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

Protocol applies to carcinomas of the intrahepatic bile ducts and combined hepatocellular-cholangiocarcinoma. This protocol does not apply to hepatocellular carcinoma, hepatoblastoma, and carcinomas of the perihilar bile ducts.

Based on:

AJCC/UICC TNM, 7th edition
CAP Cancer Protocol version 3.1.0.2
CAP Protocol Web Posting Date: October 2013
AAPA Macroscopic Examination Template Version 1.0
AAPA Web Posting Date: March 2017

Revision History:

None

Summary of Changes:

None

Procedures Covered in this Protocol:

- Wedge resection
- Partial hepatectomy
- Total hepatectomy

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Immunohistochemistry Considerations:

Greater than 90% of intrahepatic cholangiocarcinomas express keratins 7 and 19, and about 40% also express keratin 20. Most cases are also positive for expression of CEA and CA19-9.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. Formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:***
  - Liver wedge resection
  - Partial hepatectomy
    - Major hepatectomy (3 segments or more)
    - Minor hepatectomy (less than 3 segments)
  - Total hepatectomy

  *This protocol does not apply to hepatocellular carcinoma, hepatoblastoma, and carcinomas of the perihilar bile ducts.

- **Specimen Size and Extent of Resection:**
  - Liver wedge resection – record three dimensions.
  - Liver – record three dimensions and weight.
  - Gallbladder – record three dimensions.
  - Perihilar bile ducts – record length and diameter.
  - Record measurements of any other included organs or structures.

- **Explanatory Anatomical Notes:** *(Figure 1)*
  - The intrahepatic bile ducts extend from the periphery of the liver to the second-order bile ducts.
  - 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.

