Liver (Including Intrahepatic Bile Ducts)

Protocol applies to hepatocellular carcinoma and cholangiocarcinoma.

Protocol revision date: January 2004
Based on AJCC/UICC TNM, 6th edition

Procedures

- **Cytology** (No Accompanying Checklist)
- **Incisional Biopsy** (No Accompanying Checklist)
- **Hepatectomy, Partial or Complete**

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Surgical Pathology Cancer Case Summary (Checklist)

Protocol revision date: January 2004
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition

LIVER: Resection

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Right lobectomy
___ Extended right lobectomy
___ Medial segmentectomy
___ Left lateral segmentectomy
___ Total left lobectomy
___ Explanted liver
___ Other (specify): _____
___ Not specified

Focality
___ Solitary (specify location): _____
___ Multiple (specify location): _____

Tumor Size
Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

MICROSCOPIC

Histologic Type
___ Hepatocellular carcinoma
___ Fibrolamellar hepatocellular carcinoma variant (specify): _____
___ Combined hepatocellular and cholangiocarcinoma
___ Cholangiocarcinoma, intrahepatic
___ Bile duct cystadenocarcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

* Data elements ***with asterisks*** are ***not required*** for accreditation purposes for the Commission on Cancer. These elements may be clinically important, but are not yet validated or regularly used in patient management. Alternatively, the necessary data may not be available to the pathologist at the time of pathologic assessment of this specimen.

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ GI: Well differentiated
___ GII: Moderately differentiated
___ GIII: Poorly differentiated
___ GIV: Undifferentiated/anaplastic
___ Other (specify): _____

Pathologic Staging (pTNM)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pT1: Solitary tumor with no vascular invasion
___ pT2: Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
___ pT3: Multiple tumors more than 5 cm or tumor 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 perforation of visceral peritoneum

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Regional lymph node metastasis
Specify: Number examined: ___
Number involved: ___

Distant Metastasis (pM)
___ pMX: Cannot be assessed
___ pM1: Distant metastasis
*Specify site(s), if known: _____

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Margins (check all that apply)

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 (Cholangiocarcinoma Only)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
*___ Carcinoma in situ absent
*___ Carcinoma in situ present
___ Involved by invasive carcinoma

Other Margin
Specify margin: _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

***Venous (Large Vessel) Invasion (V)**
*___ Absent
*___ Present
*___ Indeterminate

***Additional Pathologic Findings (check all that apply)**
*___ None identified
*___ Hepatocellular dysplasia
*___ Ductal dysplasia
*___ Cirrhosis/fibrosis
*___ Iron overload
*___ Hepatitis (specify type): _____
*___ Other (specify): _____

***Comment(s)**

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Background Documentation

Protocol revision date: January 2004

I. Cytologic Material

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date specimen obtained
4. Other clinical information
   a. Relevant history
      (1) family history of liver tumors
      (2) prior surgery for cancer
      (3) ulcerative colitis
      (4) viral hepatitis (hepatitis B virus, hepatitis C virus, or unknown type)
      (5) hemochromatosis
      (6) cirrhosis
      (7) bile duct disease (eg, liver-fluke infection)
   b. Relevant findings (eg, serum alpha-fetoprotein levels, imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, fine-needle aspiration [FNA], other)
   e. Type of specimen (eg, aspiration)
   f. Anatomic site(s) of specimen (eg, right/left lobe of liver)

B. Macroscopic Examination

1. Specimen
   a. Description
   b. Unfixed/fixed (specify fixative)
   c. Number of slides received
   d. Quantity and appearance of fluid specimen
   e. Other (eg, tissue received for cytologic preparation)
   f. Results of intraprocedural consultation
2. Material submitted for microscopic evaluation (eg, smear, cytocentrifuge, touch or filter preparation, cell block)
3. Special studies (specify) (eg, immunohistochemical stains, histochemical stains, electron microscopy, flow cytometry, cytogenetic studies)

C. Microscopic Evaluation

1. Adequacy of specimen (if unsatisfactory for evaluation, specify reason)
2. Tumor, if present (Note **A**)
   a. Histologic type, if possible (Note **B**)
   b. Other descriptive features (eg, nuclear grade, necrosis, bile production)
3. Additional pathologic findings, if present
4. Comments
   a. Correlation with intraprocedural consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

