Gallbladder

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

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

Procedures

- **Cholecystectomy**
- **Cholecystectomy with Wedge Resection**
- **Cholecystectomy with Lymph Node Dissection**

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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

GALLBLADDER: Resection/Cholecystectomy

Patient name:
Surgical pathology number:

Note: Check 1 response unless otherwise indicated.

MACROSCOPIC

Specimen Type
___ Cholecystectomy
___ Cholecystectomy with partial hepatectomy
___ Other (specify): _____
___ Not specified

Tumor Site (check all that apply)
___ Fundus
___ Body
___ Neck
___ Indeterminate
___ Not specified

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

* 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 multiple extrahepatic organs or structures

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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)**

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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, cytogenetic 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.[2,3] 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 multiple 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, pericholedochal, 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

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	N0	M0

	T4	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.[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.

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

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.[8] 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. Mucoceles 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.[9]

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.[1]

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.

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