Gallbladder

Protocol applies to all invasive carcinomas of the gallbladder, including those showing focal endocrine differentiation.

Procedures
• Cholecystectomy
• Cholecystectomy with Partial Hepatectomy
• Cholecystectomy with Lymph Node Dissection

Author
Carolyn C. Compton, MD, PhD
Department of Pathology, McGill University, Montreal, Quebec, Canada
For the Members of the Cancer Committee, College of American Pathologists

Previous contributors: Donald E. Henson, MD; Jorge Albores-Saavedra, MD
© 2005. College of American Pathologists. All rights reserved. The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary (Checklist)” portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with the document. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.
Summary of Changes to Checklist(s)

Protocol revision date: January 2005

No changes have been made to the data elements of the checklist(s) since the January 2004 protocol revision.
**Gallbladder** • Digestive System

**Surgical Pathology Cancer Case Summary (Checklist)**

*Protocol revision date: January 2005
Applies to invasive carcinomas only
Based on AJCC/UICC TNM, 6th edition*

**GALLBLADDER: Resection/Cholecystectomy**

- Patient name:
- Surgical pathology number:

**Note: Check 1 response unless otherwise indicated.**

**MACROSCOPIC**

<table>
<thead>
<tr>
<th>Specimen Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecystectomy</td>
</tr>
<tr>
<td>Cholecystectomy with partial hepatectomy</td>
</tr>
<tr>
<td>Other (specify): ___________________________</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Site (check all that apply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fundus</td>
</tr>
<tr>
<td>Body</td>
</tr>
<tr>
<td>Neck</td>
</tr>
<tr>
<td>Indeterminate</td>
</tr>
<tr>
<td>Not specified</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greatest dimension: ___ cm</td>
</tr>
<tr>
<td>*Additional dimensions: ___ x ___ cm</td>
</tr>
<tr>
<td>____ Cannot be determined (see Comment)</td>
</tr>
</tbody>
</table>

* 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.
MICROSCOPIC

Histologic Type
___ Adenocarcinoma
___ Papillary adenocarcinoma
___ Adenocarcinoma, intestinal type
___ Adenocarcinoma, gastric foveolar type
___ Mucinous adenocarcinoma
___ Clear cell carcinoma
___ Adenosquamous carcinoma
___ Small cell carcinoma
___ Large cell neuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other (specify): ____________________________
___ Carcinoma, type cannot be determined

Histologic Grade
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): ____________________________

Pathologic Staging (pTNM)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor invades lamina propria or muscle layer
___ pT1a: Tumor invades lamina propria
___ pT1b: Tumor invades muscle layer
___ pT2: Tumor invades perimuscular connective tissue; no extension beyond serosa
or into liver
___ pT3: Tumor perforates serosa (visceral peritoneum) and/or directly invades the
liver and/or other adjacent organ or structure, such as the stomach,
duodenum, colon, or pancreas, omentum or extrahepatic bile ducts
___ pT4: Tumor invades main portal vein or hepatic artery or invades two or more
extrahepatic organs or structures

* 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.
Gallbladder • Digestive System

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: __________________________

Margins (check all that apply)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
       Distance of invasive carcinoma from closest margin: ___ mm
       Specify margin: __________________________
___ Margins involved by invasive carcinoma
       Specify margin: __________________________
___ Cystic duct margin uninvolved by in situ carcinoma
___ Cystic duct margin involved by in situ carcinoma

*Venous/Lymphatic (Large/Small Vessel) Invasion (V/L)
*___ Absent
*___ Present
*___ Indeterminate

*Perineural Invasion
*___ Absent
*___ Present
*___ Indeterminate

*Additional Pathologic Findings (check all that apply)
*___ None identified
*___ Dysplasia/adenoma
*___ Acute cholecystitis
*___ Cholelithiasis
*___ Chronic cholecystitis
*___ Other (specify): ___________________________

*Comment(s)

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.
Background Documentation

Protocol revision date: January 2004

I. Resection (Cholecystectomy)

A. Clinical Information
   1. Patient identification
      a. Name
      b. Identification number
      c. Age (birth date)
      d. Sex
   2. Responsible physician(s)
   3. Date of procedure
   4. Other clinical information
      a. Relevant history (eg, right upper abdominal pain)
      b. Relevant findings (eg, ultrasound, other imaging studies)
      c. Clinical diagnosis (eg, chronic cholecystitis)
      d. Procedure (eg, abdominal cholecystectomy)
      e. Operative findings

