Carcinoma of the Gallbladder Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

◯ Information not provided

◯ Information provided (select all that apply)

- ☐ Gallstones
- ☐ Abnormal choledochopancreatic junction
- ☐ Porcelain gallbladder
- ☐ Primary sclerosing cholangitis (PSC)
- ☐ Inflammatory bowel disease
- ☐ Genetic syndrome, *specify*
- ☐ Neoadjuvant therapy, *specify*
- ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (Note 2)

◯ Not specified

◯ Simple cholecystectomy (laparoscopic or open)

◯ Radical cholecystectomy (with liver resection and lymphadenectomy)

◯ Other, *specify*

TUMOUR SITE (select all that apply) (Note 3)

◯ Not specified

☐ Fundus

☐ Body

☐ Neck

☐ Cystic duct

☐ Other, *specify*

Specify location

☐ Hepatic side ☐ Non-hepatic/serosal

Grossly apparent

◯ No ◯ Yes

TUMOUR DIMENSIONS (Note 4)

Greatest dimension

mm

Additional dimensions

mm x mm

◯ Cannot be assessed, *specify*

BLOCK IDENTIFICATION KEY (Note 5)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (Note 6)

(Value list based on the World Health Organization (WHO) Classification of Tumours of the Digestive System (2019))

◯ Biliary type

◯ Intestinal type

◯ Mucinous

◯ Poorly cohesive (with and without signet ring cells)

◯ Adenosquamous

◯ Squamous

◯ Undifferentiated (including sarcomatoid)

◯ Small cell neuroendocrine carcinoma

◯ Large cell neuroendocrine carcinoma

◯ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

◯ Other, *specify*

HISTOLOGICAL TUMOUR GRADE (Note 7)

◯ Not applicable

◯ Cannot be assessed

◯ G1: Well differentiated

◯ G2: Moderately differentiated

◯ G3: Poorly differentiated

◯ Other, *specify*

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EXTENT OF INVASION (select all that apply) (Note 8)

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour
- ☐ Invades lamina propria
- ☐ Invades muscular layer
- ☐ Invades perimuscular connective tissue on the peritoneal side without serosal involvement
- ☐ Invades perimuscular connective tissue on the hepatic side without liver involvement
- ☐ Perforates serosa (visceral peritoneum)
- ☐ Directly invades liver
- ☐ Directly invades other adjacent organ(s) or structure(s)
  - ☐ Stomach
  - ☐ Duodenum
  - ☐ Colon
  - ☐ Pancreas
  - ☐ Extrahepatic bile ducts
  - ☐ Omentum
- ☐ Directly invades
  - ☐ Main portal vein
  - ☐ Hepatic artery
  - ☐ Other, *specify*
- ☐ Other, *specify*

LYMPHOVASCULAR INVASION (Note 9)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present
  - ◯ Lymphatic
  - ◯ Venous

PERINEURAL INVASION (Note 10)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present

MARGIN STATUS (Note 11)

Cystic duct

INVASIVE CARCINOMA

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin ____ mm
- ◯ Involved

DYSPLASIA

- ◯ Cannot be assessed
- ◯ Not involved
- ◯ Involved
  - ◯ Low grade
  - ◯ High grade

Liver parenchymal

- ◯ Cannot be assessed
- ◯ Not involved
  - Distance of tumour from closest margin ____ mm
- ◯ Involved

Other margin

- ◯ Not applicable
- ◯ Not involved
  - Distance of tumour from closest margin ____ mm
  - Specify closest margin
- ◯ Involved
  - Specify margin

LYMPH NODE STATUS (Note 12)

- ◯ No nodes submitted or found

Number of lymph nodes examined

- ◯ Not involved
- ◯ Involved
  - Number of involved lymph nodes
  - ◯ Number cannot be determined

ADDITIONAL FINDINGS (select all that apply) (Note 13)

- ◯ None identified
- ☐ Biliary intraepithelial neoplasia (BilIN) low grade/high grade
- ☐ Intracholecystic neoplasms (ICN) low grade/high grade
- ☐ Intestinal metaplasia
- ☐ Cholelithiasis
- ☐ Extension (non-clearly invasive) to Rokitansky Aschoff sinuses
- ☐ Diffuse calcification (porcelain gallbladder)
- ☐ Other, *specify*

ANCILLARY STUDIES (Note 14)

Neuroendocrine carcinomas only

◯ Not applicable

Neuroendocrine markers

◯ Not performed

Select at least two of the following

☐ Synaptophysin
☐ Chromogranin-A
☐ INSM1

Ki-67 proliferation index ____ %

◯ Not performed

p53

◯ Not performed
◯ Abnormal, *specify*

◯ Wildtype pattern

Mismatch repair (MMR) immunohistochemistry

◯ Proficient
◯ Equivocal
◯ Deficient, *specify*

Rb1

◯ Retained ◯ Deficient

Low molecular weight cytokeratin(s)

