Protocol for Examination of Specimens from Patients with Hepatocellular Carcinoma.

This protocol does not apply to cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, or hepatoblastoma.

Based on:

AJCC/UICC TNM, 7th edition
CAP Cancer Protocol version 3.1.0.0.
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Revision History:

None

Summary of Changes:

None

Procedures Covered in this Protocol:

- Partial Hepatectomy
- Complete Hepatectomy

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Ambiguous Terminology:

Visceral peritoneum and liver capsule are synonymous.

Molecular Considerations:

No single, universal sequence of molecular alterations leads to development of hepatocellular carcinoma. Activation of beta-catenin and inactivation of p53 are the two most common early mutational events.

Immunohistochemistry Considerations:

Hepatocellular carcinoma is positive for Hep Par1, AFP, and polyclonal CEA/CD10 in bile canaliculi. It is also positive for CAM 5.2, cytokeratins 8, 18, and ER/PR. PAS positive cytoplasmic glycogen, intracellular PAS positive globular inclusions, loss of pericellular reticulin may also be identified. EMA and Ber EP4 are negative. Glypican 3, HSP70, glutamine synthetase, cellular retinol-binding protein - 1, and nuclear Ki-67 are also positive.

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:***
  - Wedge resection
  - Partial hepatectomy
    - Major hepatectomy (3 segments or more)
    - Minor hepatectomy (less than 3 segments)
  - Total Hepatectomy

  *This protocol does not apply to cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, or hepatoblastoma.

- **Specimen Size and Extent of Resection:**
  - Liver* – record three dimensions and weight.
  - Gallbladder – record three dimensions.
  - Record measurements of any other included organs.

  *The liver is divided into eight segments, but assignment of the segments is best provided by the surgeon.

- **Specimen Integrity and Adequacy:***
  - Identify the cut surgical margins and the capsular surface, and provide an assessment of specimen integrity.
  - Identify the vascular pedicle.
  - Surgical defect vs tumor perforation of the liver capsule / visceral peritoneum should be clarified, if needed, as tumor perforation upstages to pT4.
  - 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.
- **Explanatory Notes:**

  In a cirrhotic liver, a solid irregular lesion > 5 cm is most likely a hepatocellular carcinoma.

  For staging purposes, multifocal tumors, satellite nodules, and intrahepatic metastases are not differentiated and are all classified as multifocal tumors.
- **Tumor Site(s):**
  - The liver is divided into eight segments, but assignment of the segments on resection specimens is best provided by the surgeon. *(Figure 1)*
  - In a partial resection, the number of segments included in the specimen determines major vs minor hepatectomy.
  - Hepatocellular carcinoma often shows a mosaic of macroscopic patterns.
    - State if the tumor is:
      - Subcapsular
      - Parenchymal
      - Vasculocentric
      - Lobar

