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 (select all that apply)

☐ 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 Classification of Digestive System Tumours, 6th Edition (2026))

◯ Adenocarcinoma, not otherwise specified (NOS)
◯ Mucinous adenocarcinoma
◯ Adenosquamous carcinoma
◯ Poorly cohesive carcinoma
◯ Undifferentiated carcinoma
◯ Neuroendocrine neoplasms[a]
- ◯ Neuroendocrine carcinoma, NOS
  - ◯ Large cell
  - ◯ Small cell
- ◯ Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

◯ Other, *specify*

[a] *Neuroendocrine tumours are not covered in this dataset.*

HISTOLOGICAL TUMOUR GRADE (Note 7)

◯ Not applicable
◯ Cannot be assessed
◯ G1: Well differentiated
◯ G2: Moderately differentiated
◯ G3: Poorly differentiated
◯ Other, *specify*

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)
Version 1.0 Published August 2026 ISBN: 978-1-922324-83-2

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour
- ☐ Tumour invades lamina propria
- ☐ Tumour invades muscular layer
- ☐ Tumour invades perimuscular connective tissue on the peritoneal side without serosal involvement
- ☐ Tumour invades perimuscular connective tissue on the hepatic side without liver involvement
- ☐ Tumour perforates serosa (visceral peritoneum)
- ☐ Tumour directly invades liver
- ☐ Tumour directly invades other adjacent organ(s)/ structure(s)
  - ☐ Stomach
  - ☐ Duodenum
  - ☐ Colon
  - ☐ Pancreas
  - ☐ Omentum
  - ☐ Extrahepatic bile ducts
  - ☐ Other, *specify*
- ☐ Tumour 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

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*

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)
Version 1.0 Published August 2026 ISBN: 978-1-922324-83-2

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

ANCILLARY STUDIES (Note 14)

- ○ Not performed
- ○ Performed (select all that apply)
  - ☐ Mismatch repair (MMR) immunohistochemistry
    - ○ Not interpretable
    - ○ Proficient
    - ○ Deficient, *specify*
  - ☐ HER2 testing, *confirm score*
    - ○ 1
    - ○ 2 (confirmed in situ hybridization)
    - ○ 3+
  - ☐ 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*

HIGH GRADE NEUROENDOCRINE NEOPLASMS ONLY[a]

Neuroendocrine markers

- ○ Not performed
- ○ Performed (select at least two of the following core options)
  - ☐ Synaptophysin
  - ☐ Chromogranin-A
  - ☐ INSM1
  - ☐ Other, *specify*

Specify test(s) performed and result(s) if available

Ki-67 proliferation index

- ○ Not performed
- ○ Performed
  - %

p53

- ○ Not performed
- ○ Performed
  - ○ Abnormal, *specify test(s) performed and result(s) if available*
  - ○ Wildtype pattern

[a] *Neuroendocrine tumours are not covered in this dataset.*

RB1

- ○ Retained
- ○ Deficient

Low molecular weight cytokeratin(s)

- ○ Positive
- ○ Negative

HISTOLOGICALLY CONFIRMED DISTANT METASTASES (Note 15)

- ○ Not applicable
- ○ Not identified
- ○ Present (M1) (select all that apply)
  - ☐ Non-regional lymph node(s)
  - ☐ Liver
  - ☐ Other, *specify*

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

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

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

Primary tumour (pT)

- ○ TX[c] 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[c] 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

[b] *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 (incorporating any errata published up until 18 July 2026).*

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

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)
Version 1.0 Published August 2026 ISBN: 978-1-922324-83-2

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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.

Back

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 (NECs), mixed neuroendocrine-non-neuroendocrine neoplasm (MiNENs) and amphicrine-like carcinoma are included. Well differentiated neuroendocrine tumours (NETs) and non-epithelial malignancies are not included.

In development of this dataset, the DAC considered evidence up until July 2026.

The authors of this dataset can be accessed here.

Back

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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]

Back

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]

Back

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 ‘not specified’ may be used sparingly.