◯ Positive ◯ Negative

Other tumours

◯ Not performed
◯ Performed (select all that apply)

☐ Immunohistochemistry, *specify test(s) and result(s)*

☐ Molecular studies, *specify test(s) and result(s)*

☐ Other, *record test(s), methodology and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 15)

◯ Not applicable
◯ Not identified
◯ Present (select all that apply)

☐ Non-regional lymph node(s)
☐ Liver
☐ Other, *specify*

PATHOLOGICAL STAGING (UICC TNM 9th edition)[a] (Note 16)

TNM Descriptors (only if applicable) (select all that apply)

☐ m - multiple primary tumours
☐ y - post-therapy
☐ r - recurrent

Primary tumour (pT)

◯ TX[b] Primary tumour cannot be assessed
◯ T0 No evidence of primary tumour
◯ Tis Carcinoma in situ
◯ T1 Tumour invades lamina propria or muscular layer
  ◯ T1a Tumour invades lamina propria
  ◯ T1b Tumour invades muscular layer
◯ T2 Tumour invades perimuscular connective tissue; no extension beyond serosa or into liver
  ◯ T2a Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa
  ◯ T2b Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver
◯ T3 Tumour perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts
◯ T4 Tumour invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures

Regional lymph nodes (pN)

◯ NX[b] Regional lymph nodes cannot be assessed
◯ N0 No regional lymph node metastasis
◯ N1 Metastases to 1-3 regional nodes
◯ N2 Metastasis to 4 or more regional nodes

[a] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 9th Edition, eds by James Brierley, Meredith Giuliani, Brian O'Sullivan, Brian Rous, Elizabeth Van Eycken. 2025, Publisher Wiley (ncorporating any errata published up until 21st January 2026).*

[b] *TX and NX should be used only if absolutely necessary.*

Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system, e.g., Pathological TNM staging, would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC.

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Scope

The dataset has been developed for the pathological reporting of carcinomas of the gallbladder and the cystic duct. It includes resection specimens designated as cholecystectomy. Cytologic specimens are excluded. Neuroendocrine carcinomas (NEC) and mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) are included. Well differentiated neuroendocrine tumours and non-epithelial malignancies are not included.

NOTE: PRIOR TO PUBLICATION THE DATASET CONTENT WILL BE UPDATED TO REFLECT WHO 6TH EDITION.

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Note 1 – Clinical information (Core and Non-core)

Risk factors for gallbladder cancer as well as any previous treatment represent relevant clinical information for the completeness of the pathology report, for assessment of overall prognosis, for personalised treatment approaches and for indication to genetic counselling.[2,3]

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Note 2 – Operative procedure (Core)

Gallbladder cancer is often detected incidentally after simple cholecystectomy performed for other reasons, most commonly stones. For gallbladder cancer in Stage T1b, there are different views on the management with the literature in high risk regions as well as Japan and Korea indicating a very good prognosis,[4,5] while those from the national databased from the West showing an aggressive behaviour leading to more radical operations.[6,7] For T2, there is wide consensus that radical cholecystectomy with gallbladder bed resection is the treatment of choice.[6,7] For T3 and T4 tumours, more extended resections are usually necessary, but their impact on survival is uncertain.[8]

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Note 3 – Tumour site (Core)

Gallbladder cancer is most commonly localised in the fundus (70%),[9] followed by the body and the neck, but significant overlap exists. Careful assessment of the tumour site (hepatic versus serosal site) is important to guide grossing and for correct margin assessment and staging, which is pivotal in directing therapy, including additional surgery. Tumour location on the hepatic site is a prognostically adverse factor in pT2 gallbladder cancer,[10] although some studies have failed to confirm this impression.[11] In addition, gallbladder cancers in the neck/cystic duct region display a more aggressive behaviour.[12] In a proportion of cases of very large tumour masses or artefactual changes (e.g., organ rupture) might be impossible to establish the exact site. In this case, the designation ‘cannot be determined’ may be used sparingly.

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Note 4 – Tumour dimensions (Core and Non-core)

Tumour size, referring to the size of the invasive cancer component, is not a key staging element for gallbladder cancer according to Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM classification, but it remains a relevant element of pathology reporting. Measurement should ideally be performed macroscopically. Gross aspect (polypoid, ulcerative, diffuse infiltrating) should be described, since it may affect correct measurement. For example, in tumours growing diffusely and infiltrating, the microscopic extent should be used to record tumour size, since it may significantly exceed macroscopic estimates. In addition, extensive intraepithelial neoplasia in flat lesions may be impossible to be distinguished from superficial invasion grossly.[13] Especially in carcinomas arising in intracholecystic neoplasms, it is important to document the size of invasion separately.[14] When sample fragmentation or disruption precludes accurate measurement, reliance on imaging or intraoperative dimensions may be necessary.

