Protocol for the Examination of Specimens From Patients With Hepatocellular Carcinoma

Cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, and hepatoblastoma are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: February 1, 2011

Procedure
• Hepatic Resection, Partial or Complete

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CAP Hepatocellular Carcinoma Protocol Revision History

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

Version: Hepatocellular 3.1.0.0

Summary of Changes
The following changes have been made since the October 2009 release.

Hepatic Resection

Regional Lymph Nodes (pN)
Specify: Number examined / Number involved, has been changed to:

___ No nodes submitted or found

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

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

+ Additional Pathologic Findings
F2 was changed to F0, as follows:

+ Fibrosis score:
+ ___ Cirrhosis/severe fibrosis (Ishak score 5-6) (F1)
+ ___ None to moderate fibrosis (Ishak score 0-4) (F0)
Surgical Pathology Cancer Case Summary

Protocol web posting date: February 1, 2011

HEPATOCELLULAR CARCINOMA: Hepatic 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) (Note B)
___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 location): ____________________________

Histologic Type (Note C)
___Hepatocellular carcinoma
___Fibrolamellar hepatocellular carcinoma
___Undifferentiated carcinoma
___Other (specify): ____________________________
___Carcinoma, type cannot be determined

Histologic Grade (Note D)
___Not applicable
___GX: Cannot be assessed
___GI: Well differentiated
___GII: Moderately differentiated
___GIII: Poorly differentiated
___GIV: Undifferentiated/anaplastic
___Other (specify): ____________________________
Tumor Extension (select all that apply)
___ Tumor confined to liver
___ Tumor involves a major branch of the portal vein
___ Tumor involves 1 or more hepatic vein(s)
___ Tumor involves visceral peritoneum
___ Tumor directly invades gallbladder
___ Tumor directly invades other adjacent organs (specify): ______________________

Margins (select all that apply) (Note E)

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

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

Lymph-Vascular Invasion (Note F)

Macroscopic Venous (Large Vessel) Invasion (V)
___ Not identified
___ Present
___ Indeterminate

Microscopic (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)

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

___ pTX: 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
___ pT3a: Multiple tumors more than 5 cm
___ pT3b: Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic veins
___ pT4: Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

**Regional Lymph Nodes (pN)**

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

___ No nodes submitted or found

**Number of Lymph Nodes Examined**
Specify: ___
___ Number cannot be determined (explain): ______________________

**Number of Lymph Nodes Involved**
Specify: ___
___ Number cannot be determined (explain): ______________________

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

+ Additional Pathologic Findings (select all that apply) (Note H)

+ Fibrosis score:
  + ___ Cirrhosis/severe fibrosis (Ishak score 5-6) (F1)
  + ___ None to moderate fibrosis (Ishak score 0-4) (F0)

+ ___ Hepatocellular dysplasia
   + ___ Low-grade dysplastic nodule
   + ___ High-grade dysplastic nodule

+ ___ Steatosis
+ ___ Iron overload
+ ___ Chronic hepatitis (specify etiology): ______________________
+ ___ Other (specify): ______________________
+ ___ None identified

+ Ancillary Studies
+ Specify: ______________________

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.
+ Clinical History (select all that apply) (Note 1)
+ ___ Cirrhosis
+ ___ Hepatitis C infection
+ ___ Hepatitis B infection
+ ___ Alcoholic liver disease
+ ___ Obesity
+ ___ Hereditary hemochromatosis
+ ___ Other (specify): ______________________________
+ ___ Not known

+ Comment(s)
Explanatory Notes

A. Application
This protocol applies only to hepatic resection specimens containing hepatocellular carcinoma. Carcinomas of the intrahepatic bile ducts (cholangiocarcinomas) are now staged using a separate TNM system.¹

B. Tumor Location, Focality and Histologic Sampling
The segmental anatomy of the liver is shown in Figure 1. Although these divisions are useful for anatomic localization of tumors, it is often not possible to assign segmental location on resection specimens, and such information is best provided by the surgeon.

Figure 1. 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.

Sections should be prepared from each major tumor nodule, with representative sampling of smaller nodules, if macroscopically different in appearance. Cirrhotic nodules appreciably larger than the surrounding background liver should also be sampled, because such nodules may harbor dysplastic changes.² For purposes of staging, satellite nodules, multifocal primary hepatocellular carcinomas, and intrahepatic metastases are not distinguished and are considered multiple tumors.

