Protocol for the Examination of Specimens from Patients with Carcinoma of the Gallbladder

Protocol applies to all invasive carcinomas of the gallbladder and cystic duct, including those showing focal endocrine differentiation. Well-differentiated neuroendocrine neoplasms (carcinoid tumors) are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2009

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

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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 these documents. 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.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

GALLBLADDER: Resection/Cholecystectomy

Select a single response unless otherwise indicated.

Specimen (select all that apply)
___ Gallbladder
___ Liver
___ Extrahepatic bile duct
___ Other (specify): _____
___ Not specified

Procedure (Note A)
___ Simple cholecystectomy (laparoscopic or open)
___ Radical cholecystectomy (with liver resection and lymphadenectomy)
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply)
___ Fundus
___ Body
___ Neck
___ Cystic Duct
___ Free peritoneal side of gallbladder
___ Hepatic side of gallbladder
___ Cannot be determined
___ Other, specify_____
___ Not specified

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

Histologic Type (Note B)
___ Adenocarcinoma
___ Papillary adenocarcinoma
___ Adenocarcinoma, intestinal type
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Clear cell carcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Small cell carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, not otherwise specified

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

Microscopic Tumor Extension
___ Tumor invades lamina propria
___ Tumor invades muscle layer
___ Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
___ Tumor perforates serosa (visceral peritoneum)
___ Tumor directly invades the liver
___ Tumor directly invades extrahepatic bile ducts
___ Tumor directly invades other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, or omentum (specify):_____

Margins (select all that apply) (Note D)
___ 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(s): _____
___ Cystic duct margin uninvolved by intramucosal carcinoma
___ Cystic duct margin involved by intramucosal carcinoma

***Lymph-Vascular Invasion (Note E)**
*___ Not identified
*___ Present
*___ Indeterminate

***Perineural Invasion (Note F)**
*___ 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 (post-treatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
pT1: Tumor invades lamina propria or muscular 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 one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
___ pT4: Tumor invades main portal vein or hepatic artery or invades 2 or more extrahepatic organs or structures

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
___pN2: Metastases to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes
Specify: Number examined ___
Number involved ___

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

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Additional Pathologic Findings (select all that apply) (Note H)**
*___ None identified
*___ Dysplasia/adenoma
*___ Cholelithiasis
*___ Chronic cholecystitis
*___ Acute cholecystitis
*___ Intestinal metaplasia
*___ Diffuse calcification (porcelain gallbladder)
*___ Other (specify): _____

***Ancillary Studies**
*****Specify: _____
*____ Not performed

***Clinical History (select all that apply) (Note I)**
*____ Cholelithiasis
*____ Primary sclerosing cholangitis
*____ Other (specify): _____

***Comment(s)**

Explanatory Notes

A. Occult Carcinomas in Cholecystectomy Specimens

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 laparoscopic tract or intra-abdominal dissemination may be a major complication of the procedure, with port site recurrences reported in up to 17% of such cases.[1] If dysplasia is found in such specimens, multiple sections should be examined to exclude invasive cancer.

B. Histologic Type

For consistency in reporting, the histologic classification proposed by the World Health Organization (WHO), shown below, is recommended.[2] 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 scattered 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-positive 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 because they may cause endocrine syndromes. In addition, small cell carcinomas and undifferentiated carcinomas are, by definition, high grade (grade 4), an adverse prognostic factor.[3]

C. 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[2] (see above).

Although tumor stage is probably the most important prognostic factor for patient outcome, histologic grade, especially for poorly differentiated and infiltrative tumors, also has an impact on survival.[4]

D. Margins

Complete surgical resection with negative margins remains the most effective therapy for gallbladder cancer, with 5-year survival advantages of 30% for patients with negative margins compared with those with microscopic residual disease.[5]

E. Venous/Lymphatic Vessel Invasion

Blood vessel and/or lymphatic invasion has been reported to be an adverse prognostic feature in some but not all studies.[6-8]

F. Perineural Invasion

Perineural invasion by neoplastic cells is very common in gallbladder carcinoma and has been identified as an adverse prognostic factor in some but not all studies.[6,9,10] Perineural invasion has been associated with spread of carcinoma beyond the gallbladder to involve the biliary tree.[11] A diagnostic pitfall may occur in cases of adenomyomatous hyperplasia, because the ductal structures of adenomyomatous hyperplasia may invade perineural spaces.[12]

G. TNM and Anatomic Stage/Prognostic Grouping

Surgical resection is the most effective therapy for gallbladder carcinomas, and the best estimation of prognosis is related to the anatomic extent (stage) of disease at the time of resection. In particular, lymph node metastases are predictors of poorer outcome.[13,14]

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.[15] The TNM system 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.[16]

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.