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Note 5 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 6 – Histological tumour type (Core)

All gallbladder tumours should be classified based on the 5th edition World Health Organization (WHO) Classification of Digestive System Tumours, 2019.[15] Adenocarcinoma of biliary-type represents the most common type. Other morphological patterns without specific molecular pathogenesis or clinical relevance include the intestinal, clear cell, foamy gland, and microglandular pattern, among others. Tubular adenocarcinomas with intestinal differentiation need to be distinguished from metastatic colorectal cancer; this pattern is therefore included in the dataset. Specific subtypes of gallbladder cancer include mucinous, poorly cohesive, adenosquamous and squamous, and undifferentiated carcinoma. Histologic subtype informs biologic behaviour and thus influences prognosis, patterns of recurrence and clinical management,[2,16] and should therefore be carefully assessed and reported.

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Note 7 – Histological tumour grade (Core)

Grading of invasive cancer has prognostic relevance, and this has been shown in numerous series from different geographic areas.[17-19] In a series of 1,422 patients with non-metastatic gallbladder cancer, grading was an independent predictor of cancer-specific survival at multivariate analysis.[20] Grading should be applied only to biliary and intestinal subtypes.[9] Other subtypes and NECs should not be graded.

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Note 8 – Extent of invasion (Core)

Extent of invasion represents one of the most relevant prognostic factors for gallbladder cancer. Gallbladder cancer can be divided into two major prognostic subgroups: early cancer (confined to the muscle wall, pT1b), and advanced, with infiltration beyond the tunica muscularis propria (≥pT2). Careful assessment of the lesions, ideally after complete embedding of the gallbladder, is pivotal for correct classification. In a recent analysis of 473 cases from Chile and United States of America (USA), it has been shown that only 5% of gallbladder cancer are up to Stage pT1b and these are characterised by an excellent prognosis with a 5 year-

disease-specific survival of 92% independently from the geographic area.[4] As already stated above, localisation on the hepatic versus peritoneal side may affect clinical behaviour and should be reported.

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Note 9 – Lymphovascular invasion (Non-core)

Microscopic lymph- and blood vessel invasion is a prognostic relevant factor in gallbladder cancer[21] and should be included in the pathology report. Distinction between lymphatic and venous invasion is recommended, since this two factors are indicated by distinct symbols in the UICC/AJCC TNM classification.[22,23] In cases of massive inflammatory infiltration or fragmentation, the category 'indeterminate' may be used sparingly. If necessary, the use of special stains (i.e., EvG) or even immunohistochemical stains (i.e., D2-40 and/or CD31) could be of help in this distinction.

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Note 10 – Perineural invasion (Non-core)

Perineural invasion is diagnostically useful since it often confirms a malignant classification e.g., in challenging cases of well-differentiated tumours. Perineural, circumferential, or intraneural invasion is defined as the presence of carcinoma juxtaposed intimately along, around, or within a nerve. Specifically, it includes the potential space between the bundles of axons and the perineurium. Perineural invasion has been identified as a relevant prognostic factor in gallbladder in numerous studies, it can be associated with other prognostic unfavourable factors, such as higher pathological stages and it has been identified as an independent predictor of early recurrence.[3,24-26] In cases of massive inflammatory infiltration or fragmentation, the category 'indeterminate' may be used sparingly.

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Note 11 – Margin status (Core)

An R0 resection remains the cornerstone of curative surgery for gallbladder cancer and has been shown to be associated with an 18 months survival benefit in a recent analysis of 1,439 patients using the USA National Cancer Database,[27] as well as in numerous single institutional studies.[28,29] This supports the necessity of more extensive resections to achieve margin clearance in surgically fit patients and underscores the relevance of careful margin status assessment by pathologists. The presence of high grade dysplasia at the cystic duct margin should also be assessed and reported, since it usually leads to more extended surgery with common bile duct resection,[30] and represents an indicator lesion for the presence of a pancreatobiliary malignancy according to a field effect.[31,32]

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Note 12 – Lymph node status (Core)

The presence of lymph node metastases is a significant adverse prognostic factor in gallbladder cancer.[2,20] According to the UICC TNM 9th edition/AJCC TNM 8th edition,[22,23] at least six lymph nodes should be examined to assess the lymph node status. Since a significant proportion of gallbladder cancers are detected incidentally after cholecystectomy, the number of lymph nodes at first assessment is usually limited to one lymph node located close to the cystic duct. The clinical relevance of extranodal extension has not been evaluated in gallbladder cancer so far, so no recommendation can be given at this point.

