Protocol for the Examination of Specimens from Patients with Carcinoma of the Intrahepatic Bile Ducts

Version: 4.3.0.0
Protocol Posting Date: June 2025
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2026
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated hepatic resection, partial or total
Tumor Type	**Description**
Carcinoma	Invasive carcinomas including combined hepatocellular-cholangiocarcinoma, small cell and large cell (poorly differentiated) neuroendocrine carcinoma

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens
Intraductal papillary neoplasm without associated invasive carcinoma
Intraductal tubulopapillary neoplasm without associated invasive carcinoma
Mucinous cystic neoplasm without associated invasive carcinoma

The following tumor types should NOT be reported using this protocol:

Tumor Type
Well-differentiated neuroendocrine tumors of liver
Hepatocellular carcinoma and fibrolamellar carcinoma (consider the Hepatocellular Carcinoma protocol)
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

Version Contributors
Cancer Committee Authors: Rondell P. Graham, MBBS*, William V. Chopp, MD*, Yue Xue, MD, PhD*, Dhanpat Jain, MD*
Other Expert Contributors:
** Denotes primary author.*

For any questions or comments, contact: cancerprotocols@cap.org.

Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.

**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.3.0.0

- Updates to cover page
- Updates to content and explanatory notes to include modifications to Histologic Type and Tumor Size questions, and SPECIAL STUDIES section
- Lymphovascular Invasion question updated to Lymphatic and / or Vascular Invasion
- Perineural Invasion question updated from optional to required
- Addition of required Treatment Effect question
- Updates to pTNM Classification

Reporting Template

Protocol Posting Date: June 2025
Select a single response unless otherwise indicated.
CASE SUMMARY: (INTRAHEPATIC BILE DUCTS)
Standard(s): AJCC 8

SPECIMEN (Note A)

Procedure
___ Wedge resection
___ Partial hepatectomy
___ Total hepatectomy
___ Other (specify): _____
___ Not specified

TUMOR

Histologic Type (Note B)
___ Large duct intrahepatic cholangiocarcinoma
___ Small duct intrahepatic cholangiocarcinoma
___ Cholangiocarcinoma, NOS
___ Combined hepatocellular-cholangiocarcinoma
___ Intraductal papillary neoplasm with associated invasive carcinoma
___ Intraductal tubulopapillary neoplasm with associated invasive carcinoma
___ Mucinous cystic neoplasm with associated invasive carcinoma
___ Undifferentiated carcinoma, NOS
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ High-grade neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) (specify component):
_____
___ Other histologic type not listed (specify): _____
+Histologic Type Comment: _____

Histologic Grade (Note C)
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____
___ Not applicable: _____

Tumor Focality (Note D)
___ Solitary tumor (specify location): _____
___ Multiple tumors (specify locations): _____

Tumor Size (Note E)
___ Unifocal invasive carcinoma
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____
___ Multifocal invasive carcinoma in association with intraductal neoplasms (intraductal papillary mucinous neoplasm, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm) and mucinous cystic neoplasm
___ Size of the largest focus of invasive carcinoma in Centimeters (cm): _____ cm
Aggregate Size that Combines Sizes of all Foci of Invasive Carcinoma in Centimeters (cm) (specify, if known): _____ cm
Invasive Component as a Percentage of Entire Tumor (specify, if known): _____ %
___ Cannot be determined (explain): _____

Tumor Extent (select all that apply)
___ Confined to intrahepatic bile ducts (carcinoma in situ / high-grade dysplasia)
___ Confined to hepatic parenchyma
___ Involves visceral peritoneal surface
___ Directly invades gallbladder
___ Directly invades adjacent structure(s) and organ(s) other than gallbladder (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

+Tumor Growth Pattern (Note F)
___ Mass-forming
___ Periductal infiltrating
___ Mixed mass-forming and periductal infiltrating
___ Other (specify): _____
___ Cannot be determined: _____

Lymphatic and / or Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

Perineural Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

Treatment Effect (Note G)
___ No known presurgical therapy
___ Present, with no viable cancer cells (complete response, score 0)

