The Royal College of Pathologists
Pathology: the science behind the cure

Dataset for histopathological reporting of liver resection specimens (including gallbladder) and liver biopsies for primary and metastatic carcinoma

September 2022

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Unique document number	G050
Document name	Dataset for histopathological reporting of liver resection specimens (including gallbladder) and liver biopsies for primary and metastatic carcinoma
Version number	3
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Date active	September 2022 **(to be implemented within 3 months)**
Date for full review	September 2025
Comments	This document will replace the 2nd edition of *Dataset for histopathological reporting of liver resection specimens (including gallbladder) and liver biopsies for primary and metastatic carcinoma* published in June 2012. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 1 June to 29 June 2022. Responses and authors' comments are available to view, following final publication of this dataset. **Dr Brian Rous** **Clinical Lead for Guideline Review (Cellular Pathology)**

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Registered charity in England and Wales, no. 261035

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Foreword

The cancer datasets published by the Royal College of Pathologists (RCPath) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices D–M) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Dataset) in England. Core data items are items that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core, data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- British Association for the Study of the Liver (BASL)
- the Pathology and Liver sections of the British Society of Gastroenterology (BSG)
- Association of Upper Gastrointestinal Surgeons (AUGIS)
- the UK Liver Pathology Group (UKLPG).

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed from August 2020 up to April 2022, previous recommendations of the College and evidence-based practice including local and international guidelines widely used in the UK. Key terms searched included hepatocellular carcinoma, cholangiocarcinoma, gall bladder cancer, metastatic colorectal cancer, liver, pathology, stage, etc. as appropriate. Published evidence was evaluated using modified SIGN guidance (see Appendix T). Consensus of evidence in the guideline was achieved by expert review. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset. However, it is noted that developments in the field of hepatobiliary cancer since the first edition of this dataset (2007), such as increasing operability due to neoadjuvant treatments and surgical advances, screening of patients with cirrhosis for hepatocellular carcinoma, increasing use of immunohistochemistry and centralisation, are increasing the demands and scope for histopathological support in hepatobiliary cancer centres.

The third edition of this dataset (2021) incorporates the changes to the classification of liver and bile duct cancers introduced in the *Union for International Cancer Control (UICC) TNM 8th edition*, 2017.[1] Changes to the TNM staging of hepatocellular carcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and gall bladder carcinoma are included, and it is intended by the Royal College of Pathologists that the staging of these cancers transfers to the criteria described in TNM8 in January 2018. Since 2010 there has been harmonisation of cancer staging between TNM and the American Joint Committee on Cancer 8th edition of the *Cancer Staging Manual* was also published in 2017.[2] The *WHO classification of tumours of the digestive system 5th edition* was published in 2019 and includes detailed descriptions of the pathology of all tumours of the liver.[3]

A formal revision cycle for all cancer datasets takes place on a three-yearly basis. However,

each year, the College will ask the author of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness team, Working Group on Cancer Services and the Lay Network and was placed on the College website for consultation with the membership from 1 June to 29 June 2022. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness team and are available on request.

1 Introduction

The primary purpose of this document is twofold:

- to define the set of data necessary for the uniform recording and staging of the core pathological features in liver cancer resection specimens
- to describe its application in sufficient detail and clarity that reports from different departments will contain equivalent information, allowing comparison of clinical practice and outcomes.

It is recommended that this dataset is used for the following reasons:

- to provide prognostic information to clinicians and patients
- to select potential patients for future trials of adjuvant therapy
- to collect accurate data for cancer registration and epidemiology
- to allow correlation of resection specimens with preoperative imaging
- to allow the accurate and equitable comparison of surgical practice in different units and the comparison of patients in clinical trials.

The dataset and guidelines describe the core data that should be provided in histopathological reports of liver and gall bladder resection specimens for primary and metastatic malignancy. Guidelines for reporting needle biopsy specimens of hepatic neoplasms are also included.