Back

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 American Joint Committee on Cancer (AJCC) TNM classification,[13,14] 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.[15] Especially in carcinomas arising in intracholecystic neoplasms, it is important to document the size of invasion separately.[16] When sample fragmentation or disruption precludes accurate measurement, reliance on imaging or intraoperative dimensions may be necessary.

Back

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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.

Back

Note 6 – Histological tumour type (Core)

All gallbladder tumours should be classified based on the 6th edition World Health Organization (WHO) Classification of Digestive System Tumours, 2026 (Table 1).[9] 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. Poorly cohesive carcinoma needs to be distinguished from metastatic lobular breast cancer and gastric cancer by immunohistochemistry and clinical correlation. Histologic subtype informs biologic behaviour and thus influences prognosis, patterns of recurrence and clinical management,[2,17] and should therefore be carefully assessed and reported.

Table 1: 6th edition of the World Health Organization Classification of tumours of the gallbladder.[9]

Descriptor	ICD-O codes[a]
Adenocarcinoma, not otherwise specified (NOS)	81400/3
Mucinous adenocarcinoma	84800/3
Adenosquamous carcinoma	85600/3
Poorly cohesive carcinoma	84901/3
Undifferentiated carcinoma	80200/3
Neuroendocrine carcinoma, NOS	82460/3
Large cell neuroendocrine carcinoma	80130/3
Small cell neuroendocrine carcinoma	80410/3
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)	81540/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, fourth edition (ICD-O-4).[18] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour: /2 for carcinoma in situ and grade lll intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

© World Health Organization/International Agency for Research on Cancer. Reproduced with permission.

Back

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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.[19-21] In a series of 1,422 patients with non-metastatic gallbladder cancer, grading was an independent predictor of cancer-specific survival at multivariate analysis.[22] Grading should be applied only to biliary and intestinal subtypes.[9] Other subtypes and NECs should not be graded.

Back

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 2023 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] Tumour extension into Rokitansky-Aschoff sinus is an adverse prognostic factor in the group of early gallbladder cancer, since it probably represents a manifestation of the field-effect phenomenon that explains late recurrences of gallbladder cancer.[23] Of note, distinguishing extension into Rokitanski-Aschoff sinus from perimuscular involvement (≥pT2) may be challenging. Serial sections can be helpful; in unresolved cases, expert consultation can be considered. As already stated above, localisation on the hepatic versus peritoneal side may affect clinical behaviour and should be reported.

Back

Note 9 – Lymphovascular invasion (Core)

Microscopic lymph and blood vessel invasion is a prognostic relevant factor in gallbladder cancer[24] 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.[13,14] In cases of massive inflammatory infiltration or fragmentation, which makes impossible to assess the presence or absence of lymphovascular invasion, 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.

Back

Note 10 – Perineural invasion (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

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

independent predictor of early recurrence.[3,25-27] In cases of massive inflammatory infiltration or fragmentation, the category 'indeterminate' may be used sparingly.

Back

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 2021 analysis of 1,439 patients using the USA National Cancer Database,[28] as well as in numerous single institutional studies.[29,30] 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. Relevant margins include the cystic duct margin and the liver parenchymal margin; other margins may be present in case of extended resections. The presence of high grade dysplasia (carcinoma in situ) at the cystic duct margin should also be assessed and reported, since it usually leads to more extended surgery with common bile duct resection,[31] and represents an indicator lesion for the presence of a pancreatobiliary malignancy according to a field effect.[32,33] So far, no study has systematically analysed the minimal margin clearance necessary to attest an R0 resection. In other words, an R1 resection in gallbladder cancer is defined by the presence of tumour cells at the resection margin. For standardisation purposes it is recommended to assess and record the minimal distance of the tumour cells from the margin (in millimetres).

Back

Note 12 – Lymph node status (Core)

The presence of lymph node metastases is a significant adverse prognostic factor in gallbladder cancer.[2,22] According to the UICC TNM 9th edition/AJCC TNM 8th edition,[13,14] 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 up to one lymph node located close to the cystic duct, which may be removed during cholecystectomy. The clinical relevance of extranodal extension has not been evaluated in gallbladder cancer so far, so no recommendation can be given at this point.