___ Present, with single cells or rare small groups of cancer cells (near complete response, score 1)
___ Present, with residual cancer showing evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
___ Present, NOS
___ Absent, with extensive residual cancer and no evident tumor regression (poor or no response, score 3)
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note H)

Margin Status for Invasive Carcinoma
___ All margins negative for invasive carcinoma
+Closest Margin(s) to Invasive Carcinoma (select all that apply)
___ Hepatic parenchymal: _____
___ Bile duct: _____
___ Other (specify): _____
___ Cannot be determined: _____
+Distance from Invasive Carcinoma to Closest Margin
Specify in Centimeters (cm)
___ Exact distance in cm: _____ cm
___ Greater than 1 cm
Specify in Millimeters (mm)
___ Exact distance in mm: _____ mm
___ Greater than 10 mm
Other
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable: _____
___ Invasive carcinoma present at margin
Margin(s) Involved by Invasive Carcinoma (select all that apply)
___ Hepatic parenchymal: _____
___ Bile duct: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Margin Status for High-Grade Intraepithelial Neoplasia (select all that apply)
___ All margins negative for high-grade intraepithelial neoplasia
___ High-grade intraepithelial neoplasia present at bile duct margin
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s): _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note I)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ (intraductal tumor)

pT1: Solitary tumor without vascular invasion, less than or equal to 5 cm or greater than 5 cm

___ pT1a: Solitary tumor less than or equal to 5 cm without vascular invasion
___ pT1b: Solitary tumor greater than 5 cm without vascular invasion
___ pT1 (subcategory cannot be determined)
___ pT2: Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
___ pT3: Tumor perforating the visceral peritoneum
___ pT4: Tumor involving local extrahepatic structures by direct invasion

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category (Note J)
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis present

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

ADDITIONAL FINDINGS (Note K)

+Additional Findings (select all that apply)
___ None identified
___ Hepatic fibrosis (specify extent with name of scheme and scale used for assessing stage of fibrosis): _____
___ Cirrhosis
___ Primary sclerosing cholangitis
___ Biliary stones
___ Chronic hepatitis (specify type): _____
___ Other (specify): _____

SPECIAL STUDIES

+Ancillary Studies (Note L)
___ Specify: _____
___ Not performed

COMMENTS

Comment(s): _____

Explanatory Notes

A. Specimen Application

This protocol applies only to hepatic resection specimens containing intrahepatic cholangiocarcinoma, combined hepatocellular-cholangiocarcinoma and primary high-grade neuroendocrine carcinomas. Hepatocellular carcinomas and carcinomas arising in the perihilar bile ducts are staged using separate TNM systems.[1]

Anatomically, the intrahepatic bile ducts extend from the periphery of the liver to the second-order bile ducts (Figure 1). The perihilar bile ducts extend from the hepatic duct bifurcation to include the extrahepatic biliary tree proximal to the origin of the cystic duct. The distal extrahepatic bile duct extends from the junction of the cystic duct-common hepatic duct to the ampulla of Vater.[1]

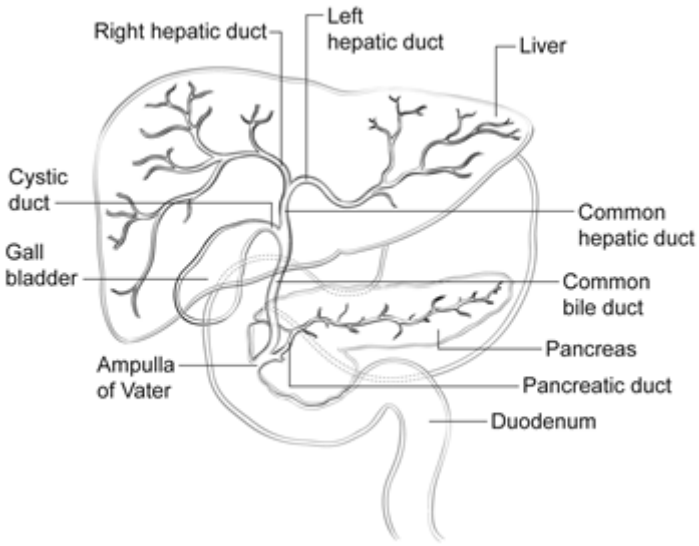

Figure 1. Anatomy of the intrahepatic and extrahepatic biliary system

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

B. Histologic Type

The protocol recommends the following modified classification of the World Health Organization (WHO).[1] In the United States, approximately 30% of the primary malignant tumors of the liver are biliary carcinomas.[1]