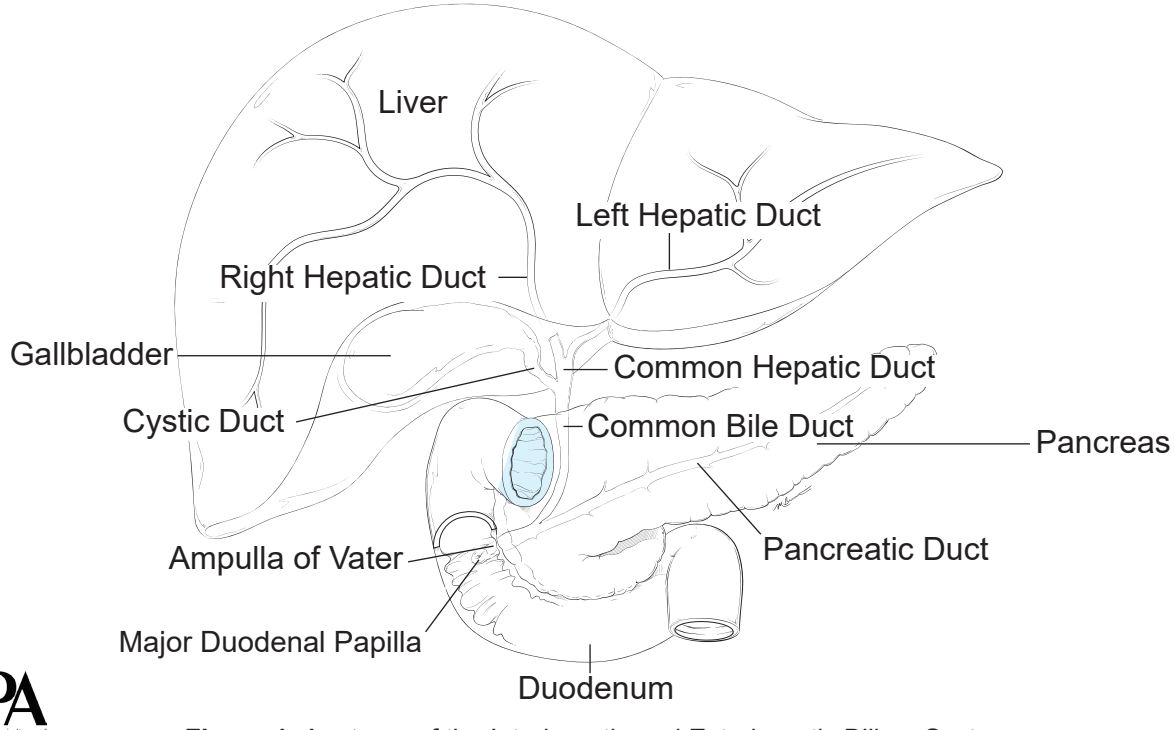

Figure 1: Anatomy of the Intrahepatic and Extrahepatic Biliary System

- **Specimen Integrity and Adequacy:***
  - Identify the cut surgical margins and the capsular surface and provide an assessment of specimen integrity.
  - Assess the overall appearance of the resected liver (e.g., normal, homogeneous parenchyma with a smooth capsule vs. the nodular and fibrotic appearance of a cirrhotic liver).
  - Identify the hepatic vascular pedicle.
    - The vessels and ducts at the porta hepatis constitute the hepatic pedicle and have many variations that are of surgical importance.
  - Surgical defect vs tumor perforation of the liver capsule / visceral peritoneum should be clarified.
  - Describe evidence of previous surgical procedures (e.g., scar, previous biopsy, etc.).

**Statements should include, with as much clarity as can be provided, the anatomic location of the defects or disruptions, and should also incorporate statements which assess the relationship of any defects or disruptions to the tumor. State whether the defect(s) appear to represent a surgical defect or a condition imposed by the tumor (e.g., breach of the liver capsule by tumor). If defects or disruptions involve the tumor and serve to hinder assessment of the final surgical margin this must be stated. Consultation with the surgeon for clarification should be considered as well as differentially inking the margins in areas affected by defects or disruptions as this may assist in creating a post-surgery treatment plan.*

TUMOR ("T" of TNM)

- **Tumor Size:**
  - Record the tumor size in three dimensions.
  - If multiple tumors, count and give dimensions of each or provide a range in size in three dimensions.
- **Tumor Site(s):** *(Figure 2)*
  - The liver is divided into eight segments, but assignment of the segments on resection specimens is best provided by the surgeon.