This third edition has been written to update this dataset following publication of the 8th edition of TNM in use from January 2018 (Appendix A).[1] This is also aligned with the AJCC 8th staging.[2] There is a comprehensive literature review in the 5th edition of the *WHO classification of tumours of the digestive system*, 2019.[3] The dataset is also aligned with the ICCR dataset for primary liver cancers published in 2020 representing an international collaboration of pathologists, and informed by a more recent literature review.[4]

Since the purpose of the dataset is to provide practical guidance to facilitate consistency of reporting and staging liver cancer specimens in the UK, the references included in this dataset are those identified through PubMed searches that address specific decisions and approaches

that have been adopted in compiling this dataset document. There are further recent references elsewhere.[2–6]

Unless otherwise stated, the level of evidence corresponds to 'Good practice point (GPP): Recommended best practice based on the clinical experience of the authors of the writing group'.

Liver resection for primary liver cancers (hepatocellular carcinoma [HCC] and intrahepatic or perihilar cholangiocarcinoma [CC]) and metastatic cancer (usually colorectal carcinoma liver metastasis [CRCLM]) is performed in a limited number of specialist centres in the UK. Patients with gallbladder cancer discovered following routine cholecystectomy should be referred to a specialist centre for consideration of further surgery. These guidelines cover all of these scenarios. The classification of hepatocellular adenoma (HCA) which encompasses morphology, immunohistochemistry and molecular criteria has developed since the second edition of the dataset in 2012, and practical diagnostic aspects of HCA diagnosis have been added to section 5.3.1. Although benign lesions, these are included in this cancer dataset because they have the potential to undergo malignant transformation. The distinction between HCA and well differentiated HCC may be problematic and the dataset is a convenient document to provide diagnostic guidance in this emerging area. Primary hepatic neuroendocrine neoplasms (NENs) are staged as for intrahepatic CC in the new AJCC guidelines (although not included in TNM8). They are not specifically intended for other types of tumour that may be resected, such as focal nodular hyperplasia (FNH), primary sarcoma (staged according to the classification for soft tissue sarcoma of the abdomen and thoracic visceral organs), metastatic sarcoma, metastatic gastrointestinal stromal tumour, cystic lesions or for paediatric tumours, although similar principles would apply. For a comprehensive account of the pathology of primary liver tumours, the reader is referred elsewhere.[3,5,6]

For primary tumours, the core items of information are those required to derive the TNM stage of the resected tumour,[1] and others which may be of prognostic significance. TNM8, published in 2017, introduced changes to the staging of HCC, intrahepatic CC, perihilar CC and gall bladder carcinoma. These are summarised in a table in Appendix B, and the TNM version used to stage the cancers should be stated in the histopathology report. They match the AJCC 8th edition staging classification, also 2017, in which there is a helpful, more detailed description of the pathological staging criteria.[2] SNOMED-CT has now replaced SNOMED; a list of SNOMED-CT codes is included in Appendix C.

Core data items of tumour site, size, number, surgical margin status, histological tumour type, differentiation, vascular invasion, extent of local invasion, lymph node status and background liver disease are important in tumour staging and/or have been found to be prognostic factors in primary liver cancers. It is good practice to record these in all resections, although the specific requirements for TNM staging vary among tumour types.

Rather than create separate documents for HCC, CC, gallbladder and CRCLM, this dataset is generic to all these scenarios in all sections, with sub-sections in specimen handling and core data items (sections 4 and 5) covering aspects specific to each tumour type. There are five separate reporting proformas (HCC, intrahepatic CC, perihilar CC, gallbladder and CRCLM) in Appendices D–H (and Appendices I–M in list format), which share common macroscopic items but reflect the different microscopic items required for staging.

1.1 Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and biomedical scientists undertaking specimen dissection, and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons, oncologists and hepatologists, cancer registries and the National Cancer Intelligence Network.

2 Clinical information required on the specimen request form

The following information should be provided (see Appendices D–M):

- the type of operative procedure, segments resected
- site of tumour with description of imaging findings (alternatively the imaging report should be available via another route, e.g. hospital intranet or results server)
- an indication as to whether this has been a potentially complete resection or whether there is known residual tumour
- details of any previous procedures or treatment such as radiofrequency ablation, trans-arterial chemo-embolisation or selective internal radiation therapy, portal vein embolisation (to induce hyperplasia of the remaining liver segments), or neoadjuvant chemotherapy
- information about background chronic liver disease, e.g. aetiological factors for chronic liver disease; evidence of primary sclerosing cholangitis (PSC) in CC
- site(s) of any lymph nodes excised – in continuity with main specimen or submitted separately
- for patients with previous surgery (in particular, gallbladder bed resection following previously unsuspected carcinoma in cholecystectomy specimen), details of the previous surgical procedure and preferably a copy of the histology report.