II. Incisional Biopsy
(Any Surgical Approach)

A. Clinical Information

1. Patient identification
    a. Name
    b. Identification number
    c. Age (birth date)
    d. Sex
2. Responsible physician(s)
3. Date specimen obtained
4. Other clinical information
    a. Relevant history
        (1) family history of liver tumors
        (2) prior surgery for cancer
        (3) ulcerative colitis
        (4) viral hepatitis (hepatitis B virus, hepatitis C virus, or unknown type)
        (5) hemochromatosis
        (6) cirrhosis
        (7) bile duct disease (eg, liver-fluke infection)
    b. Relevant findings (eg, serum alpha-fetoprotein levels, imaging studies)
    c. Clinical diagnosis
    d. Procedure (eg, needle biopsy, wedge biopsy)
    e. Type of specimen(s) (eg, tumor biopsy, random liver)
    f. Anatomic site(s) of specimen(s) (eg, right/left lobe, adjacent sites)

B. Macroscopic Examination

1. Specimen
    a. Tissue(s) received
    b. Unfixed/fixed (specify fixative)
    c. Size (3 dimensions, if appropriate)
    d. Number of cores/fragments
    e. Descriptive features (eg, color, bile stained)
    f. Orientation, if indicated by surgeon
    g. Result of intraoperative consultation
2. Tumor, if identifiable
    a. Size (3 dimensions, if possible)
    b. Descriptive features (eg, hemorrhage, necrosis, bile)
3. Additional pathologic findings, if identifiable (eg, cirrhosis)
4. Tissue submitted for microscopic evaluation
    a. Tumor (Note **C**)
    b. Other lesions (eg, regenerative nodules, cirrhosis)
    c. Frozen section tissue fragment(s)
5. Special studies (specify) (eg, immunohistochemical stains, histochemical stains, electron microscopy, flow cytometry, cytogenetic studies)

C. Microscopic Evaluation

1. Tumor
    a. Histologic type (Note **B**)
    b. Histologic grade (Note **D**)
    c. Pattern of growth, if appropriate
        (1) trabecular

(2) tubular
(3) solid
2. Venous vessel invasion
3. Additional pathologic findings, if present
   a. Benign neoplasms
   b. Cirrhosis
   c. Hemosiderosis (hepatocytes vs sinusoidal lining cells)
   d. Chronic hepatitis
   e. Liver cell dysplasia
   f. Other(s)
4. Other tissue(s)/organ(s)
5. Results/status of special studies (specify)
6. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

III. Partial or Complete Hepatectomy

A. Clinical Information

1. Patient identification
   a. Name
   b. Identification number
   c. Age (birth date)
   d. Sex
2. Responsible physician(s)
3. Date specimen obtained
4. Other clinical information
   a. Relevant history
      (1) family history of liver tumors
      (2) prior surgery for cancer
      (3) ulcerative colitis
      (4) viral hepatitis (hepatitis B virus, hepatitis C virus, or unknown type)
      (5) hemochromatosis
      (6) cirrhosis
      (7) bile duct disease (eg, liver-fluke infection)
   b. Relevant findings (eg, serum alpha-fetoprotein levels, imaging studies)
   c. Clinical diagnosis
   d. Procedure (eg, left lobectomy, partial hepatectomy, total hepatectomy)
   e. Operative findings
   f. Anatomic site (eg, right/left lobe of liver, related sites)

B. Macroscopic Examination

1. Specimen
   a. Tissue(s)/organ(s) received
   b. Unfixed/fixed (specify fixative)
   c. Size (3 dimensions)
   d. Weight
   e. Descriptive features (external/cut surfaces)
   f. Orientation, if indicated by surgeon
   g. Results of intraoperative consultation

2. Tumor(s)
   a. Number (Note **E**)
   b. Location
   c. Size (3 dimensions) for all major tumor nodules
   d. Circumscribed/infiltrative
   e. Descriptive features (eg, hemorrhage, necrosis, bile; central scar)
   f. Extension to adjacent organs/tissues (eg, adrenal gland, diaphragm) (Note **E**)
   g. Venous vessel invasion (Note **E**)
3. Margins (Note **F**)
4. Pathologic findings in noncancerous liver
   a. Cirrhosis (type)
   b. Other(s)
5. Regional lymph nodes (Note **G**)
   a. Location, if designated
   b. Number
6. Tissues submitted for microscopic evaluation
   a. Tumor
   b. Nodules (Note **H**)
   c. Margins of resection (Note **F**)
   d. Non-neoplastic liver
   e. Portal/hepatic veins
   f. Porta hepatis
   g. All lymph nodes
   h. Other lesions
   i. Gallbladder, if present
   j. Other tissues or organs (specify)
   k. Frozen section tissue fragment(s)
7. Special studies (specify, eg, immunohistochemical stains, histochemical stains, electron microscopy, flow cytometry, cytogenetic studies)

