# Protocol for the Examination of Specimens from Patients with Carcinoma of the Distal Extrahepatic 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 |
|---|---|
| Local or Segmental Bile Duct Resection | Includes Local or Segmental Bile Duct Resection and Pancreaticoduodectomy (Whipple resection) |
| **Tumor type** | **Description** |
| Carcinoma | Invasive carcinomas including 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 distal extrahepatic bile duct |
| 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*
** 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 including modification to Histologic Type, Tumor Size, and Margin Status for High-Grade Intraepithelial Neoplasia / High-Grade Dysplasia questions and SPECIAL STUDIES section
- Lymphovascular Invasion question updated to Lymphatic and / or Vascular Invasion
- 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: (DISTAL EXTRAHEPATIC BILE DUCTS)**
**Standard(s)**: AJCC 8

**SPECIMEN (Notes A, B)**

**Procedure**
___ Pancreaticoduodenectomy (Whipple resection)
___ Segmental resection of bile duct(s)
___ Choledochal cyst resection
___ Other (specify): _____
___ Not specified

**TUMOR**

**Tumor Site (select all that apply)**
___ Common bile duct, extrapancreatic: _____
___ Common bile duct, intrapancreatic: _____
___ Common bile duct, NOS: _____
___ Other (specify): _____
___ Not specified

**Histologic Type (Note C)**
___ Adenocarcinoma, biliary type (extrahepatic cholangiocarcinoma)
___ Adenocarcinoma, intestinal type
___ Mucinous adenocarcinoma
___ Clear cell adenocarcinoma
___ Poorly cohesive carcinoma
___ Signet-ring cell carcinoma
___ Adenosquamous carcinoma
___ Mucinous cystic neoplasm with associated invasive carcinoma
___ Squamous cell carcinoma
___ Undifferentiated carcinoma, NOS
___ Intraductal papillary neoplasm with associated invasive carcinoma
___ Intraductal tubulopapillary neoplasm with associated invasive carcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ High-grade neuroendocrine carcinoma
___ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEM) (specify components):
_____
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined: _____
**+Histologic Type Comment: _____**

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

**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 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)**
___ No invasion (carcinoma in situ / high-grade dysplasia)
___ Confined to the bile duct histologically
___ Invades beyond wall of bile duct
___ Invades duodenum
___ Invades pancreas
+___ Posterior surface
+___ Anterior surface
+___ Vascular bed / groove (corresponding to superior mesenteric vein / portal vein)
___ Invades gallbladder
___ Invades other adjacent structure(s)
*Select all that apply*
___ Duodenum
___ Ampulla
___ Stomach
___ Gallbladder
___ Omentum
___ Celiac axis
___ Superior mesenteric artery
___ Common hepatic artery
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Depth of Tumor Invasion**
___ No invasion (carcinoma in situ / high-grade dysplasia)
___ Less than 5 mm
___ 5 to 12 mm
___ Greater than 12 mm
___ Cannot be determined (explain): _____

**Lymphatic and / or Vascular Invasion (Note F)**
___ Not identified
___ Present
___ Cannot be determined: _____

**Perineural Invasion (Note F)**
___ 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)**
___ Proximal bile duct: _____
___ Distal bile duct: _____
___ Bile duct: _____
___ Radial: _____
___ Pancreatic neck / parenchymal: _____
___ Uncinate (retroperitoneal / superior mesenteric artery): _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ 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)**
___ Proximal bile duct: _____
___ Distal bile duct: _____
___ Bile duct: _____
___ Radial: _____
___ Pancreatic neck / parenchymal: _____
___ Uncinate (retroperitoneal / superior mesenteric artery): _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

**Margin Status for High-Grade Intraepithelial Neoplasia / High-Grade Dysplasia**
___ All margins negative for high-grade intraepithelial neoplasia / high-grade dysplasia
___ High-grade intraepithelial neoplasia / high-grade dysplasia present at margin
**Margin(s) Involved by High-Grade Intraepithelial Neoplasia / High-Grade Dysplasia (select all that apply)**
___ Proximal bile duct: _____
___ Distal bile duct: _____
___ Bile duct: _____
___ Pancreatic neck / parenchymal: _____
___ Proximal (gastric or duodenal): _____
___ Distal (duodenal or jejunal): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ 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)
___ pTis: Carcinoma in situ / high-grade dysplasia
___ pT1: Tumor invades the bile duct wall with a depth less than 5 mm

___ pT2: Tumor invades the bile duct wall with a depth of 5-12 mm
___ pT3: Tumor invades the bile duct wall with a depth greater than 12 mm
___ pT4: Tumor involves the celiac axis, superior mesenteric artery, and / or common hepatic artery