For CC resection specimens, it is helpful if the surgeon can identify and label the bile duct resection margin(s). For any complex procedure, a diagram indicating the position of the tumour in the submitted specimen and its relationship to the resection margins should be provided.

3 Preparation of the specimen before dissection

The segmental anatomy of the liver is shown in Figure 1. The boundaries of the eight segments represent the watershed between portions of liver perfused by main branches of the hepatic artery and portal vein and form the basis of the various surgical options for major liver resection. Liver tumours are resected either by segmental resection following the planes of whole liver segments defined by intra-operative ultrasound, or non-anatomical (wedge) resection for small, accessible, subcapsular lesions. The dataset should also be applied to total hepatectomy specimens from patients undergoing liver transplantation when tumour is present.

Segmentectomy procedures result in sizeable resection specimens. The surgeon should state which segments are included as this may not be clear from the topography of the specimen. The boundary of segments is defined by the course of intrahepatic vessels and cannot be inferred from surface landmarks. Wherever possible, the preoperative imaging report should be available to the pathologist at the time of specimen dissection.

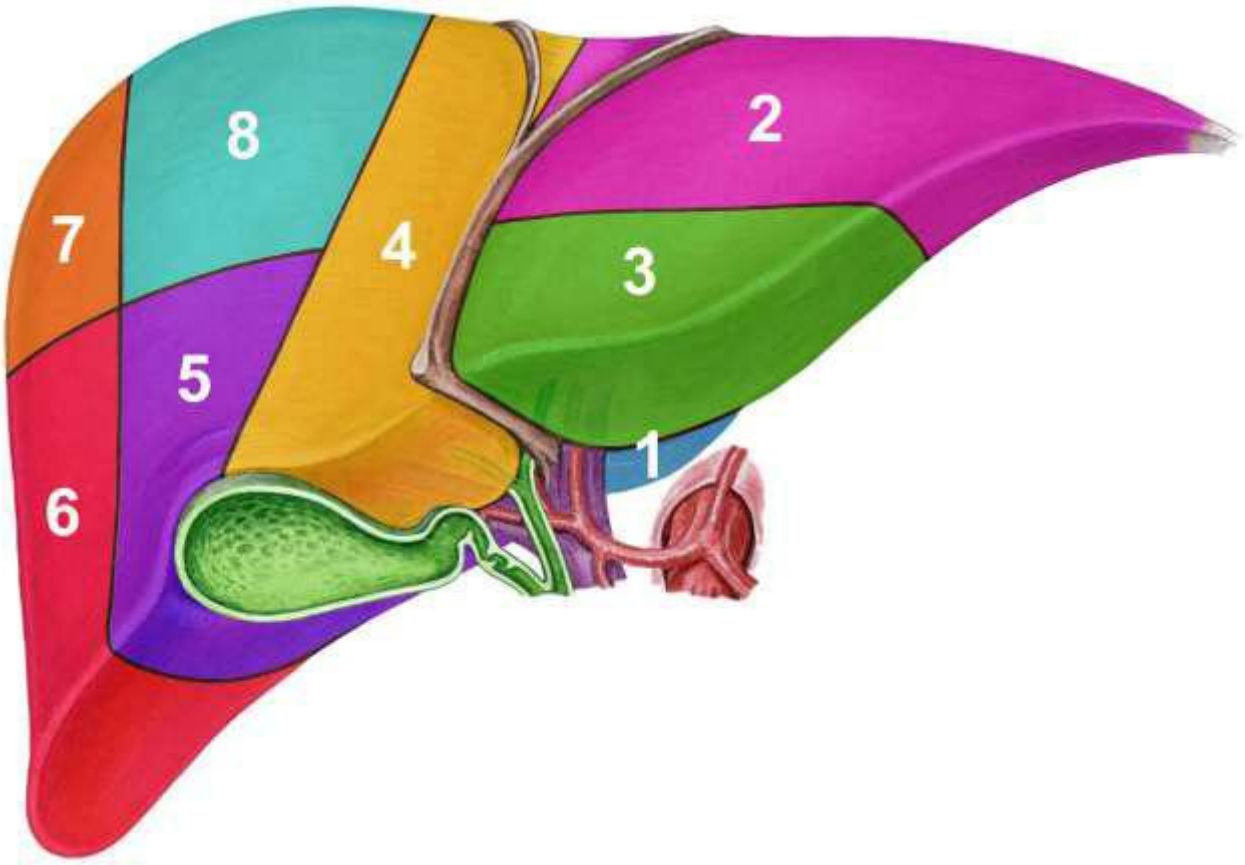

Figure 1: Segmentectomy specimens.[7] © Reproduced with permission from Leeds Teaching Hospitals NHS Trust.

Right hepatectomy	Segments 5–8
Extended right hepatectomy	Segments 4–8
Left lateral sectionectomy	Segments 2–3
Left hepatectomy	Segments 2–4
Extended left hepatectomy	Segments 1–5 and 8
Hepatectomy (at transplant)	Segments 1–8

Perihilar CC are defined anatomically as tumours located in the extrahepatic biliary tree proximal to the origin of the cystic duct, up to and including the second branches of the right and left hepatic ducts.[2] For perihilar CC, a length of extrahepatic duct will normally be resected in continuity with segments or lobes of liver depending on the extent of tumour within the bile ducts, invasion of vessels and parenchyma. There is much anatomical variability at the liver hilum, and the pathologist should consult the surgeon if the identity of the main hilar vessels and ducts is not clear from the diagram on the request form.

More distal bile duct carcinomas resected without hepatectomy should be reported as described in the dataset for the histopathological reporting of pancreatic, ampullary and bile duct carcinoma.