T Category Considerations

pTis. For gallbladder carcinomas, "carcinoma in situ" (pTis) as a staging term includes neoplastic cells cytologically indistinguishable from invasive carcinoma but confined within the glandular basement membrane.[3] Separation of high-grade dysplasia from carcinoma in situ is subjective, and because morphologic criteria are ill defined, subject to interobserver variability. The term “carcinoma in situ” is not widely applied to glandular neoplastic lesions in the gastrointestinal tract but is retained for tumor registry reporting purposes as specified by law in many states. Noninvasive gallbladder carcinomas with a papillary growth pattern are classified as pTis.

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. Dysplasia of the gallbladder mucosa is often confused with the reactive change due to inflammation or repair.

Involvement of Rokitansky-Aschoff (RA) sinuses. Distinguishing extension of dysplastic epithelium into RA sinuses from invasive carcinoma may be difficult. A recent study of 49 cases of gallbladder carcinoma extending into or originating from RA sinuses lists the following useful criteria for in situ carcinoma: connection of epithelial invaginations to the luminal surface, normal biliary epithelium admixed with neoplastic epithelium, inspissated bile in long dilated spaces, and lack of invasion of smooth muscle bundles.[17]

N Category Considerations

The frequency of nodal involvement depends on the depth of invasion into the gallbladder wall by the primary tumor. In general, carcinomas of the gallbladder spread from involvement of 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.

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 (Figure 1). 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.

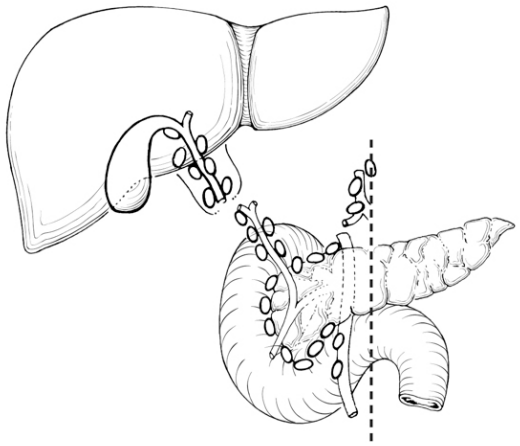

Figure 1. Regional lymph nodes of the gallbladder. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

Although it has been suggested that micrometastases detected by immunohistochemical studies for cytokeratin are associated with poor outcome in gallbladder carcinomas,[9] such studies are few in number and remain unvalidated by larger series. Routine assessment of regional lymph nodes is limited to conventional pathologic techniques (gross assessment and histologic examination), and data are currently insufficient to recommend special measures to detect micrometastasis or isolated tumor cells. Thus, neither multiple levels of paraffin blocks nor the use of special/ancillary techniques, such

as immunohistochemistry, are recommended for routine examination of regional lymph nodes.[13]