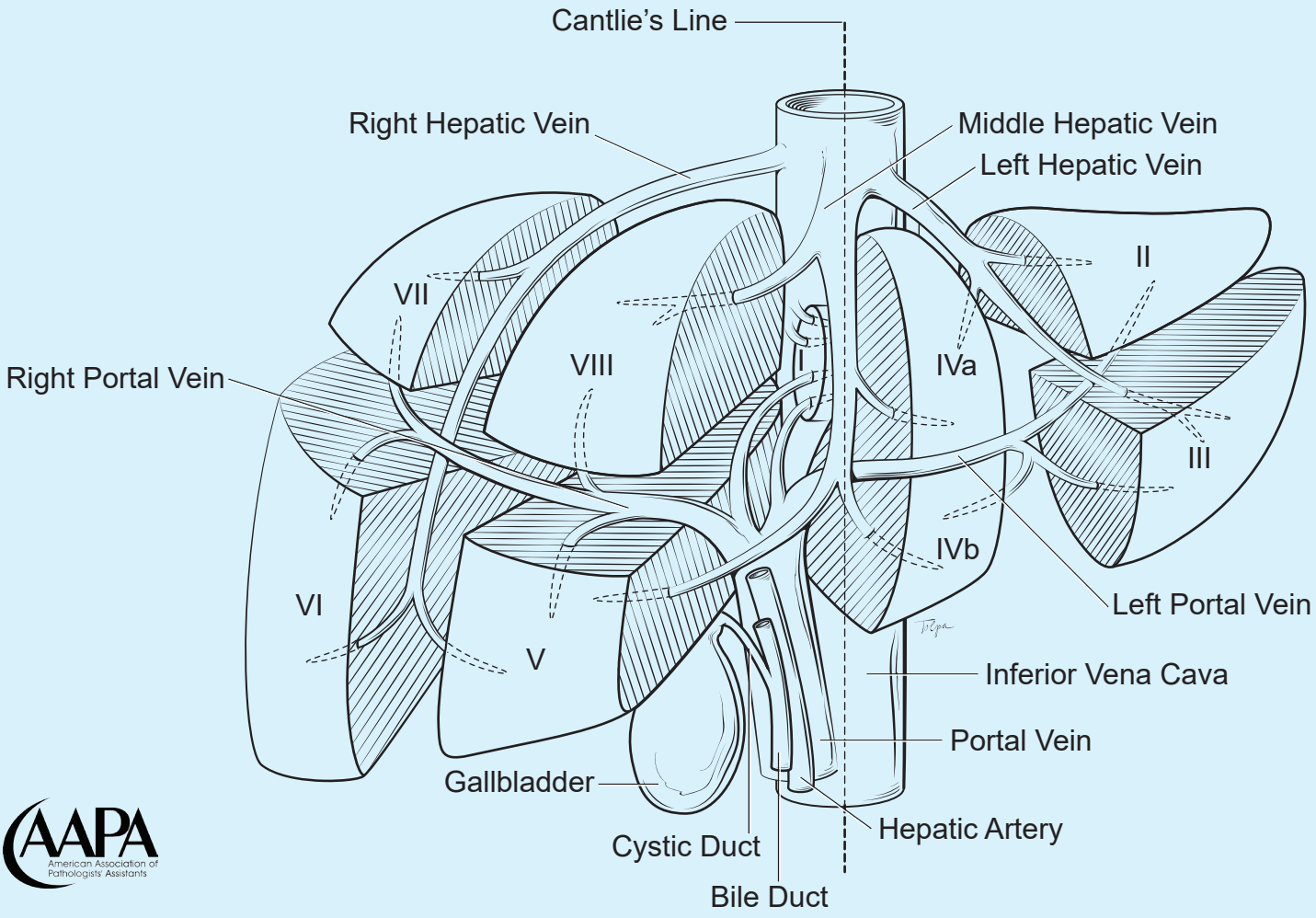

Figure 2: Liver Anatomy - Segments I-VIII with Venous Tracts

Cantlie's line is a vertical plane that divides the liver into left and right lobes creating the principal plane used for hepatectomy. It extends from the inferior vena cava posteriorly to the middle of the gallbladder fossa anteriorly. It contains the middle hepatic vein which divides the liver into left and right lobes. Segments II, III, IVa and IVb are on the left of the plane, and segments V, VI, VII and VIII are on the right.

- State if the tumor is:
  - Subcapsular
  - Parenchymal
  - Vasculocentric
  - Lobar

- Tumor Focality
  - State if the tumor is solitary, and specify the location in segment or lobe of liver.
  - State if there are multiple tumors, and specify the locations in segments or lobes and include the distance from each tumor.
  - Submit sections from each major tumor nodule, and representative sections of smaller nodules if macroscopically different in appearance.

- **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:**

  - Measure tumor to liver capsule.
  - Measure tumor to gallbladder/hepatic bed, if present.
  - Measure tumor to major vascular structures.
  - State if the tumor is:
    - Confined to the liver
    - Involves a major branch of the portal vein
    - Involves 1 or more hepatic vein(s)
    - Involves the visceral peritoneum
    - Directly invades the gallbladder
    - Directly invades other adjacent organs (specify)
    - Describe other macroscopic features (e.g., nodularity, bulging cut surface, hemorrhage, central scar).
  - If a tumor has been preoperatively embolized via transarterial chemo-embolization (TACE), macroscopic percentage of tumor necrosis should be assessed.
  - Describe tumor configuration.*

  *Intrahepatic cholangiocarcinoma is characterized by three growth patterns that may coexist:
    - Mass-forming type
      - Characteristic firm, white, or gray macroscopic appearance
      - Well-demarcated nodule growing in a radial pattern and invading liver parenchyma
    - Periductal infiltrating type
      - Spreads in a diffuse longitudinal growth pattern along the bile duct
    - Mixed mass-forming/periductal infiltrating type

Primary Tumor (T)	
pTX	Primary tumor 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***

*Note that the presence of vascular invasion is the difference between pT1 and pT2 tumors. Vascular invasion can refer to macroscopic tumor invasion of large vessels or microscopic involvement of small vessels. Ensure sufficient tumor tissue is submitted for identification of vascular invasion.

**All multiple tumor nodules are considered equal for the purpose of staging. There is no difference between satellite nodules, multifocal primary cholangiocarcinomas and intrahepatic metastases.

***Tumors with the periductal infiltrating pattern invade the length of the duct longitudinally instead of forming a mass that infiltrates into the surrounding parenchyma. This type of tumor growth pattern (including the mixed variant of the two) may be associated with a poor prognosis and is considered stage T4.