B. Macroscopic Examination
   1. Specimen
      a. Organ(s)/tissue(s) received (Note A)
      b. Unfixed/fixed (specify fixative)
      c. Previously opened
      d. Orientation, if indicated by surgeon
      e. Dimensions (measure attached tissues individually)
      f. Gallstones (number, type) (Note B)
      g. Results of intraoperative consultation
   2. Tumor
      a. Location (fundus/body/neck)
      b. Configuration (Note C)
      c. Dimensions (include entire tumor)
      d. Descriptive features (eg, color, consistency, necrosis)
      e. Extent of invasion (Note D)
   3. Margins
      a. Cystic duct
      b. Liver bed
      c. Other(s) (as appropriate)
   4. Regional lymph nodes
      a. Location (if possible)
      b. Number
   5. Additional pathologic findings, if present
   6. Tissues submitted for microscopic evaluation
      a. Tumor, including:
         (1) point of deepest penetration
         (2) overlying serosa
         (3) interface with adjacent tissue
      b. Gallbladder uninvolved by tumor
      c. Margin of cystic duct
      d. Liver, including margin of resection closest to tumor
      e. All lymph nodes
      f. Other lesion(s)
      g. Frozen section tissue fragment(s) (unless saved for special studies)
      h. Other tissue(s)/organ(s)
7. Special studies (specify) (eg, histochemistry, immunohistochemistry, morphometry, DNA analysis, cyto genetic analysis)

C. Microscopic Evaluation
1. Tumor (Note E)
   a. Histologic type (Note F)
   b. Histologic grade (Note G)
   c. Depth of invasion (Note D)
   d. Venous/lymphatic vessel invasion (Note H)
   e. Perineural invasion (Note I)
2. Margins
   a. Cystic duct
   b. Liver bed
   c. Other(s), as appropriate
3. Additional pathologic findings, if present (Note J)
   a. Dysplasia
   b. Intestinal metaplasia
   c. Other(s)
4. Regional lymph nodes (Note K)
   a. Number
   b. Number involved by tumor (specify location, if possible)
5. Other organ(s) or structure(s) (specify sites) (Note K)
   a. Involvement by tumor by direct extension
   b. Metastasis involvement
6. Other tissue(s)/organ(s)
7. Results/status of special studies (specify)
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
The protocol applies only to carcinomas of the gallbladder, including those showing endocrine differentiation, but excludes carcinoid tumors. More than 98% of malignant tumors of the gallbladder are carcinomas.

B. Gallstones
The presence or absence of stones should be reported. Gallbladder cancer occurring in the absence of stones may result from an anomalous choledocho-pancreatic junction or from an association with chronic inflammatory bowel disease.

C. Configuration
Configuration types include exophytic (fungating/polypoid), endophytic (ulcerating), or diffusely infiltrating. Since papillary carcinomas (usually polypoid) have a favorable prognosis, these lesions should be specifically reported.¹

D. TNM and Stage Grouping
The TNM staging system for carcinomas of the gallbladder of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended by the protocol and shown below.²³ The TNM does not apply to carcinoid tumors or to sarcomas. Carcinomas of the gallbladder are staged according to their depth
of penetration into the wall and extension to adjacent organs, and the extent of invasion correlates inversely with survival.\(^1\)

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 |
| Tis | Carcinoma in situ\(^#\) |
| T1 | Tumor invades lamina propria or muscle layer |
| T1a | Tumor invades lamina propria |
| T1b | Tumor invades muscle layer |
| T2 | Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver |
| T3 | Tumor perforates serosa (visceral peritoneum) and/or directly invades the liver and/or other adjacent organ or structure, such as the stomach duodenum, colon, or pancreas, omentum or extrahepatic bile ducts |
| T4: | Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures |

\(^#\) Because carcinoma in situ may be multifocal, cases of carcinoma in situ should be studied by multiple sections or by the “Swiss role” method in order to exclude invasive cancer in other areas of the gallbladder. Carcinoma in situ is often confused with the epithelial atypia of repair.\(^4\)

**Regional Lymph Nodes (N)**

| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis\(^###\) |
| N1 | Regional lymph node metastasis |

\(^###\) The frequency of nodal involvement depends on the depth of invasion into the gallbladder wall by the primary tumor. The regional lymph nodes of the gallbladder include the cystic duct, percholedochal, hilar (ie, in the hepatoduodenal ligament), peripancreatic (head only), periduodenal, periportal, celiac, and superior mesenteric lymph nodes. The hilar nodes include those along the inferior vena cava, hepatic artery, portal vein and hepatic pedicle. Peripancreatic nodes located along the body and tail of the pancreas are sites of distant metastasis.
**Regional Lymph Nodes (pN0): Isolated Tumor Cells**

