

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: October 2009

Procedure

- Hepatic Resection, Partial or Complete

Authors

Kay Washington, MD, PhD, FCAP*

Department of Pathology, Vanderbilt University Medical Center, Nashville, TN

Jordan Berlin, MD

Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Philip Branton, MD, FCAP

Department of Pathology, Inova Fairfax Hospital, Falls Church, VA

Lawrence J. Burgart, MD, FCAP

Allina Laboratories, Abbott Northwestern Hospital, Minneapolis, MN

David K. Carter, MD, FCAP

Department of Pathology, St. Mary's/Duluth Clinic Health System, Duluth, MN

Carolyn C. Compton, MD, PhD, FCAP

Office of Biorepositories and Biospecimen Research, National Cancer Institute, Bethesda, MD

Wendy L. Frankel, MD, FCAP

Department of Pathology, Ohio State University Medical Center, Columbus, OH

John Jessup, MD

Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD

Sanjay Kakar, MD, FCAP

Department of Pathology, University of California San Francisco and the Veterans Affairs Medical Center, San Francisco, CA

Bruce Minsky, MD

Department of Radiation Oncology, University of Chicago, Chicago, IL

Raouf Nakhleh, MD, FCAP

Department of Pathology, Mayo Clinic, Jacksonville, FL

Jean-Nicolas Vauthey, MD†

Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX

For the Members of the Cancer Committee, College of American Pathologists

*denotes primary author. † denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors: John R. Craig, MD; Alberto Marchevsky, MD; Stephen G. Ruby, MD; Gregorio Chejfec, MD; John A. Payne, MD; Jerome B. Taxy, MD; Christopher Willett, MD; James Williams, MD

Gastrointestinal • Intrahepatic Bile Ducts

IntrahepaticBileDuct 3.0.0.0

© 2009 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary (Checklist)" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.

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 3.0.0.0

Summary of Changes

No changes have been made since the October 2009 release.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

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
 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 with asterisks 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
 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

- Specify margin: _____
 Cannot be assessed
 Uninvolved by invasive carcinoma
 Involved by invasive carcinoma

Lymph-Vascular InvasionVenous (Major Vessel) Invasion (V)

(invasion of right or left portal vein, 1 or more hepatic veins)

- Not identified
 Present
 Indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Small Vessel Invasion (L)

- Not identified
 Present
 Indeterminate

***Perineural Invasion**

- * Not identified
 * Present
 * 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
 Specify: Number examined: ____
 Number involved: ____

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

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***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)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

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

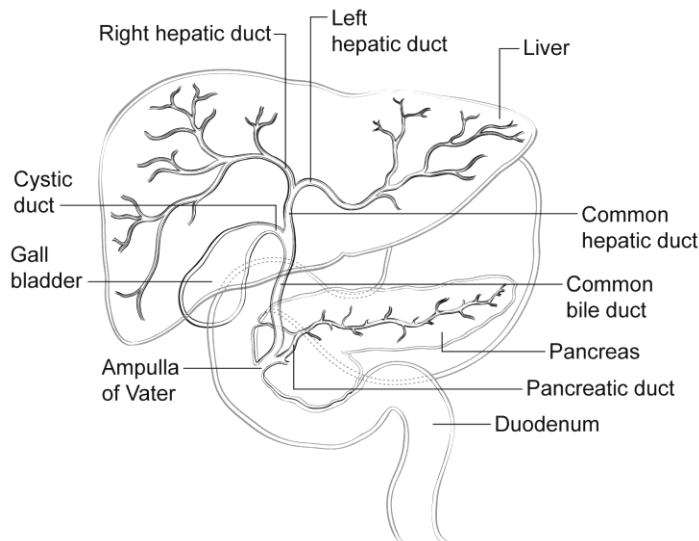


Figure 1. Anatomy of the intrahepatic and extrahepatic biliary system.