The intrahepatic cholangiocarcinoma iCCA, have been now classified as large duct-type and small duct-type iCCA and show several clinicopathologic correlations.[1] Large duct-type iCCA tend to form hilar masses, present with obstructive cholestasis and share risk factors with extrahepatic bile duct adenocarcinomas. Small duct-type iCCA form peripheral liver masses, present with larger tumors and share risk factors with hepatocellular carcinomas.

Combined or mixed hepatocellular-cholangiocarcinoma should show histologic evidence of both hepatocellular and biliary differentiation by morphology, and supported by immunohistochemistry.[1] Hepatocellular markers with high sensitivity and specificity such as arginase-1 should be included in the panel (in addition to markers like Hep Par 1),[2] and a cholangiocarcinoma component should not be diagnosed based solely on immunoreactivity with markers like CK7, CK19, and/or MOC31, which can be positive in a subset of HCC, especially in variants like scirrhous HCC.[3] Discrete gland formation with or without mucin, positive staining of these areas with CK7, CK19, and/or MOC31, and negative results in these areas with hepatocellular markers is the most reliable evidence of a cholangiocarcinoma component. The proportion of each component can be provided. The size of the entire tumor is used for staging. The demographics and clinical features of combined HCC-cholangiocarcinoma such as age, sex, viral hepatitis status, and cirrhosis tend to resemble that of HCC,[4,5] while some studies have reported molecular changes similar to cholangiocarcinoma.[6] Many studies show that combined HCC-cholangiocarcinoma is more aggressive compared to classical HCC and has a higher recurrence rate after liver transplantation.[7,8] Carcinosarcoma is mentioned as a histologic type in the AJCC 8th edition.

References

1. WHO Classification of Tumours Editorial Board. *Digestive system tumours*. Lyon (France): International Agency for Research on Cancer; 2019. (WHO classification of tumours series, 5th ed.; vol. 1).
2. Nguyen T, Phillips D, Jain D, et al. Comparison of 5 Immunohistochemical Markers of Hepatocellular Differentiation for the Diagnosis of Hepatocellular Carcinoma. *Arch Pathol Lab Med.* 2015; 139(8):1028-1034.
3. Krings G, Ramachandran R, Jain D, et al. Immunohistochemical pitfalls and the importance of glypican 3 and arginase in the diagnosis of scirrhous hepatocellular carcinoma. *Mod Pathol.* 2013; 26(6):782-791.
4. Yano Y, Yamamoto J, Kosuge T, et al. Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. *Jpn J Clin Oncol.* 2003; 33:283-287.
5. Tang D, Nagano H, Nakamura M, et al. Clinical and pathological features of Allen's type C classification of resected combined hepatocellular and cholangiocarcinoma: a comparative study with hepatocellular carcinoma and cholangiocellular carcinoma. *J Gastrointest Surg*. 2006; 10:987-998.
6. Cazals-Hatem D, Rebouissou S, Bioulac-Sage P, et al. Clinical and molecular analysis of combined hepatocellular-cholangiocarcinomas. *J Hepatol.* 2004; 41(2):292-298.
7. Wu CH, Yong CC, Liew EH, et al. Combined hepatocellular carcinoma and cholangiocarcinoma: diagnosis and prognosis after resection or transplantation. *Transplant Proc.* 2016; 48(4):1100-1104.
8. Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. *Liver Transpl.* 2011;17(8):934-942.