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

**pN Category**
___ 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: Metastasis in one to three regional lymph nodes
___ pN2: Metastasis in four or more regional lymph nodes

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

**ADDITIONAL FINDINGS (Note J)**

**+Additional Findings (select all that apply)**
___ None identified
___ Choledochal cyst
___ Dysplasia
___ Primary sclerosing cholangitis (PSC)
___ Biliary stones
___ Other (specify): _____

**SPECIAL STUDIES**

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

**COMMENTS**

**Comment(s): _____**

## Explanatory Notes

### A. Specimen Application

Tumors arising in the biliary tree are classified into 3 groups: intrahepatic, perihilar, and distal (Figure 1). Perihilar tumors are defined as those involving the hepatic duct bifurcation or extrahepatic biliary tree proximal to the origin of the cystic duct;[1] distal tumors as those lesions arising between the junction of the cystic duct with common hepatic duct and the ampulla of Vater.[2] This protocol applies only to cancers arising in the distal extrahepatic bile ducts above the ampulla of Vater (Figure 1) and includes malignant tumors that develop in congenital choledochal cysts and tumors that arise in the intrapancreatic portion of the common bile duct. It does not include well-differentiated neuroendocrine tumors or tumors arising in the ampulla of Vater. Carcinomas arising in the cystic duct are grouped for staging purposes with carcinomas of the gallbladder. Tumors arising within the intrahepatic bile ducts or perihilar bile ducts are classified and staged using the intrahepatic bile duct protocol or the perihilar bile duct protocol. Tumors of the pancreas and ampulla of Vater are classified separately. Tumors arising from intrapancreatic portion of common bile duct can be difficult to distinguish from pancreatic adenocarcinomas. Symmetric tumor growth around the bile duct and presence of biliary intraepithelial neoplasia favors a bile duct origin.[3]

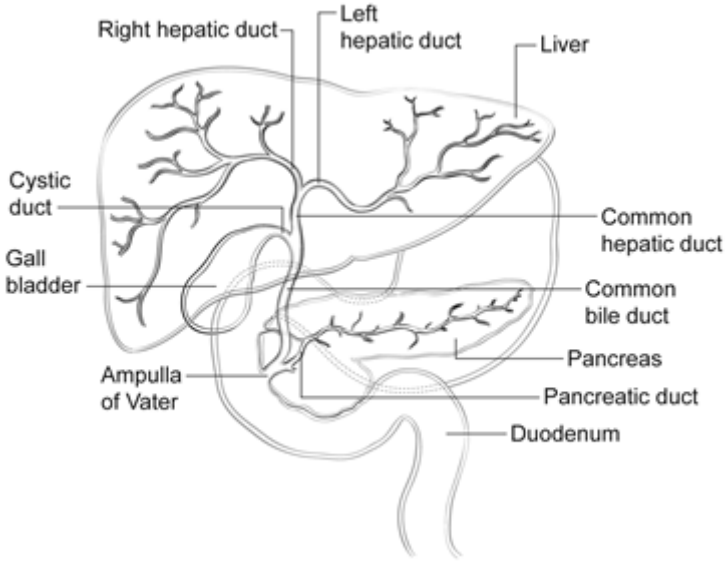


**Figure 1.** Anatomy of the biliary system.

References

1. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*. 2007; 245(5):755-762.
2. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
3. Gonzalez RS, Bagci P, Basturk O, et al. Intrapancreatic distal common bile duct carcinoma: analysis, staging considerations, and comparison with pancreatic ductal and ampullary adenocarcinomas. *Mod Pathol*. 2016; 29(11):1358-1369.

**B. Choledochal Cyst**
Carcinomas may arise in choledochal cysts (congenital cystic dilatation or duplications) of the bile duct. Histologically, they are classified in the same way as those arising in the gallbladder or bile ducts. Stones may be found in these cysts. If dysplasia or carcinoma in situ is found on initial microscopic sections, then multiple additional sections should be examined to exclude invasive cancer in other areas of the cyst.

**C. Histologic Type**
For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.[1] However, this protocol does not preclude the use of other systems of classification or histologic types. By WHO convention, the term *cholangiocarcinoma* is reserved for carcinomas arising in the intrahepatic bile ducts (see intrahepatic bile ducts protocol).

Intraductal neoplasms have a relatively favorable prognosis,[2,3] while signet-ring cell carcinoma, high-grade neuroendocrine carcinomas, and undifferentiated carcinomas are associated with a poorer prognosis.