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or nonmorphological techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.\(^5,6\)

- **pN0** No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
- **pN0(i-)** No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hemotoxylin-eosin and immunohistochemistry) findings for ITCs
- **pN0(i+)** No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hemotoxylin-eosin and immunohistochemistry) findings for ITCs
- **pN0(mol-)** No regional lymph node metastasis histologically, negative nonmorphologic (molecular) findings for ITCs
- **pN0(mol+)** No regional lymph node metastasis histologically, positive nonmorphologic (molecular) findings for ITCs

**Distant Metastasis (M)**

- **MX** Presence of distant metastasis cannot be assessed
- **M0** No distant metastasis
- **M1** Distant metastasis

**Stage Groupings**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**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).
For Information Only

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.\(^7\)

- 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.

- LX: Lymphatic vessel invasion cannot be assessed
- L0: No lymphatic vessel invasion
- L1: Lymphatic vessel invasion

- VX: Venous vessel invasion cannot be assessed
- V0: No venous invasion
- V1: Microscopic venous invasion
- V2: Macroscopic venous invasion

**E. Occult Carcinomas**
Occasionally carcinoma is found in gallbladders removed by laparoscopic surgery. Not recognized clinically or by imaging techniques, tumor is discovered during pathologic evaluation of the resected specimen. In this setting, tumor spillage with seeding along the endoscopic tract or intra-abdominal dissemination may be a major complication of the procedure. If carcinoma in situ is found in such specimens, multiple sections should be examined to exclude invasive cancer.

To exclude occult carcinoma in gallbladders excised intact, at least 3 sections, 1 from the fundus, 1 from the body, and 1 from the neck should be submitted if no gross lesions are found.
F. Histologic Type
For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO), shown below, is recommended. However, this protocol does not preclude use of other systems of classification or histologic types.

WHO Classification of Gallbladder Carcinomas
Adenocarcinoma
Papillary adenocarcinoma
Adenocarcinoma, intestinal type
Adenocarcinoma, gastric foveolar type
Mucinous adenocarcinoma
Clear cell adenocarcinoma
Signet-ring cell carcinoma
Adenosquamous carcinoma
Squamous cell carcinoma
Small cell carcinoma
Large cell neuroendocrine carcinoma
Undifferentiated carcinoma
Biliary cystadenocarcinoma

# Many adenocarcinomas contain neuroendocrine cells. These tumors should not be considered neuroendocrine carcinomas.

## These histologic types are not usually graded (see below).

### A mucocele may be mistaken for a mucinous carcinoma. Mucocles often contain macrophages that have engulfed mucin (muciphages). Consequently these macrophages may resemble signet-ring cells. Neoplastic signet-ring cells are cytokeratin- and carcinoembryonic antigen (CEA)-positive, whereas muciphages do not stain for these markers.

^ By convention, signet-ring cell carcinomas are assigned grade 3 (see below).

^^ Small cell carcinomas and undifferentiated (histologic type) carcinomas are assigned grade 4 (see below). Small cell carcinomas should be specifically reported since they may cause endocrine syndromes. In addition, small cell carcinomas and undifferentiated carcinomas are, by definition, high-grade (grade 4), an adverse prognostic factor.

G. Histologic Grade
The following grading system, based on the extent of glandular formation in the tumor, is suggested.

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 (49% or less of tumor composed of glands)

Grade 4 carcinomas are classified as undifferentiated carcinomas (histologic type) by the WHO classification (see above).

Published data indicate that histologic grade is prognostically significant.
H. Venous/Lymphatic Vessel Invasion
Published data indicate that blood vessel and/or lymphatic invasion has an adverse effect on outcome and should be specifically recorded.1

I. Perineural Invasion
Perineural invasion by neoplastic cells is an adverse prognostic factor and should be reported. A diagnostic pitfall may occur in cases of adenomyomatous hyperplasia, since the ductal structures of adenomyomatous hyperplasia may invade perineural spaces.10

J. Additional Pathologic Findings
Other common lesions include chronic cholecystitis, dysplasia, carcinoma in situ, and various types of metaplasia such as squamous, pyloric gland, and intestinal metaplasia. Occasionally changes consistent with inflammatory bowel disease are found in the gallbladder.

K. Lymph Node Metastasis
In general, carcinomas of the gallbladder spread from some focus in the hepatoduodenal ligament toward the nodes around the head of the pancreas. The cystic and pericholedochal nodes are the key stations for spread toward the peripancreatic nodes. Lymph flows through the pericholedochal nodes to these other regional nodes. Most often, the tumor initially metastasizes to the pericholedochal lymph nodes.

References
Bibliography