Protocol for the Examination of Specimens From Patients With Carcinoma of the Intrahepatic Bile Ducts

Protocol applies to carcinomas of the intrahepatic bile ducts and mixed hepatocellular-cholangiocarcinoma. Hepatocellular carcinoma, hepatoblastoma, and carcinomas of the perihilar bile ducts are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: June 2012

Procedure
• Hepatic Resection, Partial or Complete

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CAP Intrahepatic Bile Duct Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: IntrahepaticBileDuct 3.1.0.1

Summary of Changes
The following changes have been made since the February 2011 release.

Resection

Histologic Type
The following was added:
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma

Explanatory Notes

Histologic Type: Histologic types were updated, as detailed above.

References
Reference #4 was updated.

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

INTRAHEPATIC BILE DUCTS: Resection (Note A)

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___Liver
___Gallbladder
___Other (specify): _____
___ Not specified

Procedure (select all that apply)
___ Wedge resection
___ Partial hepatectomy
+ ___ Major hepatectomy (3 segments or more)
+ ___ Minor hepatectomy (less than 3 segments)
___ Total hepatectomy
___ Other (specify): _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see "Comment")

Tumor Focality (Note B)
___ Solitary (specify location): _____
___ Multiple (specify locations): _____

Histologic Type (Note C)
___ Cholangiocarcinoma
___ Combined hepatocellular and cholangiocarcinoma
___ Bile duct cystadenocarcinoma
___ High-grade neuroendocrine carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Other (specify): _____

Histologic Grade (Note D)
___ Not applicable
___ GX: Cannot be assessed
___ GI: Well differentiated
___ GII: Moderately differentiated
___ GIII: Poorly differentiated
___ GIV: Undifferentiated
___ Other (specify): _____

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Tumor Growth Pattern (Note E)
___ Mass-forming
___ Periductal infiltrating
___ Mixed mass-forming and periductal infiltrating
___ Cannot be determined

Microscopic Tumor Extension (select all that apply)
___ Cannot be assessed
___ No evidence of primary tumor
___ Tumor confined to the intrahepatic bile ducts histologically (carcinoma in situ)
___ Tumor confined to hepatic parenchyma
___ Tumor involves visceral peritoneal surface
___ Tumor directly invades gallbladder
___ Tumor directly invades adjacent organs other than the gallbladder
(specify): _____

Margins (select all that apply) (Note F)

Hepatic Parenchymal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest margin: ___ mm *or* ___ cm
Specify margin: _____
___ Involved by invasive carcinoma

Bile Duct Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ ___ Dysplasia/carcinoma in situ not identified
+ ___ Dysplasia/carcinoma in situ present
___ Involved by invasive carcinoma

Other Margin (required only if applicable)
Specify margin: _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Lymph-Vascular Invasion

Venous (Major Vessel) Invasion (V) (invasion of right or left portal vein, 1 or more hepatic veins)
___ Not identified
___ Present
___ Indeterminate

Small Vessel Invasion (L)
___ Not identified
___ Present
___ Indeterminate

+ Perineural Invasion
+ ___ Not identified
+ ___ Present

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

+ ___ Indeterminate

Pathologic Staging (pTNM) (Note G)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ (intraductal tumor)
___ pT1: Solitary tumor without vascular invasion
___ pT2a: Solitary tumor with vascular invasion
___ pT2b: Multiple tumors, with or without vascular invasion
___ pT3: Tumor perforating the visceral peritoneum or involving the local extrahepatic structures by direct invasion
___ pT4: Tumor with periductal invasion

Regional Lymph Nodes (pN) (Note H)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis

___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply) (Note I)
+ ___ Cirrhosis/severe fibrosis (Ishak fibrosis score 5-6)
+ ___ Primary sclerosing cholangitis
+ ___ Biliary stones
+ ___ Chronic hepatitis (specify type): _____
+ ___ Other (specify): _____
+ ___ None identified

+ Ancillary Studies
+ Specify: _____

+ Clinical History (select all that apply) (Note J)

+ ____ Cirrhosis
+ ____ Primary sclerosing cholangitis
+ ____ Inflammatory bowel disease
+ ____ Hepatitis C infection
+ ____ Other (specify): _____
+ ____ Not known

+ Comment(s)

Explanatory Notes

A. Application

This protocol applies only to hepatic resection specimens containing carcinomas arising in the intrahepatic bile ducts. Hepatocellular carcinomas and carcinomas arising in the perihilar bile ducts are staged using separate TNM systems.[1] A separate staging system for intrahepatic cholangiocarcinoma is warranted on the basis of biological differences in tumor behavior and prognostic factors, such as lack of prognostic impact of tumor size for cholangiocarcinoma compared with hepatocellular carcinoma.[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 the junction of the cystic duct-bile duct to the ampulla of Vater.[1]