Back

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 data obtained by whole-exome sequencing and loss of heterozygosity (LOH) analysis as well as phylogenetic tree reconstruction.[34] 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)[16] and intracholecystic tubular neoplasms (ICTN).[35] Pyloric gland adenoma is now included in ICPN in case of lesions >10 mm or with high grade dysplasia.[36] ICNs

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

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.[37]

Back

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]

If a pure or mixed neuroendocrine neoplasm is suspected on morphology, positivity for at least two markers of neuroendocrine differentiation by immunohistochemistry is required (core) to confirm neuroendocrine differentiation, usually synaptophysin, chromogranin A and/or INSM1. As with other gastrointestinal tract and pancreatic neuroendocrine neoplasms, assessment of proliferation index by Ki-67 immunohistochemistry is a core component as it is fundamental to grading of the neuroendocrine component.[9] For the differential diagnosis with grade 3 NET, p53 (core) and Rb1 (non-core) can be applied. Low molecular weight cytokeratins can be used (non-core). MMR stains may also be considered for NECs (non-core). A Ki-67 proliferation index <55% is associated with better overall survival in NECs.[40] TP53 mutations are found in over 69% of NEC compared to 10-15% of NET grade 3 (G3),[41,42] while RB1 loss is found in 40-60% of NEC and only very rarely in NET G3.[43]

Back

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.[13,14] 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.[44] 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.[45]

Back

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

Note 16 – Pathological staging (Core)

TNM staging should be assessed according to the agreed criteria of the UICC 9th edition/AJCC 8th edition Cancer Staging Manuals.[13,14]

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. As indicated in UICC TNM9/AJCC TNM8,[13,14] the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.. 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**).[13,14] 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).

Back

References

1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.

2 Roa JC, García P, Kapoor VK, Maithel SK, Javle M and Koshiol J (2022). Gallbladder cancer. *Nat Rev Dis Primers* 8(1):69.

3 Tirca L, Savin C, Stroescu C, Balescu I, Petrea S, Diaconu C, Gaspar B, Pop L, Varlas V, Hasegan A, Martac C, Bolca C, Stoian M, Zgura A, Gorecki GP and Bacalbasa N (2024). Risk Factors and Prognostic Factors in GBC. *J Clin Med* 13(14):4201.

4 Pehlivanoglu B, Akkas G, Memis B, Basturk O, Reid MD, Saka B, Dursun N, Bagci P, Balci S, Sarmiento J, Maithel SK, Bandyopadhyay S, Escalona OT, Araya JC, Losada H, Goodman M, Knight JH, Roa JC and Adsay V (2023). Reappraisal of T1b gallbladder cancer (GBC): clinicopathologic analysis of 473 in situ and invasive GBCs and critical review of the literature highlights its rarity, and that it has a very good prognosis. *Virchows Arch* 482(2):311–323.

5 Kim HS, Park JW, Kim H, Han Y, Kwon W, Kim SW, Hwang YJ, Kim SG, Kwon HJ, Vinuela E, Járufe N, Roa JC, Han IW, Heo JS, Choi SH, Choi DW, Ahn KS, Kang KJ, Lee W, Jeong CY, Hong SC, Troncoso A, Losada H, Han SS, Park SJ, Yanagimoto H, Endo I, Kubota K, Wakai T, Ajiki T, Adsay NV and Jang JY (2018). Optimal surgical treatment in patients with T1b gallbladder cancer: An international multicenter study. *J Hepatobiliary Pancreat Sci* 25(12):533–543.

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

6 Okumura K, Gogna S, Gachabayov M, Felsenreich DM, McGuirk M, Rojas A, Quintero L, Seshadri R, Gu K and Dong XD (2021). Gallbladder cancer: Historical treatment and new management options. *World J Gastrointest Oncol* 13(10):1317–1335.