About 50% of gallbladder cancer resections are for tumours previously diagnosed on imaging. The other 50% are staged procedures following incidental detection in routine cholecystectomy specimens, where excision of the gallbladder bed is indicated for stage 1b and stage 2 cancers.[8] Biliary tree resection is undertaken if the cystic duct resection margin is involved. The gallbladder bed lies between segments 4b and 5, and either a limited hepatic resection of this area or a more radical resection may be performed with the aim of resecting any residual tumour and local lymph nodes.

4 Specimen handling and block selection

Specimens can be dissected in the fresh or fixed state. Although formalin penetrates the liver poorly, intrahepatic tumours are usually clearly demarcated within the liver and examination after 24–48 hours does not significantly impair morphology. Specimen hardening following fixation facilitates accurate slicing. If a fresh tumour is required, this can be obtained either by slicing the specimen fresh after painting the resection margin, or (if identifiable from the external appearance) by excising a portion of tumour through the capsule, so long as the capsule appears intact and is not covered by adherent fatty tissue which may result from underlying capsular breach by the tumour. The surfaces of the specimen other than the capsule (i.e. parenchymal resection plane, extrahepatic biliary tree, any tissue adherent to the liver capsule) should be painted with ink or silver nitrate to allow identification in histological sections.

Block-taking strategy for all liver specimens:

- tumour with nearest hepatic resection margin (when this is close enough to the tumour to be included in the block)
- other blocks of tumour with adjacent liver tissue (for microscopic vascular invasion)
- any site macroscopically suggestive of vascular or bile duct invasion
- liver capsule if there is a possibility of capsular invasion, i.e. where there is subjacent tumour and overlying adherent tissue or macroscopic capsular invasion. Where the capsule appears intact over subcapsular tumour, with a smooth shiny surface, histology is not required to confirm capsular integrity
- gallbladder bed where there is adjacent intrahepatic tumour
- background liver (taken as far away as possible from the tumour).

The number of tumour blocks will depend on the tumour type but should include samples from areas of differing macroscopic appearance in heterogeneous tumours. For HCC, which often has a mosaic of different macroscopic appearances, a minimum of three tumour blocks is recommended, and all macroscopically distinctive areas should be sampled, because tumour heterogeneity is common and histological subtype and differentiation is related to prognosis.[9,10]

[Level of evidence B – Histological subtype and differentiation related to prognosis.]