C. Histologic Type
The protocol recommends the following modified classification of the World Health Organization (WHO).³ In the United States, almost 70% of the primary malignant tumors of the liver are hepatocellular carcinomas.³⁴

WHO Classification of Carcinomas of the Liver (Modified)
Hepatocellular carcinoma
    Variant: Fibrolamellar hepatocellular carcinoma
Undifferentiated carcinoma

Multiple histologic architectural patterns, such as trabecular, solid, and pseudoglandular patterns, are often found in the same tumor in hepatocellular carcinoma,⁴ but only the fibrolamellar variant appears to have
prognostic significance, although the relatively longer survival for this variant may relate to its occurrence in younger patients and in the noncirrhotic liver. Tumors that contain areas of both fibrolamellar carcinoma and typical hepatocellular carcinoma should not be classified as fibrolamellar carcinoma; this term should be reserved for those tumors showing only the fibrolamellar pattern.

D. Histologic Grade

Grading of Hepatocellular Carcinoma

The grading system of Edmondson and Steiner is recommended for hepatocellular carcinomas by this protocol and by the AJCC Cancer Staging Manual, 7th edition. However, the use of other grading systems is not precluded.

Grade I
Reserved for hepatocellular carcinomas where the difference between the tumor cells and hyperplastic liver cells is so minor that a diagnosis of carcinoma rests upon the demonstration of more aggressive growths in other parts of the neoplasm. Because grade is assigned based upon the highest grade present, in effect grade I is rarely if ever used for overall tumor grade designation.

Grade II
Cells show marked resemblance to normal hepatic cells. Nuclei are larger and more hyperchromatic than in normal cells. Cytoplasm is abundant and acidophilic. Cell borders are sharp and clear cut. Acini are frequent and variable in size. Lumina are often filled with bile or protein precipitate.

Grade III
Nuclei are larger and more hyperchromatic than in grade II cells. The nuclei occupy a relatively greater proportion of the cell (high nuclear to cytoplasmic [N:C] ratio). Cytoplasm is granular and acidophilic, but less so than grade II tumors. Acini are less frequent and not as often filled with bile or protein precipitate. More single-cell growth in vascular channels is seen than in grade II.

Grade IV
Nuclei are intensely hyperchromatic. Nuclei occupy a high percentage of the cell. Cytoplasm is variable in amount, often scanty. Cytoplasm contains fewer granules. The growth pattern is medullary in character, trabeculae difficult to find, and cell masses seem to lie loosely without cohesion in vascular channels. Only rare acini are seen. Spindle cell areas have been seen in some tumors. Short plump cell forms, resembling "small cell" carcinoma of the lung, are seen in some grade IV tumors.

The pathologist should specify the grading system used. The higher the grade, the less the resemblance of the tumor to "normal" liver, and the more obvious its morphologic features are to malignant growth.

Histologic grade has been shown to have a relationship to tumor size, tumor presentation, and metastatic rate. Low histologic grade has been shown to be predictive of disease-free survival, but not of overall actuarial survival.

E. 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. 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.

F. Venous and Small Vessel Invasion
Vascular invasion includes gross as well as microscopic invasion of vessels. Macroscopic venous invasion is generally accompanied by microscopic invasion, but it is less commonly found than microscopic invasion alone (15% versus 43%). Both are associated with lower survival post-resection. Larger tumors (greater than 5 cm) or multiple tumors are more likely to exhibit vascular invasion than single small lesions.

**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 hepatocellular carcinomas. It does not apply to hepatic sarcomas or to metastatic tumors of the liver. The T classification depends on the number of tumor nodules, the size of the largest nodule, and the presence or absence of blood vessel invasion. The TNM classification does not discriminate between multiple independent primary tumors or intrahepatic metastasis from a single primary hepatic carcinoma. Vascular invasion includes either the gross or the histologic involvement of vessels. Portal vein invasion is an important adverse prognostic factor and should be reported.

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.
Primary Tumor (T) (Figures 2 through 5)

T0  No evidence of primary tumor
T1  Solitary tumor without vascular invasion
T2  Solitary tumor with vascular invasion; or multiple tumors, none more than 5 cm in greatest dimension
T3  Multiple tumors more than 5 cm in greatest dimension or tumor involving a major branch of the portal or hepatic veins(s)
T3a Multiple tumors more than 5 cm
T3b Tumor(s) any size involving a major branch of the portal or hepatic vein(s)
T4  Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum

Figure 2. T1 is defined as a solitary tumor without vascular invasion. From Greene et al.\textsuperscript{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.