C. Histologic Grade

For cholangiocarcinomas, definitive criteria for histologic grading have not been established; however, the following quantitative grading system based on the proportion of gland formation within the tumor is suggested:

Grade X	Grade cannot be assessed
Grade 1	Well-differentiated (more than 95% of tumor composed of glands)
Grade 2	Moderately differentiated (50% to 95% of tumor composed of glands)
Grade 3	Poorly differentiated (less than 49% of tumor composed of glands)

Undifferentiated category is rarely used and is reserved for tumors that do not show obvious glandular, squamous, or neuroendocrine differentiation on morphology and/or immunohistochemistry. It is more appropriate to categorize these as undifferentiated carcinomas rather than cholangiocarcinoma. This category is not included in the AJCC scheme. There is no separate grading scheme for combined hepatocellular-cholangiocarcinoma; both the components can be separately graded. This grading system is not applicable to poorly differentiated neuroendocrine carcinoma.

D. Tumor Focality

Sections should be prepared from each major tumor nodule, with representative sampling of smaller nodules. For purposes of staging, satellite nodules, multifocal primary cholangiocarcinomas, and intrahepatic metastases are considered to be multiple tumors.[1] In intrahepatic cholangiocarcinoma, multiple tumor deposits have been associated with poorer survival.[2,3]

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Ohtsuka M, Ito H, Kimura F, et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. *Br J Surg*. 2002; 89(12):1525-1531.
3. Sano T, Shimada K, Sakamoto Y, Ojima H, Esaki M, Kosuge T. Prognosis of perihilar carcinoma: hilar bile duct cancer versus intrahepatic cholangiocarcinoma involving the hepatic hilus. *Ann Surg Oncol.* 2008; 15(2):590-599.

E. Tumor Size Evaluation of Invasive Carcinoma Associated with Intraductal Neoplasms and Mucinous Cystic Neoplasm

The invasive component in intraductal neoplasms (intraductal papillary neoplasm and intraductal tubulopapillary neoplasm) and mucinous cystic neoplasm may be unifocal or multifocal. In multifocal invasive carcinoma, it is recommended to include the size of the largest focus, the combined size of all invasive foci, and/or the percentage of invasive tumor relative to the gross tumor size (see also note I).

F. Tumor Growth Pattern

Three tumor growth patterns of intrahepatic cholangiocarcinoma are described: the mass-forming type, the periductal infiltrating type, and mixed mass-forming/periductal-infiltrating type. Mass-forming intrahepatic cholangiocarcinoma (60% of cases) forms a well-demarcated nodule growing in a radial pattern and invading the adjacent liver parenchyma (Figure 2). In contrast, the periductal-infiltrating type of cholangiocarcinoma (20% of cases) spreads in a diffuse longitudinal growth pattern along the bile duct. The remaining 20% of cases of intrahepatic cholangiocarcinoma grow in a mixed mass-forming/periductal-infiltrating pattern. Earlier studies suggested a poor outcome for diffuse periductal-infiltrating type, while some recent studies have suggested a relatively favorable prognosis.[1,2,3,4]

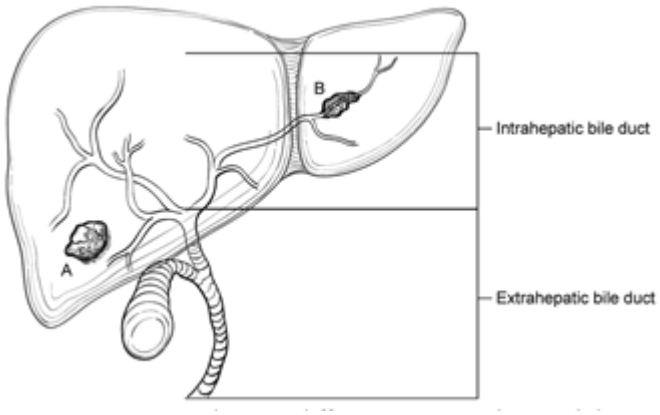

Figure 2. Tumor growth pattern in intrahepatic cholangiocarcinoma. From Amin MB et al.[5] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 8th edition (2017), published by Springer Science and Business Media LLC, www.springerlink.com.