Deposits of metastatic colorectal carcinoma are often multiple and do not require separate datasets for each deposit. A minimum of one block per tumour deposit is sufficient, although more may be taken in patients who have had neoadjuvant chemotherapy, especially if initial blocks show no viable tumour.

A block of representative background liver should be taken, whether or not it looks abnormal macroscopically. The appearance should be included in the text description of the specimen but is a core item in the dataset proforma only in the histology section since microscopy provides the more reliable assessment of fibrosis/cirrhosis.

The following additional blocks are required as appropriate:

- where there is tumour tissue close to the hepatic hilum, the hilum should be sampled to include large vessels. Specifically, label blocks of main left or right portal vein or bile duct, if present
- hepatic vein margin (if there is tumour nearby)
- extrahepatic biliary tree (when included); for perihilar CC specimens see section 4.2 below

- gallbladder – optional when this is macroscopically normal; for gallbladder cancer specimens see section 4.3 below
- the site of lymph nodes should be specified if known (hilar, hepatic artery, portal vein, cystic duct). More distant lymph nodes (coeliac axis, periduodenal, periaortic) may be submitted separately by the surgeon. Large lymph nodes that do not show macroscopic involvement should be serially sliced and embedded in their entirety since nodes at this site are often enlarged as a result of reactive changes and may harbour micrometastases, especially in CC.

4.1 Hepatectomy and segmentectomy specimens for intrahepatic tumours (includes complete hepatectomy at transplant, hepatocellular carcinoma, hepatocellular adenoma, intrahepatic cholangiocarcinoma and metastatic tumours)

Record the segments resected and the specimen weight after opening the gallbladder and rinsing out the bile. The specimen dimensions (antero-posterior, medio-lateral and supero-inferior) should also be measured. When included with the specimen, record the length of extrahepatic duct, number and site of lymph nodes, size and appearance of gallbladder.

The specimen should be sliced at right angles to the parenchymal resection plane, and preferably in the horizontal plane to facilitate correlation with preoperative cross-sectional imaging. Slices should be as thin as possible, and no more than 10 mm thick. The minimum size of tumours detectable by imaging is now less than 5 mm.

Record the number, site, maximum diameter, and distance from hepatic margin of the tumour(s). For multiple tumours, the sites should be recorded in the text of the report in such a way that allows correlation with preoperative imaging. For example, this can conveniently be recorded by numbering the horizontal slices from the top and specifying the slices and approximate segments of each tumour. ‘Multiple tumours’ encompasses satellitosis, multifocal tumours and intrahepatic metastases. The presence of satellite nodules (see section 5.3.1) should be noted. The appearance of the background liver (normal, bile-stained, nutmeg, fibrotic/cirrhotic) should be recorded. It is good practice to keep a photographic record of the macroscopic features of the specimen for use during multidisciplinary team (MDT) meetings.

The specimen should be inspected carefully for macroscopically apparent vascular invasion, and any suspected vascular invasion should be sampled for histological confirmation. Involvement of the main left or right branch of the portal vein or any of the three main hepatic veins should be specifically recorded, as this information is relevant to TNM staging.

4.2 Perihilar cholangiocarcinoma

‘Perihilar CC’ is the term used by TNM and AJCC for CC arising in the large ducts including main right or left duct and common hepatic duct above the cystic duct origin. This includes but is not restricted to the classical ‘Klatskin’ hilar CC,[11] which was originally described in 1965 before modern imaging as a small tumour at the confluence of the right and left duct in patients presenting with obstructive jaundice, and tends to cause death by liver failure rather than dissemination. The terms ‘perihilar’ and ‘hilar’ are used variably in the literature; for the purposes of cancer reporting, this dataset follows TNM in using ‘perihilar’ throughout.[1]

Perihilar CC may be associated with occult metastases to the peritoneum or lymph nodes, not identifiable on scanning. For this reason, staging laparoscopy has been recommended to assess resectability with biopsy of any peritoneal lesion.[12] Biopsy specimens should be processed urgently to avoid delay to surgical resection.