C. Microscopic Evaluation

1. Tumor(s)
   a. Histologic type (Note **B**)
   b. Histologic grade (Note **D**)
   c. Pattern of growth, if appropriate
      (1) trabecular
      (2) tubular
      (3) solid
   d. Number and location
   e. Venous vessel invasion
2. Additional pathologic findings, if present (Note **I**)
   a. Benign tumor
   b. Cirrhosis (type)
   c. Hemosiderosis (hepatocellular vs sinusoidal lining cells)
   d. Portal vein thrombosis
   e. Liver cell dysplasia
   f. Hepatitis
   g. Other(s)
3. Margins (Note **F**)

4. Regional lymph nodes (pN) (Note **E**)
   a. Number
   b. Number with metastasis (specify location of nodes with metastasis, if possible)
5. Other tissues/organs (specify)
6. Status/results of special studies (specify)
7. Metastasis to other organ(s) or structure(s)
8. Comments
   a. Correlation with intraoperative consultation, as appropriate
   b. Correlation with other specimens, as appropriate
   c. Correlation with clinical information, as appropriate

Explanatory Notes

A. Application

This protocol applies only to primary carcinomas of the liver (hepatocellular carcinoma [hepatoma] and cholangiocarcinoma). It excludes hepatoblastoma.

B. Histologic Type

The protocol recommends the following modified classification of the World Health Organization (WHO). In the United States, almost 70% of the primary malignant tumors of the liver are hepatocellular carcinomas.[1]

WHO Classification of Carcinomas of the Liver (Modified)

Hepatocellular carcinoma
    Variant: Fibrolamellar hepatocellular carcinoma
Combined hepatocellular and cholangiocarcinoma
Cholangiocarcinoma, intrahepatic
Bile duct cystadenocarcinoma
Undifferentiated carcinoma

C. Submission of Tissue

For most biopsies, the entire specimen should be submitted for histologic examination. Portions may be retained for specific reasons only if the specimen is of sufficient size that histologic evaluation will not be compromised. In a wedge biopsy, sections should be submitted perpendicular to the capsule.

D. Histologic Grade

Grading of Hepatocellular Carcinoma

The grading system of Edmondson and Steiner is recommended for hepatocellular carcinomas.[2]

Grade I	Reserved for those 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.
Grade II	Cells show marked resemblance to normal hepatic cells. Nuclei are larger and more hyperchromatic than 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 grade II cells. The nuclei occupy a relatively greater proportion of the cell (high 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.[3,4] Low histologic grade has been shown to be predictive of disease-free survival, but not of overall actuarial survival.[5]

Grading of Cholangiocarcinoma
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. TNM and Stage Groupings
The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC)[6,7] applies to all primary carcinomas of the liver, including hepatocellular carcinomas, intrahepatic bile duct carcinomas, and mixed tumors. 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 intra-hepatic 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.

By 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 unfeasible) 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.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
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)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

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)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Groupings

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

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 following 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 prior to 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.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion
By AJCC/UICC convention, vessel invasion (lymphatic or venous) does not affect the T category indicating local extent of tumor unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumor are coded separately as follows.

Lymphatic Vessel Invasion (L)
LX Lymphatic vessel invasion cannot be assessed
L0 No lymphatic vessel invasion
L1 Lymphatic vessel invasion

Venous Invasion (V)
VX Venous invasion cannot be assessed
V0 No venous invasion
V1 Microscopic venous invasion
V2 Macroscopic venous invasion

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. In cases of cholangiocarcinoma, 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. 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, and caval lymph nodes. Nodal involvement of the inferior phrenic lymph nodes or other lymph nodes distal to the hilar, hepatoduodenal ligament, and caval lymph nodes are considered as distant metastasis (pM1).

H. Histologic Sampling
Sections should be prepared from each major tumor nodule with representative sampling of smaller nodules, if macroscopically different in appearance.

I. Additional Pathologic Findings
Cirrhosis should be specifically reported since it has an adverse effect on outcome. Specific types of underlying disease, such as viral hepatitis or hemochromatosis, should be separately evaluated and graded, if appropriate.

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