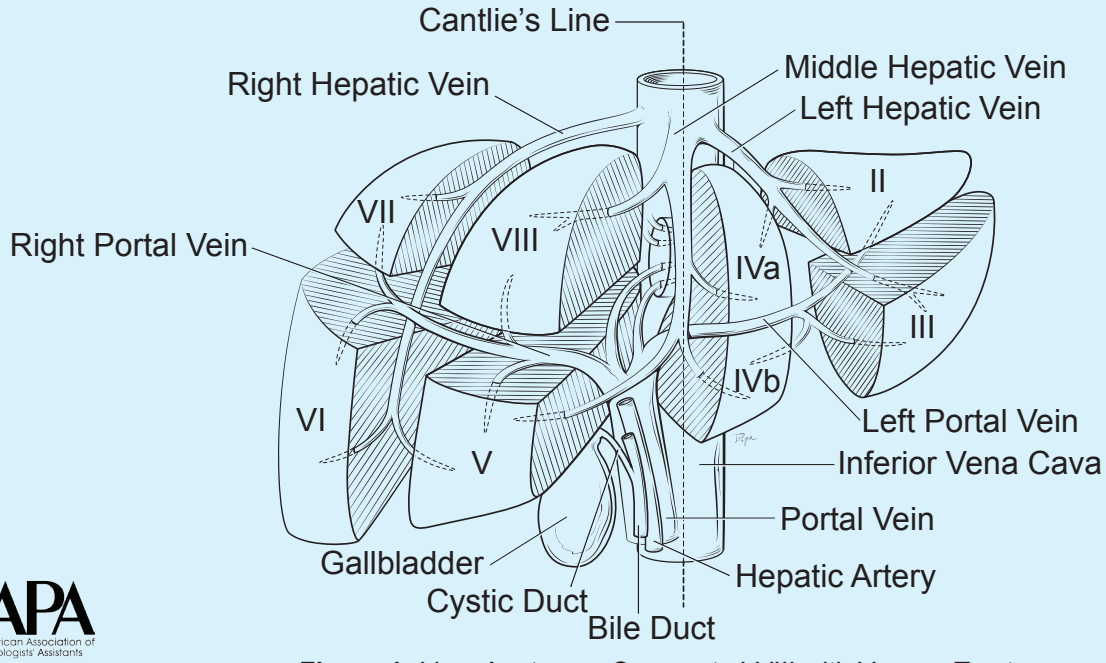


Figure 1: Liver Anatomy - Segments I-VIII with Venous Tracts

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.

- Tumor Focality
  - State if the tumor is solitary, and specify the location.
  - State if there are multiple tumors, and specify the locations.
  - Each major nodule should be sampled, as well as any smaller nodules that appear macroscopically different.
  - Larger cirrhotic nodules should also be sampled, as there could be dysplastic changes.

- **Explanatory Notes:**

  Intrahepatic venous dissemination cannot be differentiated from satellitosis or multifocal tumors and is classified as multiple tumors. Multiple tumors include multiple independent primaries or intrahepatic metastases from a single hepatic carcinoma. A multicentric distribution is associated with a poor prognosis.

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

  The number of tumors, size of tumor(s), presence of vessel invasion, and presence of adjacent organ invasion contribute to upstaging.

  - 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

pTX	**Primary tumor cannot be assessed**
pT0	**No evidence of primary tumor**
pT1	**Solitary tumor without vascular invasion**
pT2	**Solitary tumor with vascular invasion; or multiple tumors, none more than 5 cm in greatest dimension**
pT3a	**Multiple tumors more than 5 cm**
pT3b	**Tumor(s) any size involving a major branch of the portal or hepatic vein(s)**
pT4	**Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum/capsule**

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 "p" indicator refers to classification based on gross and microscopic exam.

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).

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.

- **Margins:**

  Evaluation of margins for total or partial hepatectomy specimens depends on the method and extent of resection.

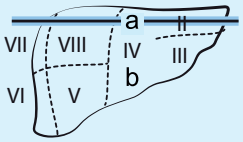
  - Hepatectomy
    - Submit representative sections of all margins at the closest approach of the tumor.
    - Submit vascular margins (if identified).

  - Partial hepatectomy transection margin
    - State if the parenchymal margin is uninvolved or involved by tumor.
    - If margins are macroscopically free of tumor, judicious sampling of the cut surface in the region closest to the nearest identified tumor nodule is indicated.
    - Record the distance of tumor from the closest margin.
    - For multiple tumors, record the distance from the nearest tumor.
    - Other margins would include those of attached structures / organs.
      - State if margins are uninvolved or involved by tumor.

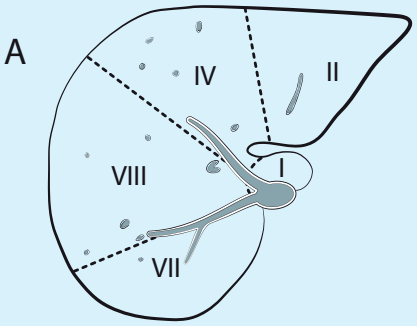
- **Explanatory Notes:**

  Vessels *(Figure 2)*
  Macroscopic (vs. microscopic) involvement of vessels is differentiated in the CAP protocol, therefore, make a clear statement as to the presence or absence of macroscopic vessel involvement, and demonstrate in sections. Involvement of a branch of the portal vein (right or left) vs. hepatic vein (right, middle, or left) are further distinguished in the protocol. Tumors larger than 5 cm or multiple tumors are more likely to show vascular invasion than single small lesions.

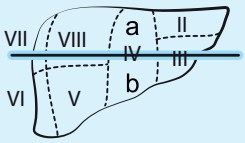
Superior liver segments are divided by the right and middle hepatic veins and the falciform ligament.