The liver resection is handled as in section 4.1. In addition, carefully documented dissection and block taking from the biliary tree is necessary to delineate the extent and margin status of perihilar CC.

For resections of perihilar CC, the distal transection margin of the biliary tree and the proximal margin of the left or right duct(s) should be identified prior to dissection. This is aided if the surgeon identifies and marks the structures, e.g. with a coloured tie(s). The transection margins of these ducts may be submitted separately by the surgeon, with or without a request for frozen section.

Involvement of main left or right portal vein or hepatic artery is important for staging and may have been suspected from pre-operative imaging. The surgeon should also specifically indicate if these are included in the resection specimen, and indicate the structure, e.g. with a long suture.

Examination of the biliary tree can be achieved by longitudinal opening or serial transverse sections, according to the preference of the pathologist. These approaches give different emphasis on reported tumour characteristics: longitudinal opening allows precise measurement of the mucosal extent of the tumour, while complete embedding in serial transverse sections allows more extensive examination of the circumferential surface of the biliary tree. Margin involvement may be at the proximal or distal duct transection margin, a vascular margin or the hepatic resection plane. In addition, the presence of tumour at the circumferential surface of the tissue surrounding the biliary tree (dissection margin) should be sought.[13] This represents the peritoneal surface anteriorly and to the right, and a surgical plane posteriorly and to the left. Particular attention needs to be paid to the periductal dissection plane as it is frequently overlooked but is a major cause of residual disease.

4.3 Gallbladder

Gallbladder cancer may be discovered during histopathological examination of routine cholecystectomy specimens.[14] Following diagnosis, a subsequent liver resection of the gallbladder bed may be undertaken. Alternatively, when gallbladder cancer is known or suspected pre-operatively, the gallbladder will be resected en bloc with a portion of liver from the gallbladder bed, or as a more extensive segmental resection.

Record whether the gallbladder has been opened prior to receipt and the presence and characteristics of any gall stones (present in >80% gallbladder cancers).

Gallbladders should be opened longitudinally from the serosal surface to avoid disruption of the cystic duct margin and gallbladder bed margin in cholecystectomy specimens. For cholecystectomy specimens, ink the gallbladder bed margin if neoplasia is suspected either on preoperative imaging or after opening (i.e. if the wall is thickened or the mucosal surface is roughened or polypoid). Record the gross appearance of any abnormality, including the size and site of focal lesions in the gallbladder, their macroscopic appearance (polypoid, ulcerating, plaque-like/infiltrative, calcification), and whether on the free peritoneal or the hepatic side of the gallbladder. In TNM8, the pT2 stage is designated a or b depending on whether the carcinoma invades beyond the muscle wall of the serosal or hepatic aspect of the gallbladder respectively, and so blocks must be taken in such a way as to enable this distinction to be recorded.[15] Record the macroscopic depth of involvement, including any adherent tissues and whether they appear to be invaded.

For a staged liver resection following cholecystectomy with incidental carcinoma, the site of the gallbladder bed should be inked. Unless there is obvious extensive tumour, it is recommended that the entire gallbladder bed is embedded in serial blocks, since focal residual carcinoma cannot be distinguished macroscopically from scarring in the surgical site. If there is resection of the biliary tree, this should be blocked as described for perihilar CC.

4.4 Lymph nodes

Specimens may include lymph nodes, either separately dissected by the surgeon or at the liver hilum. A regional lymphadenectomy specimen will ordinarily include at least three lymph nodes

for HCC, six lymph nodes for intrahepatic CC and gallbladder cancer, and 15 lymph nodes for perihilar CC.[1] Regional lymph nodes are those in the hepatoduodenal ligament: hilar, cystic duct, pericholedochal, hepatic artery, portal vein (see also section 5.3.2). More distant nodes, e.g. coeliac, caval, superior mesenteric are occasionally resected and involvement of such nodes is classified as either within the pN criteria or as distant metastasis (M1) depending on the tumour. A pN2 category is introduced in TNM8 for perihilar CC and gallbladder cancer with involvement of 4 or more lymph nodes. There is no pN2 category for HCC or intrahepatic CC. Resections for metastatic colorectal cancer may also include lymph nodes if nodal metastasis is suspected at surgery.