References

1. Hirohashi K, Uenishi T, Kubo S, et al. Macroscopic types of intrahepatic cholangiocarcinoma: clinicopathologic features and surgical outcomes. *Hepatogastroenterology.* 2002;49(44):326-329.
2. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. *World J Surg.* 2007;31(10):2016-2022.
3. Imai K, Yamamoto M, Ariizumi S. Surgery for periductal infiltrating type intrahepatic cholangiocarcinoma without hilar invasion provides a better outcome than for mass-forming type intrahepatic cholangiocarcinoma without hilar invasion. *Hepatogastroenterology.* 2010;57(104):1333-1336.
4. Uno M, Shimada K, Yamamoto Y, et al. Periductal infiltrating type of intrahepatic cholangiocarcinoma: a rare macroscopic type without any apparent mass. *Surg Today.* 2012;42(12):1189-1194.
5. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

G. Treatment Effect

Response of tumor to previous chemotherapy or radiation therapy should be reported. Several scoring systems have been described, and a modified Ryan scheme[1] is recommended, as below:

Modified Ryan Scheme for Tumor Regression Score[1]

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Sizable pools of acellular mucin may be present after chemoradiation but should not be interpreted as representing residual tumor. It is suggested that to estimate the approximate size of the tumor by adding the size of all the viable tumor foci within the tumor mass based in the histologic evaluation. Only the size or extent of the viable tumor should be used to assign the ypT category as appropriate, and this requires a combined assessment of both gross and microscopic findings.

This protocol does not preclude the use of other systems for assessment of tumor response.[2,3] A modification of the above scoring scheme into a 3-tier scheme has been shown to correlate better with outcome: no residual carcinoma (grade 0), minimal residual carcinoma defined as single cells or small groups of cancer cells, <5% residual carcinoma (grade 1), 5% or more residual carcinoma (grade 2).[4,5]

References

1. Ryan R, Gibbons D, Hyland JMP, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology.* 2005; 47:141-146.
2. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg.* 1992; 127:1335-1339.
3. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. *Ann Surg Oncol.* 2001;8(2):123-132.
4. Chatterjee D, Katz MH, Rashid A, et al. Histologic grading of the extent of residual carcinoma following neoadjuvant chemoradiation in pancreatic ductal adenocarcinoma: a predictor for patient outcome. *Cancer.* 2012;118(12):3182-3190.
5. Lee SM, Katz MH, Liu L, et al. Validation of a proposed tumor regression grading scheme for pancreatic ductal adenocarcinoma after neoadjuvant therapy as a prognostic indicator for survival. *Am J Surg Pathol.* 2016;40(12):1653-1660.

H. Margins

The evaluation of margins for total or partial hepatectomy specimens depends on the method and extent of resection. It is recommended that the surgeon be consulted to determine the critical foci within the margins that require microscopic evaluation. The transection margin of a partial hepatectomy may be large, rendering it impractical for complete examination. In this setting, grossly positive margins should be microscopically confirmed and documented. If the margins are grossly free of tumor, judicious sampling of the cut surface in the region closest to the nearest identified tumor nodule is indicated. In selected cases, adequate random sampling of the cut surface may be sufficient. The histologic examination of the bile ducts at the cut margin is recommended to evaluate the lining epithelium for in situ carcinoma or dysplasia. If the neoplasm is found near the surgical margin, the distance from the margin should be reported. For multiple tumors, the distance from the nearest tumor should be reported.