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. Albores-Saavedra J, Murakata L, Krueger JE, Henson DE. Noninvasive and minimally invasive papillary carcinomas of the extrahepatic bile ducts. *Cancer.* 2000; 89(3):508-515.
3. Luvira V, Pugkhem A, Bhudhisawasdi V, Pairojkul C. Long-term outcome of surgical resection for intraductal papillary neoplasm of the bile duct. *J Gastroenterol Hepatol*. 2017; 32(2):527-533.

**D. Histologic Grade**
For adenocarcinomas, a quantitative grading system based on the proportion of gland formation in the tumor is suggested and shown below.[1]

Grade X Grade cannot be assessed
Grade 1 Well-differentiated (greater 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 50% of tumor composed of glands)

By convention, signet-ring cell carcinomas are assigned grade 3. Undifferentiated carcinomas lack morphologic or immunohistochemical evidence of glandular, squamous or neuroendocrine differentiation. This grading scheme is not applicable to poorly differentiated neuroendocrine carcinomas.

For squamous cell carcinomas, a rare tumor type in the extrahepatic bile ducts, a suggested grading system is shown below. If there are variations in the differentiation within the tumor, the highest (least favorable) grade is recorded.

Grade X Grade cannot be assessed
Grade 1 Well-differentiated

Grade 2 Moderately differentiated
Grade 3 Poorly differentiated

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).

**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. Lymphatic and/or Vascular Invasion and Perineural Invasion**

Perineural and lymphovascular invasion are common in extrahepatic bile duct carcinomas, although they are found less often in early stage cancers (11%).[1] They should be specifically evaluated because they are associated with adverse outcome on univariate analysis.[2] Although perineural invasion is sometimes useful for distinguishing carcinoma from non-neoplastic glands, caution should be used in interpretation of this finding in ducts affected by primary sclerosing cholangitis because perineural invasion by benign hyperplastic intramural glands has been reported in this setting[3] and in adenomatous hyperplasia.

References

1. Cha JM, Kim MH, Lee SK, et al. Clinicopathological review of 61 patients with early bile duct cancer. *Clin Oncol*. 2006;18(9):669-677.
2. Murakami Y, Uemura K, Hayashidani Y, Sudo T, Ohge H, Sueda T. Pancreatoduodenectomy for distal cholangiocarcinoma: prognostic impact of lymph node metastasis. *World J Surg*. 2007; 31(3):337-342; discussion 343-344.
3. Katabi N, Albores-Saavedra J. The extrahepatic bile duct lesions in end-stage primary sclerosing cholangitis. *Am J Surg Pathol.* 2003; 27(3):349-355.

**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 extent of the viable tumor should be used to assign the ypT category as site 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**

Locoregional recurrence, as opposed to distant metastases, is usually the first site of disease recurrence and is often related to residual tumor located in the proximal or distal surgical margins of the bile duct or from tumor located along the dissected soft-tissue margin in the portal area. Local recurrence (usually at the surgical margins) can be attributed in many cases to tumor spread longitudinally along the duct wall and to perineural and lymphovascular invasion.[1]

Complete surgical resection with microscopically negative surgical margins is an important predictor of outcome in multivariate analysis for both perihilar and distal bile duct carcinomas.[2,3]

Malignant tumors of the extrahepatic bile ducts are often multifocal.[4] Therefore, microscopic foci of carcinoma or intraepithelial neoplasia may be found at the margin(s) even though the main tumor mass has been resected. In some cases, it may be difficult to evaluate margins on frozen-section preparations because of inflammation and reactive change of the surface epithelium or within the intramural mucous glands. If surgical margins are free of carcinoma, the distance between the closest margin and the tumor edge should be measured.

Because 5% of patients with bile duct carcinoma have synchronous carcinomas of the gallbladder, examination of the entire surgical specimen, including the gallbladder, is advised.

References
1. Jarnagin WR. Cholangiocarcinoma of the extrahepatic bile ducts. *Semin Surg Oncol*. 2000;19(2):156-176.
2. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg.* 2007; 245(5):755-762.
3. Chung YJ, Choi DW, Choi SH, Heo JS, Kim DH. Prognostic factors following surgical resection of distal bile duct cancer. *J Korean Surg Soc.* 2013; 85(5):212-218.
4. 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).

**I. pTNM Classification**

Surgical resection is the most effective therapy for extrahepatic biliary tract carcinomas, and the best estimation of prognosis is related to the anatomic extent (stage) of disease at the time of resection. In particular, lymph node metastases are predictors of poorer outcome.[1,2]

For malignant tumors of the distal extrahepatic bile ducts, the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.[3] The staging system also applies to tumors arising in choledochal cysts.

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The designation “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 (i.e., 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

Tis 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. The term carcinoma in situ is not widely applied to glandular neoplastic lesions but is retained for tumor registry reporting purposes as specified by law in many states.