TNM Descriptors

cTNM: The "c" prefix is used when clinical staging is performed by the referring physician or when pathological assessment is not possible.

pT(m)NM: The "m" suffix is added within parentheses after the pT indicator and is used when there are multiple primary tumors within a single site.

ypTNM: The "y" prefix is used when neoadjuvant therapy has been performed.

rTNM: The "r" prefix is used when tumor recurrence is staged after a disease-free interval.

aTNM: The "a" prefix indicates when the stage is determined at autopsy.

ADDITIONAL SECTIONS

Additional sections of uninvolved liver parenchyma should be submitted for sufficient evaluation for hepatobiliary parasitosis, chronic viral hepatitis and primary sclerosing cholangitis, all of which are predisposing factors to cholangiocarcinoma.

Margins:

Evaluation of margins for total or partial hepatectomy specimens depends on the method and extent of resection. Consultation with the surgeon is recommended to determine the critical foci within the margins that require microscopic evaluation.

- Hepatectomy
  - Submit representative sections of all margins at the closest approach of the tumor.
  - Submit vascular margins (if identified).
  - Gallbladder hepatic bed margin.
  - Bile duct margin
    - State if the bile duct margin is involved or uninvolved by tumor.

- Partial hepatectomy resection margin
  - Apply ink to the surgical resection margin.
  - State if the parenchymal margin is uninvolved or involved by tumor.
  - If margins are macroscopically free of tumor, judicious sampling of the margin in the region closest to the nearest identified tumor nodule is indicated.
  - Take sections of the bile ducts at the margin to evaluate the lining epithelium for in situ carcinoma or dysplasia.
  - Record the distance of tumor from the closest margin.
  - For multiple tumors, record the distance of the nearest tumor to the margin.
  - Submit vascular margins (if identified).
  - Gallbladder hepatic bed margin, if present.
  - Other margins would include those of attached structures / organs.
    - State if margins are uninvolved or involved by tumor.

Explanatory Notes:

Surgery for partial hepatectomy may or may not follow anatomic boundaries. Consequently, before sectioning, it is important to understand the procedure that was performed; review the imaging studies and reports, and consult with the surgeon if necessary. Often, the perihilar bile duct margins will be evaluated by frozen section analysis. If no frozen section is performed, ensure the documentation of margins prior to dissection.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:** (if applicable)

pNX	**Cannot be assessed**
pN0	**No regional lymph node metastasis**
pN1	**Regional lymph node metastasis**

The lymph node drainage patterns from the intrahepatic bile ducts demonstrate laterality. Lymph node involvement patterns for intrahepatic bile duct tumors varies with location in the liver.

Regional lymph nodes

- Right lobe biliary tumors (segments 5-8):
  - Hilar lymph nodes (common bile duct, hepatic artery, portal vein and cystic duct)
  - Periduodenal lymph nodes
  - Peripancreatic lymph nodes

- Left lobe tumors (segments 2-3):
  - Hilar
  - Gastrohepatic lymph nodes

Note: Celiac, periaortic or caval lymph nodes are considered to be distant metastasis. Inferior phrenic nodes are considered regional nodes.

Histologic examination of a regional lymphadenectomy specimen usually involves examination of 3 or more lymph nodes:

- State the number of lymph nodes identified.
- Specify the location, if known.
- Measure the lymph nodes in three dimensions.
- Describe the cut surface of the lymph nodes.
- Submit all lymph nodes for microscopic examination.
  - Submit small lymph nodes in toto.
  - Section and entirely submit larger macroscopically negative lymph nodes.
  - Representative sections from macroscopically positive nodes are adequate.
- If possible, submit lymph sections so that the long axis of the lymph node can be demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

- **Explanatory Notes:**

Direct invasion of the portal lymph nodes is considered a T3 disease and not as metastases.

METASTASIS ("M" of TNM)

- **Metastasis:**

pM0	**No distant metastasis**
pM1	**Distant metastasis**

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  - Intrahepatic cholangiocarcinomas commonly metastasize to other sites within the liver (referenced in the pT2b classification - multiple tumors) and to the peritoneum, lungs and pleura.
  - Nodal involvement of the celiac, periaortic, or caval lymph nodes are considered to be distant metastasis instead of regional nodal involvement.
  - Extraregional nodal involvement and other distant metastatic sites are classified as M1 disease.

- **Explanatory Notes:**

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

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