I. pTNM Classification

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors
For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or after initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor before multimodality therapy (i.e., before initiation of neoadjuvant therapy). A formal tumor regression grading system has not been specifically developed for this tumor type. If there has been neoadjuvant treatment, at least a semi-quantitative assessment of residual viable tumor should be included in the report (see also Note G).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

T Category Considerations
T includes high-grade biliary intraepithelial neoplasia (BilIn-3), intraductal papillary neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia. For intraepithelial lesions, a 3-tier biliary intraepithelial neoplasia classification has been proposed.[1]

The T categories are based on size, vascular invasion and extrahepatic spread. For invasive carcinoma associated with intraductal papillary neoplasms, tubulopapillary and mucinous cystic neoplasms, only the invasive component should be used to determine the T category. The synoptic report is not required for intraductal papillary neoplasms, intraductal tubulopapillary neoplasms and mucinous cystic neoplasms in the absence of an invasive component for accreditation purposes. The invasive portion in these cases can be multifocal. In addition to the size of the largest focus, it is suggested to include the combined/cumulative size of all invasive carcinoma foci, and/or their percentage relative to the gross tumor size (see also note E). However, till further data becomes available, the T category should be determined based on either size of the largest invasive focus or the deepest invasion as applicable. Vascular invasion includes either gross or microscopic involvement of vessels. Major vascular invasion is

defined as invasion of the branches of the main portal vein or hepatic artery (first and second order branches) or as invasion of 1 or more of the 3 hepatic veins (right, middle or left).

Direct invasion of visceral peritoneum is considered as T3, while adjacent organs, including colon, duodenum, stomach, common bile duct, portal lymph nodes, abdominal wall, and diaphragm, is considered as T4 disease. Due to inconsistent criteria for defining tumors with periductal growth pattern and its unclear association with outcome, this growth pattern is no longer a part of the T classification.

Additional Descriptors

Lymphovascular Invasion

Lymphovascular invasion (LVI) indicates whether microscopic lymphovascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymphovascular invasion.

References

1. Zen Y, Adsay NV, Bardadin K, et al. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. *Mod Pathol*. 2007;20(6):701-709.

J. Lymph Nodes

Lymph node metastases have consistently been identified as an important predictor of outcome for intrahepatic cholangiocarcinoma.[1,2,3] The significance of isolated tumor cells and micrometastases have not been formally studied in this tumor type. Where present, these nodes should be interpreted as positive and a comment describing the isolated tumor cells or micrometastases included.

The lymph node involvement pattern for intrahepatic cholangiocarcinomas varies with location in the liver (Figure 3). For carcinomas arising in the right lobe of the liver (segments 5-8), the regional lymph nodes include the hilar (common bile duct, hepatic artery, portal vein, and cystic duct), periduodenal, and peripancreatic lymph nodes. For tumors arising in the left lobe, the regional lymph nodes are the hilar, inferior phrenic and gastrohepatic lymph nodes. Nodal involvement of the celiac, periaortic, or pericaval lymph nodes is considered to be distant metastasis (pM1).[1]

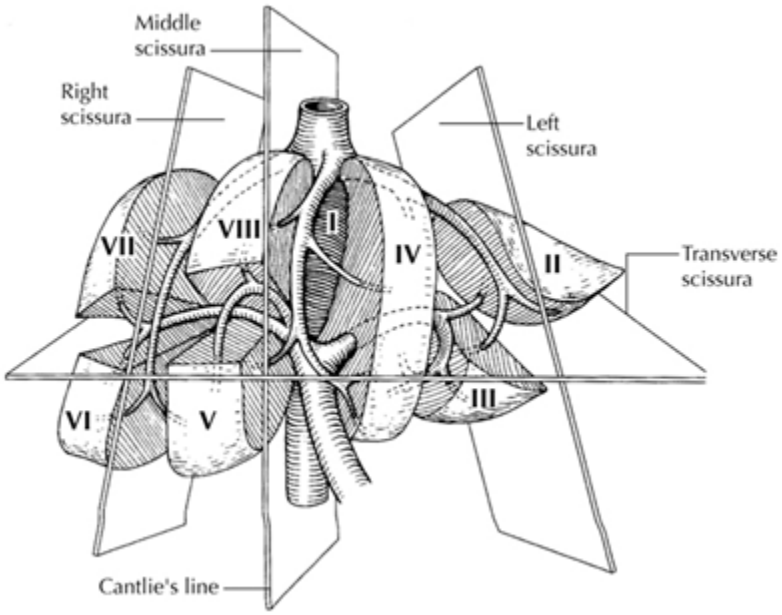

Figure 3. Segmental anatomy of the liver. From Greene et al.[4] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Ohtsuka M, Ito H, Kimura F, et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. *Br J Surg.* 2002;89(12):1525-1531.
3. Mavros MN, Economopoulos KP, Alexiou VG and Pawlik TM (2014). Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA Surg.* 149(6):565-574.
4. Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas*. New York, NY: Springer; 2006.