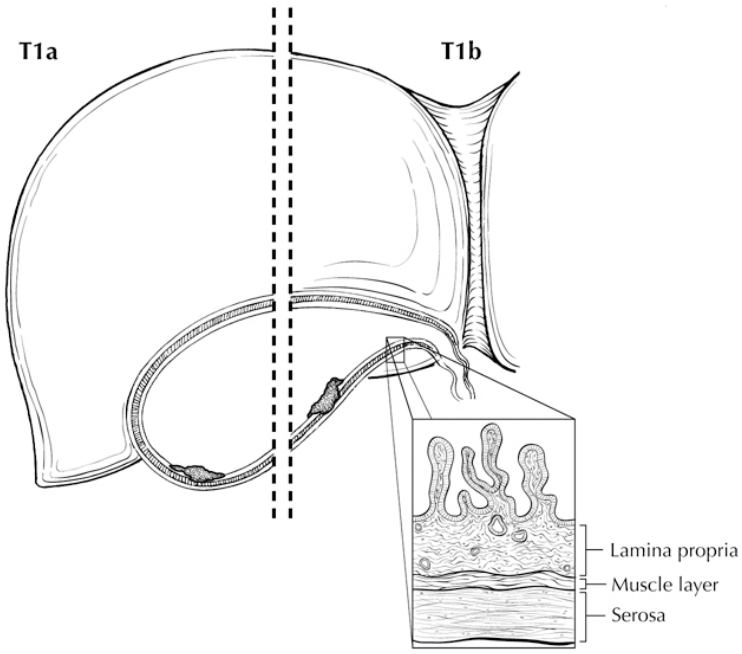

Figure 2. T1a is defined as tumor invading lamina propria; T1b is defined as tumor invading muscle layer. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

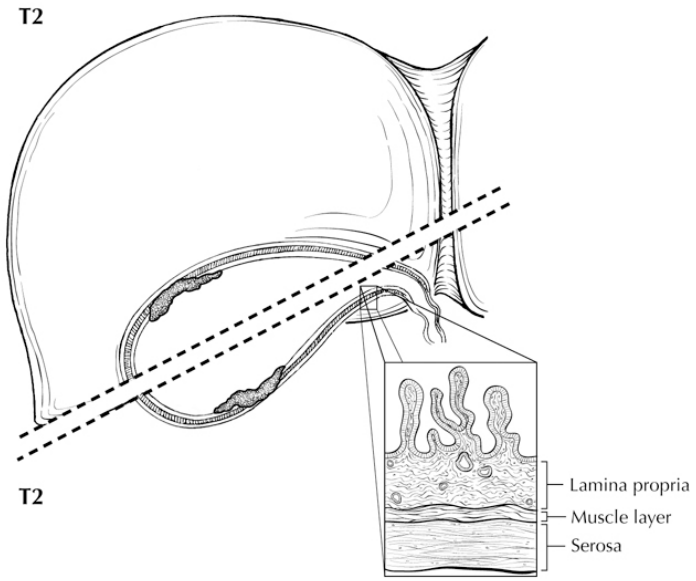

Figure 3. Two views of T2: tumor invading perimuscular connective tissue (below dotted line) and tumor with no extension beyond serosa or into the liver (above dotted line). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

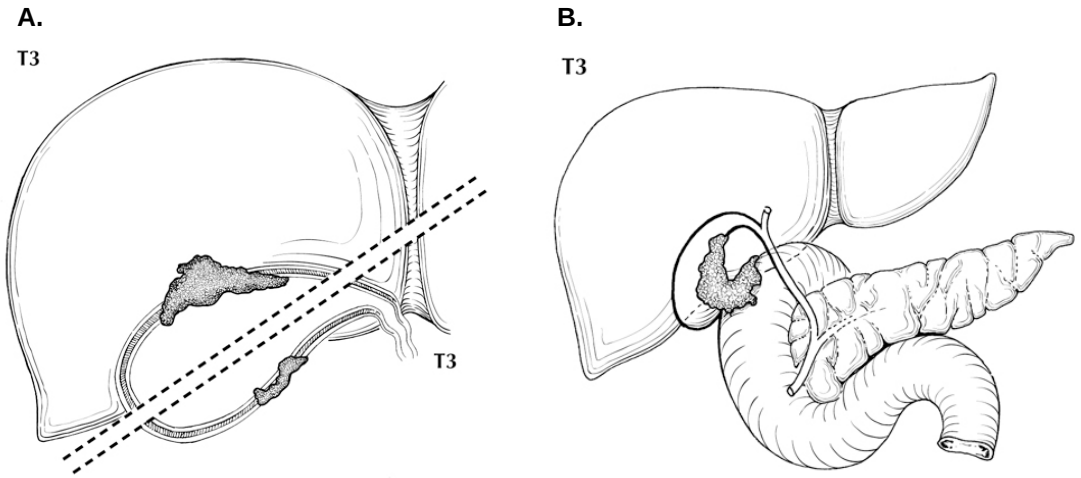

Figure 4. Two views of T3. A. tumor perforating the serosa (visceral peritoneum) (below dotted line) and/or directly invading the liver (above dotted line). B. T3 may also be defined as tumor invading one other adjacent organ or structure, such as the duodenum (illustrated. From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