5 Core items

5.1 Clinical data

The following should be supplied:

- name
- date of birth
- hospital
- hospital number
- NHS/CHI number
- date of procedure
- surgeon/physician.

5.2 Pathological data

The core data items are all those that are necessary for complete classification of the primary tumour stage according to TNM8, or of prognostic importance for resection of metastatic carcinoma. This section covers core data items that are common to all tumours; specific data items for each tumour type are included in section 5.3.

5.2.1 Macroscopic

This section is common to all three intrahepatic tumour dataset proformas; it is modified for perihilar CC and gallbladder cancer. The type of intrahepatic tumour may not be known until histology. However, the same core items are required for all:

- type of specimen
- specimen weight
- specimen dimensions (where orientation is known, provide antero-posterior, medio-lateral and superior-inferior dimensions)
- tumour site, number and size
- presence of satellite tumours (regarded as multiple tumours for TNM staging). In the WHO Classification, satellite tumours are defined as lesions which occur in close proximity to a single large dominant nodule, are often multiple, and usually within 2 cm of the main tumour.[3,4]
- distance from nearest hepatic resection margin(s)
- for HCC and intrahepatic CC: macroscopic involvement of vessels; specify if main left or right portal vein or a main hepatic vein, and record diameter of vessel involved
- integrity of liver capsule (including bare area on postero-superior aspect) and presence of adherent tissues (e.g. diaphragm) or other organs

- for perihilar CC: describe attached extrahepatic bile ducts, including length and site of any macroscopic abnormality
- for gallbladder carcinoma: dimension, including length of cystic duct, description of abnormality including invasion of liver for en bloc resection
- presence and number of lymph nodes received.

5.2.2 Microscopic

This section is specific for each dataset since staging parameters and prognostic indicators differ according to tumour type. They are summarised here; full information on specific datasets is given in section 5.3:

- tumour type and subtype
- tumour differentiation
- minimum distance to resection margin (hepatic, and where appropriate bile duct or vascular transection margin) measured microscopically when less than 5 mm, see below
- invasion through liver capsule (Glisson's capsule)
- vascular invasion including confirmation of macroscopic vessel invasion
- perineural invasion (CC)
- effects of ablative or neoadjuvant therapy on tumour (if applicable)
- background liver – presence and stage of fibrosis, and other chronic liver disease (see section 5.3.1 below)
- lymph node involvement (where appropriate); number of nodes with metastasis.

The TNM classification includes the status of residual tumour following treatment as the R classification, defined as R0 – no residual tumour; R1 – microscopic residual tumour and R2 – macroscopic residual tumour. This has been variably adopted by pathologists, generally for cancers of the hollow GI tract and pancreas with tumours <1 mm from the surgical margin being regarded as R1. However, there is no evidence base or consensus regarding the definition of R1 resection for liver cancer resections. Therefore, to avoid confusion the minimal distance between tumour cells and resection margin should be included in the report.[16] This should be measured microscopically when the margin is close.

Certain items in the dataset (vascular and perineural invasion) have the option of recording 'uncertain' or 'cannot be assessed' in line with College guidelines for datasets, to enable uncertainty to be recorded and avoid blank items. 'Uncertain' would be when the configuration of the tumour (especially HCC) suggests it may have expanded and obliterated a vascular channel but the strict definition of vascular invasion provided by the TNM helpdesk (page 16) isn't met. 'Cannot be assessed' would be recorded if there was no surrounding tissue to look for invasion or if the specimen was so poorly preserved that autolysis prevented assessment.

5.3 Specific information for individual tumours

5.3.1 Hepatocellular carcinoma tumour classification, staging and grading

Staging depends on the maximum size ($\leq$ or >20 mm and 50 mm), number of tumours (single or multiple) and venous invasion. The sub-division of pT1 depending on size $\leq$20 or >20 mm is added in TNM8. A solitary tumour $\leq$20 mm with or without vascular invasion is staged as pT1a.[17] A solitary tumour >20 mm without vascular invasion is stage pT1b; if there is vascular invasion (for definition see below) then this becomes pT2. Multiple tumours where none is greater than 50 mm in diameter are also staged as pT2. While microscopic vascular invasion is thus (unusually) a parameter that is used for T staging, the distinction between intravascular spread and other intrahepatic nodules of HCC does not affect T stage.