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Note 13 – Additional findings (Non-core)

It is important to include in the report all relevant additional findings observed in the specimens. These include both precursor lesions of gallbladder cancer and other conditions that are associated with gallbladder cancer and/or an increased risk thereof, such as intestinal metaplasia, cholelithiasis, diffuse calcification and primary sclerosing cholangitis (PSC). The biliary intraepithelial neoplasia (BilIN)- gallbladder cancer progression model has been substantiated by recent data obtained by whole-exome sequencing and loss of heterozygosity (LOH) analysis as well as phylogenetic tree reconstruction.[33] On the other hand, this study has shown the presence of BilIN-independent mechanisms of cancer development, associated with early extensive mutational and LOH events. Intracholecystic neoplasms (ICN) of the gallbladder include lesions known as intracholecystic papillary neoplasms (ICPN)[14] and intracholecystic tubular non-mucinous neoplasms (ICTN).[34] Pyloric gland adenoma is now included in ICPN.[35] ICNs have been associated with chronic inflammatory conditions, such as PSC and cholelithiasis, and hereditary syndromes (Peutz-Jeghers, familial adenomatous polyposis (FAP)). Their recognition is important for accurate staging, since tumour size is only referred to the invasive component. Intestinal metaplasia is described in association with reflux cholecystectomy in cases of pancreatobiliary maljunction, which is a recognised risk factor for gallbladder cancer.[36] Tumour extension into Rokitansky-Aschoff sinus is an adverse prognostic factor in the group of early gallbladder cancer (up to Stage pT1b), since it probably represents a manifestation of the field-effect phenomenon that explains late recurrences of gallbladder cancer.[37]

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Note 14 – Ancillary studies (Core and Non-core)

Ancillary studies should be reported if performed. They may include immunohistochemistry for subtyping of ICN or invasive cancer (e.g., intestinal, adenosquamous), but especially immunohistochemistry (mismatch repair (MMR) proteins, HER2/neu) and molecular studies (next generation sequencing (NGS)) performed for therapeutic purposes. The characterisation of the genomic landscape of gallbladder has led to the identification of possible therapeutic strategies and personalised treatment options.[38] Most promising targets for gallbladder cancer include HER2 overexpression and/or amplification and MMR-protein deficiency/microsatellite instability (MSI)-high status; other targets are under investigation.[39]

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Note 15 – Histologically confirmed distant metastases (Core)

Stage of the disease is a relevant prognostic factor for gallbladder cancer across numerous studies. In addition, it is the main determinant of therapeutic management and may set the indication for extensive genetic analysis for target discovery. Staging is performed according to the latest version of the TNM classification by grouping the T, N and M categories and is based on a combination of pathological staging and other clinical and imaging information.[22,23] Stage IVB indicates the presence of distant metastases, which may occur in non-regional lymph nodes, such as coeliac, superior mesenteric, periaortic and pericaval lymph nodes, or other organs, including the liver, lung, peritoneum and pleura.[40] The presence of distant metastases is usually a contraindication to resection. However, patients classified in Stage IVB disease due to the presence of non-regional lymph node metastases had a longer survival than patients with metastases in other organs in one study.[41]

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Note 16 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC 9th edition/AJCC 8th edition.[22,23]

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting the resection specimen. A pT category is not assigned on biopsy. pT1 describe early tumours confined to the mucosa or the muscular wall; pT2-pT4 describe advanced tumours with infiltration of the perimuscular tissue (pT2), the serosa, the liver or one adjacent digestive structure (e.g., stomach, duodenum) (pT3), or the hepatic pedicle or more than one adjacent digestive structure (pT4). The pT2 category is distinguished in pT2a (invasion of the perimuscular tissue on the peritoneal side) and pT2b (invasion of the perimuscular tissue on the hepatic side), due to the adverse prognostic value of the latter,[10] although other studies have failed to confirm this impression.[11] Major vascular invasion (pT4) is usually a contraindication to resection. The involvement of regional lymph nodes, which include lymph nodes along the bile duct, the hepatic artery, the portal vein and the cystic duct, is categorised in pN1 if 1-3 lymph nodes are involved and pN2 if more than 3 lymph nodes are involved. Assessment of the pN category presupposes the examination of at least 6 lymph nodes.

The M category includes both non-regional lymph node metastases and distant metastases to other organs (liver, lung) or body cavities (peritoneum, pleura) (refer to **Note 15 – HISTOLOGICALLY CONFIRMED DISTANT METASTASES**).[22,23] Stage I and II include cancers limited to the gallbladder. While Stage III and IV cancers are those with direct spread outside the gallbladder (pT3/4) and/or with regional or non-regional/distant metastases (pN+, pM1).

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