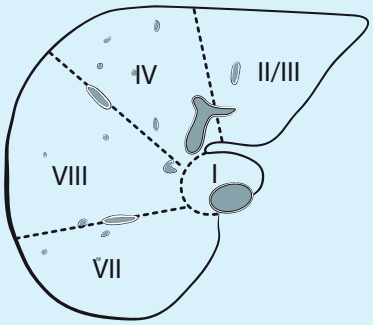
Level of the superior liver segments



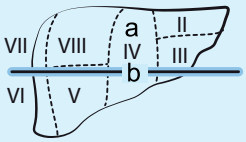
The left portal vein divides the left lobe into superior segments (II and IVa) and inferior segments (III and IVb). The left portal vein is at a higher level than the right portal vein.



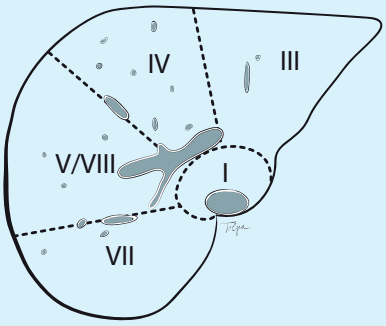
Level at the left portal vein



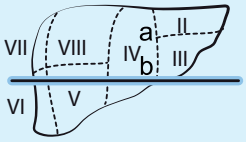
The right portal vein divides the right lobe of the liver into superior segments (VII and VIII) and the inferior segments (V and VI). The level of the right portal vein is inferior to the level of the left portal vein.



Level at the right portal vein



Only the inferior segments are visible at the level of the splenic vein, which is below the level of the right portal vein.



Level at the splenic vein

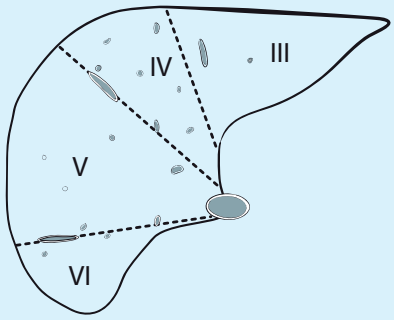


Figure 2: Transverse Anatomy of Liver Segments

Visceral Peritoneum
Perforation of the visceral peritoneum / capsule indicates pT4 tumor. Areas of possible involvement should be adequately sampled.

Uninvolved Liver
Sample the uninvolved liver parenchyma to document other pathologic findings, such as cirrhosis, fibrosis, dysplasia, steatosis, iron overload, or chronic hepatitis. The severity of underlying disease (namely cirrhosis) is a predictor of long term survival.

Prognostic Features
For patients who undergo tumor resection, the main predictor of poor outcome is a positive surgical margin. The effect of the extent of surgical clearance at the closest margin (<10 mm vs. >10 mm) remains controversial. Other prognostic features associated with decreased survival include major vessel invasion and tumor size >5 cm in patients with multiple tumors.

LYMPH NODES ("N" of TNM)

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

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

- **Regional lymph nodes of the liver include:**
  - Hilar lymph nodes
  - Hepatoduodenal ligament lymph nodes
  - Inferior phrenic lymph nodes
  - Caval lymph nodes
  - Most prominent are the hepatic artery and portal vein lymph nodes.
- Involved nodes distal to these regional lymph nodes are considered distant metastases.

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

Macroscopically negative lymph nodes:

- Describe the cut surface of the identified lymph nodes.
- Submit all lymph nodes for microscopic examination.
  - Measure the lymph nodes in three dimensions; if multiple, provide a range in size.
  - Submit smaller nodes in toto.
  - Section and entirely submit larger macroscopically negative lymph nodes.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

Macroscopically positive lymph nodes:

- Provide a measurement for the lymph node metastasis.
- Representative sections from macroscopically positive nodes are adequate.
- Any areas suspicious for extra-nodal tumor extension should be sampled.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

METASTASIS ("M" of TNM)

- **Metastasis:**

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

- The main mode of dissemination of liver carcinomas is via the portal veins and hepatic veins.
- The most common sites of extrahepatic dissemination are the lungs and bones.
- Tumors may extend through the liver capsule to adjacent organs, such as the adrenal glands, diaphragm, and colon.
- These tumors may rupture, causing acute hemorrhage and peritoneal metastasis.

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