The histology of the extrahepatic biliary tree varies along its length, with little smooth muscle in the wall of the proximal ducts as compared with the distal bile duct. The common bile duct lacks serosa, and the fibromuscular wall is surrounded by fat. Tumor infiltration into the fat beyond the fibromuscular wall is considered as extension beyond the bile duct. These anatomic features make it difficult to assess the anatomic level of tumor invasion. Inflammatory changes in the bile ducts and desmoplastic stromal response to tumor may also cause distortion of tissue boundaries. This has led to change in the T categories in the AJCC 8$^{th}$ edition, with T1-T3 being defined by the measurement of depth of invasion of tumor. The depth is measured from the basement membrane of adjacent normal or dysplastic epithelium to the point of deepest tumor invasion.[4,5] Properly oriented longitudinal sections through the tumor and including adjacent mucosa are necessary to accurately measure depth of invasion. If the depth is difficult to determine, a best estimate is used. Cutoffs using 0.5 cm and 1.2 cm have yielded better prognostic stratification compared to anatomic level of invasion.[3]

A 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. For invasive carcinoma associated with intraductal papillary neoplasms and mucinous cystic neoplasms, the invasive portion can be multifocal and the deepest focus of the invasive component should be used for assigning the T-category. It is also suggested that in addition to the size of the largest focus, also include the combined/cumulative size of all invasive carcinoma foci and/or their percentage relative to the gross tumor size (see also note E).

Even though the anatomic level of invasion and direct invasion into the pancreas, duodenum, gallbladder, colon, stomach, and omentum does not affect the T category, it should be included in the pathology report. Lymphatic or venous invasion does not affect the T category. T4 tumors are characterized by involvement of superior mesenteric artery, celiac axis and/or common hepatic artery. In most instances, these tumors are considered unresectable and hence T4 category is determined by radiologic studies and is not usually assigned by pathologists.

N Category Considerations

The regional nodes for distal bile duct carcinomas are the same as those for carcinomas of the pancreatic head and include the following: lymph nodes along the common bile duct, and hepatic artery; posterior and anterior pancreaticoduodenal nodes; and nodes along the right lateral wall of the superior mesenteric artery.

Tumor involvement of other nodal groups is considered distant metastasis. Anatomic division of regional lymph nodes is not necessary, but separately submitted lymph nodes should be reported individually as received. A minimum number of lymph nodes examined for accurate staging has not been determined, but examination of at least 12 lymph nodes is suggested.[3,6]

Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination), and data are currently insufficient to recommend special measures to detect micrometastasis or isolated tumor cells. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques, such as immunohistochemistry, are recommended for routine examination of regional lymph nodes. 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.

References

1. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*. 2007; 245(5):755-762.
2. Hong SM, Cho H, Lee OJ, Ro JY. The number of metastatic lymph nodes in extrahepatic bile duct carcinoma as a prognostic factor. *Am J Surg Pathol*. 2005;29(9):1177-1183. [erratum in *Am J Surg Pathol*. 2005; 29(11):1548].
3. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017
4. Hong SM, Cho H, Moskaluk CA, Yu E. Measurement of the invasion depth of extrahepatic bile duct carcinoma: an alternative method overcoming the current T classification problems of the AJCC staging system. *Am J Surg Pathol*. 2007; 31(2):199-206.
5. Hong S-M, Pawlik TM, Cho H, et al. Depth of tumor invasion better predicts prognosis than the current American Joint Committee on Cancer T classification for distal bile duct carcinoma. *Surgery.* 2009; 146(2):250-257.
6. Adsay NV, Basturk O, Altinel D, et al. The number of lymph nodes identified in a simple pancreatoduodenectomy specimen: comparison of conventional vs orange-peeling approach in pathologic assessment. *Mod Pathol.* 2009; 22(1):107-112.

**J. Additional Findings**

Chronic inflammatory conditions affecting the bile ducts are associated with higher risk for biliary tract carcinomas. The most common risk factor for cholangiocarcinoma of the extrahepatic bile ducts in Western countries is primary sclerosing cholangitis (PSC), characterized by multifocal strictures and inflammation of the extrahepatic and intrahepatic biliary tree. Patients with PSC are at risk for multifocal biliary carcinomas. In Japan and Southeast Asia, hepatolithiasis due to recurrent pyogenic cholangitis with biliary stones is a more common risk factor for biliary malignancy. Biliary parasites such as *Clonorchis sinensis* and *Opisthorchis viverrini*, prevalent in parts of Asia, are also associated with carcinomas of the extrahepatic bile ducts.

**K. 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.