7 Goetze TO and Paolucci V (2010). Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. *Surg Endosc* 24(9):2156–2164.

8 Aloia TA, Járufe N, Javle M, Maithel SK, Roa JC, Adsay V, Coimbra FJ and Jarnagin WR (2015). Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 17(8):681–690.

9 WHO Classification of Tumours Editorial Board (ed) (2026). *WHO Classification of Tumours, Digestive System Tumours, 6th Edition*, IARC, Lyon.

10 Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G, Javle M, Conrad C, Maru DM, Aoki T, Vigano L, Ribero D, Kokudo N, Capussotti L and Vauthey JN (2015). Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. *Ann Surg* 261(4):733–739.

11 Kwon W, Kim H, Han Y, Hwang YJ, Kim SG, Kwon HJ, Vinuela E, Járufe N, Roa JC, Han IW, Heo JS, Choi SH, Choi DW, Ahn KS, Kang KJ, Lee W, Jeong CY, Hong SC, Troncoso AT, Losada HM, Han SS, Park SJ, Kim SW, Yanagimoto H, Endo I, Kubota K, Wakai T, Ajiki T, Adsay NV and Jang JY (2020). Role of tumour location and surgical extent on prognosis in T2 gallbladder cancer: an international multicentre study. *Br J Surg* 107(10):1334–1343.

12 Kim KH, Moon JI, Park JW, You Y, Jung HI, Choi H, Hwang SE and Jo S (2024). Impact of longitudinal tumor location on postoperative outcomes in gallbladder cancer: Fundus and body vs. neck and cystic duct, a retrospective multicenter study. *Ann Hepatobiliary Pancreat Surg* 28(4):474–482.

13 Brierley JD, Giuliani M, O'Sullivan B, Rous B and Van Eycken E (eds) (2025). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 9th Edition*, Wiley, USA.

14 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.

15 Roa JC, Basturk O and Adsay V (2021). Dysplasia and carcinoma of the gallbladder: pathological evaluation, sampling, differential diagnosis and clinical implications. *Histopathology* 79(1):2–19.

16 Adsay V, Jang KT, Roa JC, Dursun N, Ohike N, Bagci P, Basturk O, Bandyopadhyay S, Cheng JD, Sarmiento JM, Escalona OT, Goodman M, Kong SY and Terry P (2012). Intracholecystic papillary-tubular neoplasms (ICPN) of the gallbladder (neoplastic polyps, adenomas, and papillary neoplasms that are ≥1.0 cm): clinicopathologic and immunohistochemical analysis of 123 cases. *Am J Surg Pathol* 36(9):1279–1301.

17 Samuel S, Mukherjee S, Ammannagari N, Pokuri VK, Kuvshinoff B, Groman A, LeVea CM and Iyer R (2018). Clinicopathological characteristics and outcomes of rare histologic subtypes of gallbladder cancer over two decades: A population-based study. *PLoS One* 13(6):e0198809.

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

18 International Agency for Research on Cancer (IARC) (2026). *International Classification of Diseases for Oncology, Fourth edition ICD-O-4*. Available from: tumourclassification.iarc.who.int/icd-o-4/ (Accessed 20 August 2026).

19 Deng K, Xing J, Xu G, Ma R, Jin B, Leng Z, Wan X, Xu J, Shi X, Qiao J, Yang J, Song J, Zheng Y, Sang X and Du S (2024). Novel multifactor predictive model for postoperative survival in gallbladder cancer: a multi-center study. *World J Surg Oncol* 22(1):263.

20 Cai ZQ, Guo P, Si SB, Geng ZM, Chen C and Cong LL (2017). Analysis of prognostic factors for survival after surgery for gallbladder cancer based on a Bayesian network. *Sci Rep* 7(1):293.

21 Feroz Z, Gautam P, Tiwari S, Shukla GC and Kumar M (2022). Survival analysis and prognostic factors of the carcinoma of gallbladder. *World J Surg Oncol* 20(1):403.

22 Zhang W, Hong HJ and Chen YL (2018). Establishment of a Gallbladder Cancer-Specific Survival Model to Predict Prognosis in Non-metastatic Gallbladder Cancer Patients After Surgical Resection. *Dig Dis Sci* 63(9):2251–2258.