K. Additional Findings

The extent of hepatic fibrosis, especially cirrhosis or advanced fibrosis, are known to have an adverse effect on outcome. The scoring system described by Ishak[1] is recommended by the *AJCC Cancer Staging Manual,* 8th edition,[2] but other commonly used schemes (Batts-Ludwig, Metavir) can be used. The name of the staging scheme and its scale should be included.

The presence of underlying disease, such as primary sclerosing cholangitis,[3] should be included in the pathology report. Biliary parasites and recurrent pyogenic cholangitis may be present along with cholangiocarcinoma in Asian countries. Hepatitis C infection, nonalcoholic fatty liver disease, obesity, and smoking are also risk factors for cholangiocarcinoma.[4,5]

References
1. Ishak K, Baptista A, Bianchi L, et al. Histologic grading and staging of chronic hepatitis. *J Hepatol.* 1995; 22:696-699.
2. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
3. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis.* 2004;24(2):115-125.
4. Welzel TM, Graubard BI, El-Serag HB, et al. Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin Gastroenterol Hepatol.* 2007;5(10):1221-1228.
5. Ben-Menachem T. Risk factors for cholangiocarcinoma [comment]. *Eur J Gastroenterol Hepatol.* 2007;19(8):615-617.

L. Ancillary Studies

Immunohistochemistry (MMR IHC) and/or microsatellite instability (MSI) testing are now essential not only for identifying Lynch syndrome but also for detecting mismatch repair deficient (dMMR) tumors because FDA approved immune checkpoint inhibitors are now available for any malignancy irrespective of histologic type or location.[1,2] Now NCCN also suggests considering testing it for adenocarcinomas of the small intestine, stomach, pancreas, and biliary tract.[3] Similarly, targeted therapies for HER2 have expanded beyond non-breast and non-gastric gastrointestinal cancers.[4,5] HER2 testing for advanced gastrointestinal cancers (stage IV, recurrent, or unresectable) is becoming more common, although standardized reporting guidelines for non-gastric gastrointestinal cancers are still lacking. While criteria applicable for colorectal cancer have been developed,[6,7] the ASCO/College of American Pathology guidelines for gastric cancer HER2 scoring have been applied in recent clinical trials for other gastrointestinal cancers.[8] It is suggested that while reporting HER2 it is a good practice to indicate the criteria used. Further details about mismatch repair enzyme immunohistochemistry and PCR for MSI testing, as well as other ancillary molecular testing can be found in the CAP Biomarkers protocol.

References
1. Bartley AN, Mills AM, Konnick E, et al. Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: Guideline from the College of American Pathologists in Collaboration with the Association for Molecular Pathology and Fight Colorectal Cancer. *Arch Pathol Lab Med.* 2022, 146(10):1194-1210.
2. Abrha A, Shukla ND, Hodan R, et al. Universal Screening of Gastrointestinal Malignancies for Mismatch Repair Deficiency at Stanford. *JNCI Cancer Spectr.* 2020, 19;4(5): pkaa054.
3. Weiss JM, Gupta S, Burke CA, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2021. *J Natl Compr Canc Netw.* 2021, 15;19(10):1122-1132.
4. Yoon J and Do-Youn Oh DY. HER2-targeted therapies beyond breast cancer - an update. *Nat Rev Clin Oncol.* 2024, 21(9):675-700.
5. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2.
6. Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. *Mod Pathol.* 2015, 28(11):1481-91.

7. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol.* 2019, 20 (4): 518-530.
8. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients with HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial. *J Clin Oncol.* 2024, 42(1):47-58.