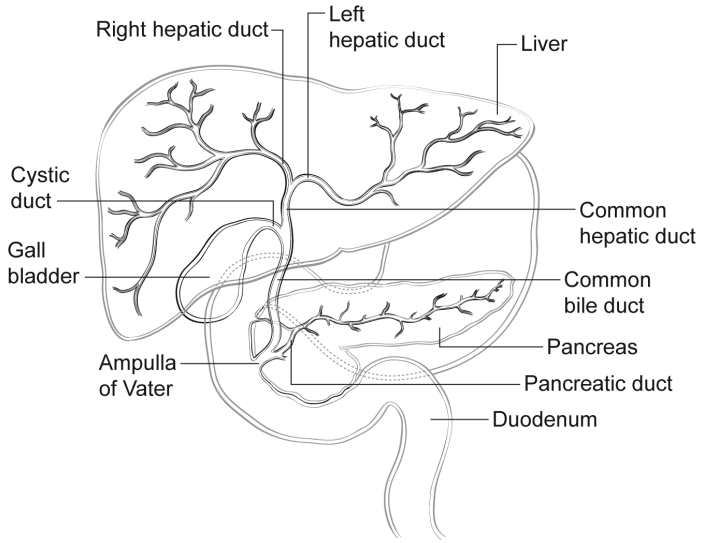

Figure 1. Anatomy of the intrahepatic and extrahepatic biliary system.

B. Tumor Focality

Sections should be prepared from each major tumor nodule, with representative sampling of smaller nodules if macroscopically different in appearance. For purposes of staging, satellite nodules, multifocal primary cholangiocarcinomas, and intrahepatic metastases are not distinguished and are considered multiple tumors.[1] In intrahepatic cholangiocarcinoma, multiple tumor deposits have been associated with poorer survival.[2,3]

C. Histologic Type

The protocol recommends the following modified classification of the World Health Organization (WHO).[4] In the United States, approximately 30% of the primary malignant tumors of the liver are biliary carcinomas.[4]

WHO Classification of Carcinomas of the Intrahepatic Bile Ducts (Modified)
Cholangiocarcinoma
Combined hepatocellular and cholangiocarcinoma
Bile duct cystadenocarcinoma

High-grade neuroendocrine carcinoma
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma

Combined or mixed hepatocellular-cholangiocarcinoma accounts for less than 5% of primary liver carcinomas[5] and should show histologic evidence of both hepatocellular differentiation and bile duct differentiation, such as production of mucin. These tumors generally have a poor prognosis and often arise in the setting of cirrhosis.[5,6] Recent studies have found genetic changes similar to those seen in cholangiocarcinoma.[7]

D. 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 (5% to 49% of tumor composed of glands)
Grade 4	Undifferentiated (less than 5% of tumor composed of glands)

E. 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. Limited analyses suggest that the diffuse periductal-infiltrating type is associated with a poor prognosis.[2,8]

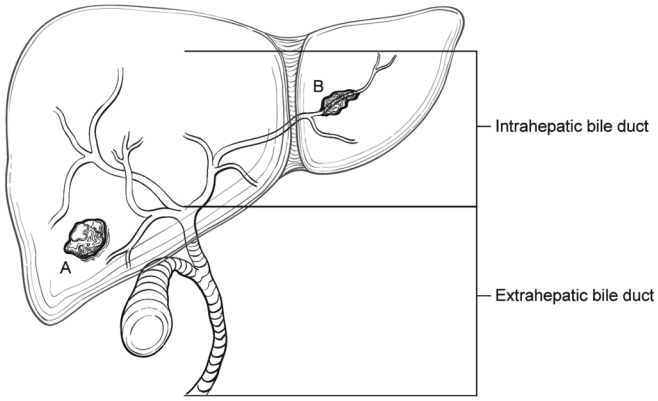

Figure 2. Tumor growth pattern in intrahepatic cholangiocarcinoma. From Edge et al.[1] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and Business Media LLC, www.springerlink.com.

F. 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.

G. TNM and Anatomic Stage/Prognostic Groupings

The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) applies to all primary carcinomas of the intrahepatic bile ducts and mixed hepatocellular-cholangiocarcinomas.[1] It does not apply to hepatic sarcomas or to metastatic tumors of the liver.

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 (eg, 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 (ie, before initiation of neoadjuvant therapy).

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

Intraductal papillary bile duct tumors may be identified in some patients with biliary obstruction and are classified as in situ tumors (Tis).

The T classification depends on the number of tumor nodules and the presence or absence of blood vessel invasion.