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

Combined or mixed hepatocellular-cholangiocarcinoma accounts for less than 5% of primary liver carcinomas⁵ 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}

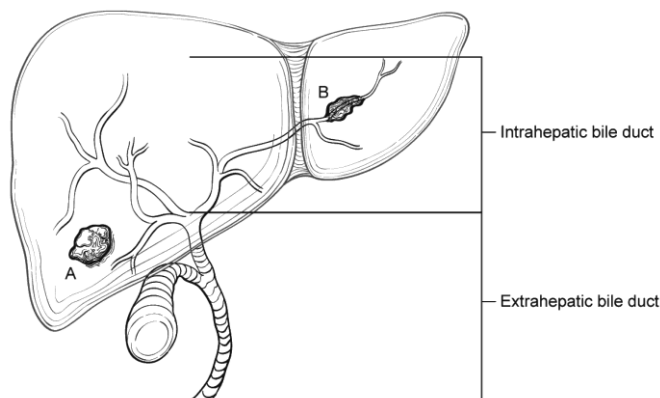


Figure 2. Tumor growth pattern in intrahepatic cholangiocarcinoma. From Edge et al.¹ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Manual*, 7th edition (2009) published by Springer Science and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

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

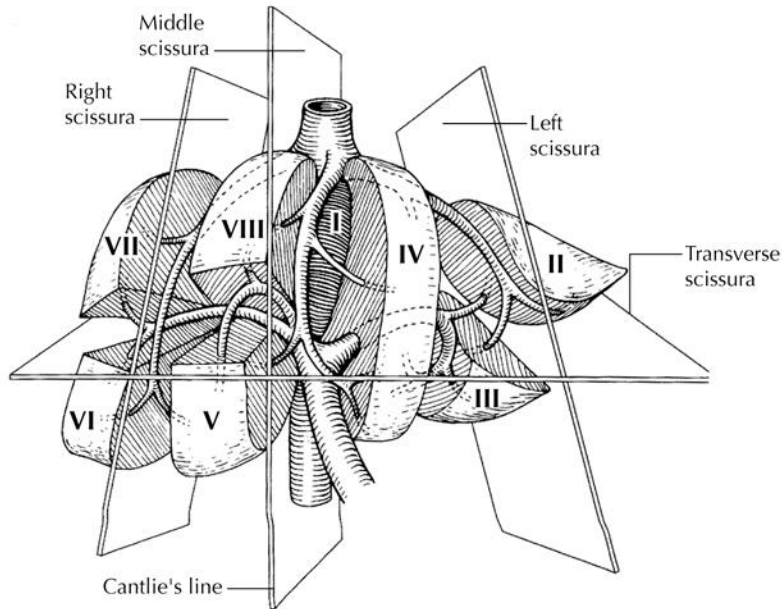


Figure 3. Segmental anatomy of the liver. From Greene et al.¹⁴ Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the *AJCC Cancer Staging Atlas* (2006) published by Springer Science and Business Media LLC, www.springerlink.com.

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}

References

1. Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
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.

4. Hamilton SR, Aaltonen LA, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Digestive System*. Lyon, France: IARC Press; 2000.
5. Lee W-S, Lee K-W, Heo J-S, et al. Comparison of combined hepatocellular and cholangiocarcinoma with hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Surg Today*. 2006;36(10):892-897.
6. Koh KC, Lee H, Choi MS, et al. Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. *Am J Surg*. 2005;189(1):120-125.
7. 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.
8. 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.
9. Ishak KG, Goodman ZD, Stocker JT. *Tumors of the Liver and Intrahepatic Bile Ducts*. Vol 3rd series, fascicle 31. Washington, DC: Armed Forces Institute of Pathology; 2001.
10. Ishak K, Baptista A, Bianchi L, et al. Histologic grading and staging of chronic hepatitis. *J Hepatol*. 1995;22:696-699.
11. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis*. 2004;24(2):115-125.
12. 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.
13. Ben-Menachem T. Risk factors for cholangiocarcinoma.[comment]. *Eur J Gastroenterol Hepatol*. 2007;19(8):615-617.
14. Greene FL, Compton CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas*. New York, NY: Springer; 2006.