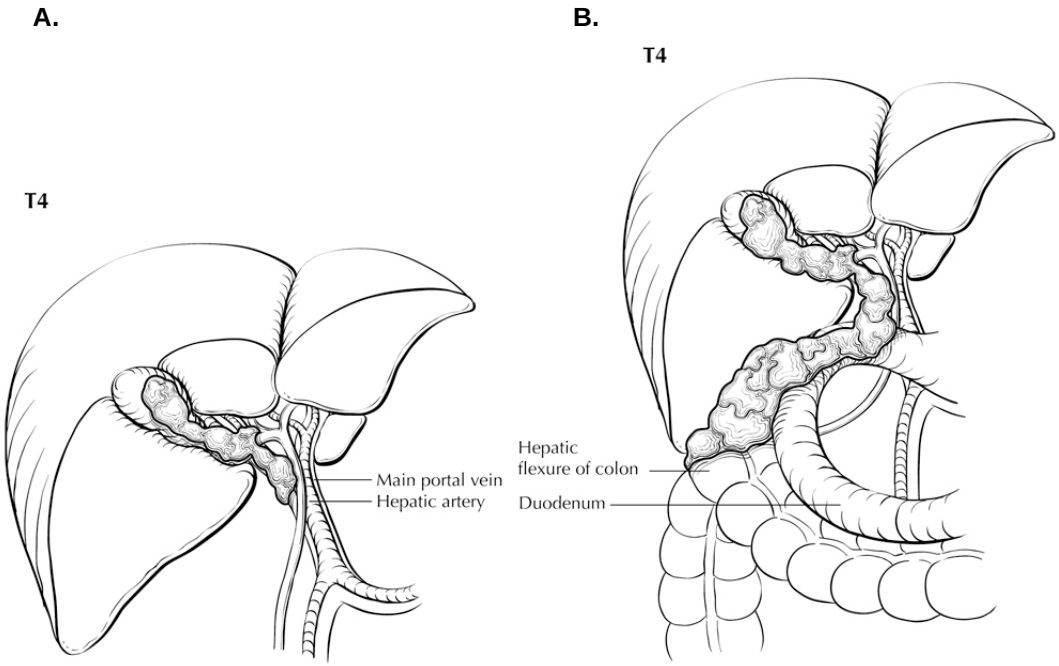

Figure 5. A. T4 is defined as tumor invading the main portal vein or hepatic artery (illustrated) or invading two or more extrahepatic organs or structures. B. T4 invading two or more extrahepatic organs or structures (here, invading colon and duodenum). From: Greene FL, Compton, CC, Fritz AG, et al, eds. *AJCC Cancer Staging Atlas.* New York: Springer; 2006. Copyright © American Joint Committee on Cancer. Used with permission.

Primary Tumor (T) (Figures 2 through 5)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor invades lamina propria or muscular layer
T1a Tumor invades lamina propria
T1b Tumor invades muscular layer
T2 Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3 Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4 Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2 Metastases to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1, T2, or T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	N 2	Any M
	Any T	Any N	M1

Vessel Invasion

According to 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.

H. Additional Pathologic Findings

Other common lesions include chronic cholecystitis 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. Diffuse calcification of the gallbladder (porcelain gallbladder) has historically been associated with gallbladder carcinoma, although this relationship has been questioned.[18,19] Recent

publications indicate that selective mucosal calcification, rather than diffuse intramural calcification, may be more closely associated with gallbladder cancer.[18]

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.

I. Clinical History

In addition to long-standing cholelithiasis and chronic cholecystitis, other conditions causing chronic inflammation may predispose to gallbladder carcinoma. Gallbladders from patients with primary sclerosing cholangitis (PSC) should be carefully examined for dysplasias, reported in 37% of cases, and adenocarcinoma, reported in 14% of cases in a recent study examining gallbladders from patients with PSC undergoing orthotopic liver transplantation.[20]

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