The TNM classification does not discriminate between multiple independent primary tumors, tumor satellite nodules, or intrahepatic metastasis from a single primary carcinoma.

Vascular invasion includes either the gross involvement of large vessels or the microscopic involvement of small vessels identified on histologic examination. Major vascular invasion is defined as invasion of the branches of the main portal vein (right or left portal vein) or as invasion of 1 or more of the 3 hepatic veins (right, middle or left).

Direct invasion of adjacent organs, including colon, duodenum, stomach, common bile duct, portal lymph nodes, abdominal wall, and diaphragm, is considered T3 disease, not as metastases.

Tumors with periductal growth pattern (diffuse longitudinal growth pattern along the intrahepatic bile ducts on both gross and microscopic examination) or mixed mass-forming and periductal-infiltrating growth pattern are classified as T4.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor without vascular invasion
T2a	Solitary tumor with vascular invasion
T2b	Multiple tumors, with or without vascular invasion
T3	Tumor perforates the visceral peritoneum or involves local extrahepatic structures by direct invasion
T4	Tumor with periductal invasion

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage I	T1	N0	M0	
Stage II		T2	N0	M0
Stage III	T3	N0	M0	
Stage IVA	T4	N0	M0	
	Any T	N1	M0	
Stage IVB	Any T	Any N	M1	

Additional Descriptors

<u>Lymph-Vascular Invasion</u>

Lymph-vascular invasion (LVI) indicates whether microscopic lymph-vascular invasion is identified in the pathology report. LVI includes lymphatic invasion, vascular invasion, or lymph-vascular invasion. By AJCC/UICC convention, LVI does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category.

H. Lymph Nodes
Lymph node metastases have consistently been identified as an important predictor of outcome for intrahepatic cholangiocarcinoma.[1,2,9] Histologic examination of a regional lymphadenectomy specimen usually involves examination of 3 or more lymph nodes.

The lymph node involvement pattern for intrahepatic cholangiocarcinomas varies with location in the liver (Figure 3). For biliary 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 and gastrohepatic lymph nodes. Nodal involvement of the celiac, periaortic, or caval lymph nodes is considered to be distant metastasis (pM1).[1]

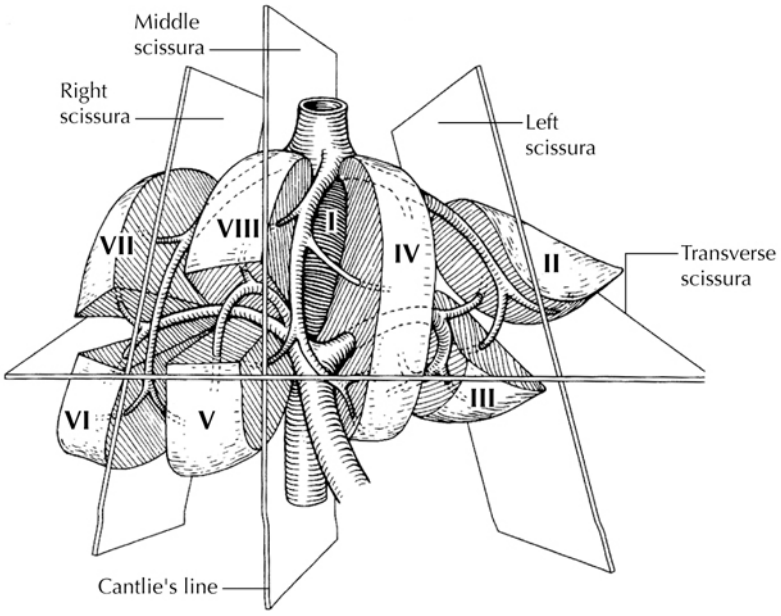

Figure 3. Segmental anatomy of the liver. From Greene et al.[14] Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

I. Additional Pathologic Findings
Cirrhosis (Ishak score 6) or severe fibrosis (Ishak score 5, marked bridging fibrosis with occasional nodules)[10] should be specifically reported because it has an adverse effect on outcome. The presence of underlying disease, such as primary sclerosing cholangitis, should be included in the pathology report.

J. Clinical History
Approximately 10% of intrahepatic cholangiocarcinomas arise in the setting of chronic inflammatory conditions affecting the intrahepatic bile ducts.[11] The most common risk factor for intrahepatic cholangiocarcinoma in the United States is biliary cirrhosis, generally in the setting of primary sclerosing cholangitis. In Asian countries, biliary parasites and recurrent pyogenic cholangitis are also etiologic factors. Recent studies suggest that hepatitis C infection, nonalcoholic fatty liver disease, obesity, and smoking are also risk factors for the development of this tumor.[12,13]

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