23 Roa JC, Tapia O, Manterola C, Villaseca M, Guzman P, Araya JC, Bagci P, Saka B and Adsay V (2013). Early gallbladder carcinoma has a favorable outcome but Rokitansky-Aschoff sinus involvement is an adverse prognostic factor. *Virchows Arch* 463(5):651–661.

24 Ramalhosa F, Amaral MJ, Serôdio M, Oliveira RC, Teixeira P, Cipriano MA and Tralhão JG (2022). Clinicopathological prognostic factors for gallbladder carcinoma: a retrospective study. *J Gastrointest Oncol* 13(4):1997–2006.

25 Yang SQ, Feng H, Tian Y, Zou RQ, Dai YS, Hu HJ and Li FY (2024). Unraveling early recurrence of risk factors in Gallbladder cancer: A systematic review and meta-analysis. *Eur J Surg Oncol* 50(7):108372.

26 Feo CF, Cossu ML, Ginesu GC, Ginesu GC, Fancellu A, Scanu AM, Piras N, Cherchi G, Cossu A, Sotgiu G, Pazzona M and Porcu A (2017). Perineural infiltration as a prognostic factor in surgically treated gallbladder cancer A single center experience and literature review. *Ann Ital Chir* 88:485–490.

27 Lv TR, Hu HJ, Liu F, Ma WJ, Jin YW and Li FY (2023). The significance of peri-neural invasion in patients with gallbladder carcinoma after curative surgery: a 10 year experience in China. *Updates Surg* 75(5):1123–1133.

28 Littau MJ, Kulshrestha S, Bunn C, Kim P, Luchette FA and Baker MS (2021). Is positive histologic surgical margin associated with overall survival in patients with resectable gallbladder cancer? *Surg Open Sci* 6:15–20.

29 Lim H, Seo DW, Park DH, Lee SS, Lee SK, Kim MH and Hwang S (2013). Prognostic factors in patients with gallbladder cancer after surgical resection: analysis of 279 operated patients. *J Clin Gastroenterol* 47(5):443–448.

30 D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH and Jarnagin WR (2009). Analysis of the extent of resection for adenocarcinoma of the gallbladder. *Ann Surg Oncol* 16(4):806–816.

31 You DD, Lee HG, Paik KY, Heo JS, Choi SH and Choi DW (2008). What is an adequate extent of resection for T1 gallbladder cancers? *Ann Surg* 247(5):835–838.

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

32 Bickenbach KA, Shia J, Klimstra DS, DeMatteo RP, Fong Y, Kingham TP, Allen PJ, Jarnagin WR and D'Angelica MI (2011). High-grade dysplasia of the cystic duct margin in the absence of malignancy after cholecystectomy. *HPB (Oxford)* 13(12):865–868.

33 Moslim MA, Tang A and Morris-Stiff G (2017). Management of high-grade dysplasia of the cystic duct after cholecystectomy. *BMJ Case Rep* 2017.

34 Lin J, Peng X, Dong K, Long J, Guo X, Li H, Bai Y, Yang X, Wang D, Lu X, Mao Y, Sang X, Ji X, Zhao H and Liang H (2021). Genomic characterization of co-existing neoplasia and carcinoma lesions reveals distinct evolutionary paths of gallbladder cancer. *Nat Commun* 12(1):4753.

35 Pehlivanoglu B, Balci S, Basturk O, Bagci P, Erbarut Seven I, Memis B, Dursun N, Jang KT, Saka B, Ohike N, Tajiri T, Roa JC, Sarmiento JM, Reid MD and Adsay V (2021). Intracholecystic tubular non-mucinous neoplasm (ICTN) of the gallbladder: a clinicopathologically distinct, invasion-resistant entity. *Virchows Arch* 478(3):435–447.

36 Nakanuma Y, Sugino T, Nomura K, Terada T, Sato Y and Ohnishi Y (2022). Pathological features of pyloric gland adenoma of the gallbladder in comparison with gastric subtype of intracholecystic papillary neoplasm. *Ann Diagn Pathol* 56:151879.