Figure 3. A. Solitary tumors with vascular invasion, regardless of size, are classified as T2. B. Multiple tumors, none measuring 5 cm in greatest dimension, are classified as T2. From Greene et al.\textsuperscript{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.
Figure 4. A. Multiple tumors, any more than 5 cm, are classified as T3a. B. Tumor involving a major branch of the portal or hepatic vein(s) is classified as T3b. From Greene et al. 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.

Figure 5. Tumor with direct invasion of adjacent organs other than gallbladder or with perforation of the visceral peritoneum is classified as T4. From Greene et al. 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.

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 IIIA: T3a N0 M0
- Stage IIIB: T3b N0 M0
- Stage IIIC: T4 N0 M0
Lymph Nodes
Histologic examination of a regional lymphadenectomy specimen usually involves examination of 3 or more lymph nodes. The regional lymph nodes of the hepatic region include the hilar, hepatoduodenal ligament, inferior phrenic, and caval lymph nodes. Nodal involvement of lymph nodes distal to the hilar, hepatoduodenal ligament, and caval lymph nodes are considered as indicative of distant metastasis (pM1).

H. Additional Pathologic Findings

Fibrosis
Cirrhosis or severe fibrosis (Ishak score 5 or 6) should be specifically reported because it has an adverse effect on outcome. The scoring system described by Ishak is recommended by the AJCC Cancer Staging Manual, 7th edition, and by this protocol.

<table>
<thead>
<tr>
<th>Degree of Fibrosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas, with or without short fibrous septa</td>
<td>1</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas</td>
<td>2</td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas with occasional portal-portal bridging</td>
<td>3</td>
</tr>
<tr>
<td>Fibrous expansion of portal areas with marked bridging as well as portal-to-central bridging</td>
<td>4</td>
</tr>
<tr>
<td>Marked bridging with occasional nodules (incomplete cirrhosis)</td>
<td>5</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>6</td>
</tr>
</tbody>
</table>

Source: Ishak et al.

Dysplastic Nodules
Reporting of dysplastic changes in cirrhotic nodules is optional in specimens with hepatocellular carcinoma, but it may be helpful in assessing risk for second primary tumors in patients undergoing partial hepatectomy. Dysplastic nodules are generally considered important precursors to hepatocellular carcinoma. The criteria outlined by the International Working Party are recommended, although difficulties in assessment of these lesions and variation in interobserver agreement are recognized.

In brief, dysplastic nodules are nodular lesions displaying some degree of cytologic or architectural atypia but lacking definitive histologic features of malignancy. Dysplastic nodules are further subdivided into low and high grades, depending on the degree of histologic abnormality.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low-Grade Dysplastic Nodule</th>
<th>High-Grade Dysplastic Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear atypia</td>
<td>Minimal</td>
<td>Hyperchromasia and pleomorphism</td>
</tr>
<tr>
<td>Small cell change$</td>
<td>Rare</td>
<td>May be present</td>
</tr>
<tr>
<td>Clone-like growth pattern (uniform population of hepatocytes with map-like growth pattern)</td>
<td>Present</td>
<td>Present; may have nodule-within-nodule growth pattern suggestive of subclone evolution</td>
</tr>
<tr>
<td>Liver cell plates</td>
<td>1 to 2 cell layers thick</td>
<td>Focal areas more than 2 cells thick</td>
</tr>
</tbody>
</table>
Background Documentation

Gastrointestinal • Hepatocellular Carcinoma

Hepatocellular 3.1.0.0

<table>
<thead>
<tr>
<th>Feature</th>
<th>Low-Grade Dysplastic Nodule</th>
<th>High-Grade Dysplastic Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpaired arteries</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Characterized by smaller cell size, a greater nuclear to cytoplasmic ratio, cytoplasmic basophilia, and denser cellularity in comparison with the surrounding extranodular hepatocytes.

Specific types of underlying disease, such as viral hepatitis or hemochromatosis, should be separately evaluated and graded, if appropriate.

I. Clinical History

Hepatocellular carcinoma (HCC) is highly linked to chronic liver disease, in particular chronic hepatitis B (HBV) and C (HCV) infection and alcoholic liver disease. Overall, 50% to 55% of cases of HCC worldwide are attributed to HBV and 25% to 30% to HCV, but virtually any condition associated with chronic hepatic injury and especially with cirrhosis may predispose to HCC. The annual risk of HCC developing in a cirrhotic liver is estimated at 1% to 6%, with the risk generally highest in the context of chronic viral infection and hereditary hemochromatosis. Nonalcoholic fatty liver disease is increasingly recognized as a risk factor for HCC.

References