.

Complete resection of the tumor in well-selected patients is currently the best available potentially curative treatment. Consideration of locoregional therapy is included as an option for patients with unresectable or metastatic intrahepatic CCA. Palliative RT may be used in patients with unresectable gallbladder cancer or extrahepatic CCA.

The combination of durvalumab with gemcitabine and cisplatin, as well as the combination of gemcitabine, and cisplatin, are included as category 1 systemic therapy recommendations for patients with unresectable or metastatic BTCs. Durvalumab/gemcitabine/cisplatin is the preferred first-line systemic therapy option. Drugs such as entrectinib, larotrectinib, pembrolizumab, dostarlimab-gxly, nivolumab plus ipilimumab, dabrafenib plus trametinib, futibatinib, pemigatinib, ivosidenib, trastuzumab plus pertuzumab, pralsetinib, and selpercatinib, may benefit certain patients with advanced disease harboring specific genomic mutations.

Consultation with a multidisciplinary team is recommended for the assessment of resectability for patients with gallbladder cancer presenting with jaundice and for intrahepatic and extrahepatic CCAs. Careful patient selection for treatment and patient engagement are essential. There are relatively few high-quality RCTs of patients with BTCs, and patient participation in prospective clinical trials is a preferred option for the treatment of patients with all stages of disease.

## Figure 1: Classification of Cholangiocarcinoma

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