37 Muraki T, Memis B, Reid MD, Uehara T, Ito T, Hasebe O, Okaniwa S, Horigome N, Hisa T, Mittal P, Freedman A, Maithel S, Sarmiento JM, Krasinskas A, Koshiol J and Adsay V (2017). Reflux-Associated Cholecystopathy: Analysis of 76 Gallbladders From Patients With Supra-Oddi Union of the Pancreatic Duct and Common Bile Duct (Pancreatobiliary Maljunction) Elucidates a Specific Diagnostic Pattern of Mucosal Hyperplasia as a Prelude to Carcinoma. *Am J Surg Pathol* 41(9):1167–1177.

38 Giraldo NA, Drill E, Satravada BA, Dika IE, Brannon AR, Dermawan J, Mohanty A, Ozcan K, Chakravarty D, Benayed R, Vakiani E, Abou-Alfa GK, Kundra R, Schultz N, Li BT, Berger MF, Harding JJ, Ladanyi M, O'Reilly EM, Jarnagin W, Vanderbilt C, Basturk O and Arcila ME (2022). Comprehensive Molecular Characterization of Gallbladder Carcinoma and Potential Targets for Intervention. *Clin Cancer Res* 28(24):5359–5367.

39 Song X, Hu Y, Li Y, Shao R, Liu F and Liu Y (2020). Overview of current targeted therapy in gallbladder cancer. *Signal Transduct Target Ther* 5(1):230.

40 Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, Pisa E, Barberis M, Vanoli A, Buzzoni R, Pusceddu S, Concas L, Sessa F, Solcia E, Capella C, Fazio N and La Rosa S (2017). The Clinicopathologic Heterogeneity of Grade 3 Gastroenteropancreatic Neuroendocrine Neoplasms: Morphological Differentiation and Proliferation Identify Different Prognostic Categories. *Neuroendocrinology* 104(1):85–93.

41 Venizelos A, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, Couvelard A, Hjortland GO, Sundlöv A, Svensson J, Garresori H, Kersten C, Hofsli E, Detlefsen S, Krogh M, Sorbye H and Knappskog S (2021). The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 29(1):1–14.

42 Sciarra A, Libera L, Destro A, Maragliano R, Furlan D, Guastafierro V, Marchiori D, Vanoli A, Gonzalez RS, Letovanec I, Lazzi S, La Rosa S and Uccella S (2026). Molecular Profiling of Digestive Grade 3 Neuroendocrine Tumors Reveals a Shared Molecular Framework with Lower-Grade Tumors, Marked Heterogeneity, and Therapeutic Opportunities. *Endocr Pathol* 37(1):23.

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).

43 Chen R, Tihy M, Lacroix L, de Rycke O, Lacombe C, Just PA, Cazes A, Svrcek M, de Montpreville VT, Antoine M, Scoazec JY, de Mestier L, Couvelard A and Cros J (2025). Performance of Immunohistochemistry to Detect Rb/p53 Alterations in High-Grade Neuroendocrine Neoplasms: Staining Patterns and Comparison with Genetic Testing. *Endocr Pathol* 36(1):40.

44 Liao X and Zhang D (2021). The 8th Edition American Joint Committee on Cancer Staging for Hepato-pancreato-biliary Cancer: A Review and Update. *Arch Pathol Lab Med* 145(5):543–553.

45 Wang J, Bo X, Shi X, Suo T, Xin Y, Nan L, Wang C, Ni X, Liu H, Pan H, Shen S, Li M, Lu P, Zhang D, Wang Z, Wang Y and Liu H (2020). Modified staging classification of gallbladder carcinoma on the basis of the 8(th) edition of the American Joint Commission on Cancer (AJCC) staging system. *Eur J Surg Oncol* 46(4 Pt A):527–533.

Use of this dataset is only permitted subject to the details described at: Disclaimer - International Collaboration on Cancer Reporting (iccr-cancer.org)

© 2026 International Collaboration on Cancer Reporting Limited (ICCR).