In TNM8, stage pT3 is no longer divided into two categories. For multiple tumours where any individual HCC is more than 50 mm, the stage is pT3. Involvement of a major branch of the portal or hepatic vein (i.e. main left or right portal vein or left, middle or right hepatic vein) becomes stage pT4 in TNM8 based on the prognosis following resection;[18] pT4 is also used for HCC with direct invasion of adjacent organs (including the diaphragm but not the gallbladder) or with perforation of the visceral peritoneum.

Tumour grade is also independently related to prognosis.[9,10] Recent authors, including those of the WHO classification, favour a three-point grading system (well, moderately or poorly differentiated); where there is heterogeneity, the worst grade should be assigned. Use of a three-point grading system was also recommended in the recently published ICCR dataset.[4] For practical purposes, well-differentiated HCCs are those where the tumour cells closely resemble hepatocytes such that the differential diagnosis is with high grade dysplastic nodule (in cirrhosis) or HCA (in non-cirrhotic livers). Well-differentiated HCC is rarely seen in isolation except in small (<20 mm) tumours. Poorly differentiated HCC are those where the hepatocellular nature of the tumour is not evident from the morphology. The diagnosis of poorly differentiated HCC depends on identifying adjacent areas of better-differentiated tumour, the use of immunohistochemistry to demonstrate a hepatocellular phenotype (see Appendices P–Q), or the presence of raised serum α-fetoprotein (AFP).

The same staging system is used for the rare fibrolamellar subtype of hepatocellular carcinoma; this usually arises in young patients without background liver disease or is present as a component of an otherwise conventional HCC.[19] Diagnosis can be aided by immunohistochemistry for K7 and CD68.[20] Although fibrolamellar carcinomas carry a characteristic fusion (DNAJB1-PRKACA), it is not specific and is not necessary to identify it for routine diagnosis.[21]

The recent WHO classification recognises a number of other morphological subtypes of HCC, some of which have specific molecular correlations and/or distinct clinical behaviour.[3,22] In addition to the fibrolamellar subtype, these include steatohepatitic, clear cell, macrotrabecular massive, scirrhous, chromophobe, neutrophil rich and lymphocyte rich subtypes. While fibrolamellar HCC has recognised and well-defined histological features, the definition and characterisation of the other subtypes are evolving and therefore they are a non-core item in this database. These are summarised in Appendix M, based on the table in the WHO classification, and illustrative photographs are available in that publication and in recent reviews.[3,23,24]

Other rare histological variants of sarcomatoid and undifferentiated HCC are described in the WHO publication and are associated with a poor prognosis.[3,25]

There is an increasing recognition of a morphological spectrum between HCC and intrahepatic CC, reflecting the recognition that a significant number of these tumours arise from a common hepatic progenitor cell origin and express ‘stemness’-related markers, such as keratin 19 (K19), epithelial cell adhesion molecule (EpCAM), CD133, SALL4 etc.[26–30] Poorly differentiated HCCs that are K19-positive (in >5% of tumour cells) but do not have morphological features of CC appear to have a poorer prognosis,[27,28] but are regarded as HCC for staging and treatment purposes. A recent review summarises the clinical, imaging and pathological features of K19-positive HCCs and highlights the poor patient outcome following curative resection or liver transplantation, as well as resistance to systemic chemotherapy and locoregional treatment.[31]

[Level of evidence D – Prognostic importance of K19.]

For tumours that show mixed features of HCC and CC (combined HCC/CC,) there is now an international consensus on terminology based primarily on morphological features, which may be supplemented by immunohistochemistry.[32] These tumours should be staged as for intrahepatic CC and are further considered in the section on intrahepatic cholangiocarcinoma.

Premalignant changes, including small cell and large cell change
In cirrhotic or fibrotic liver
The terms 'small cell change' and 'large cell change' are used to describe cytological alterations in the background liver. These are seen either as microscopic foci or form macroscopically identifiable nodules, usually in cirrhotic livers. This terminology has replaced small and large cell dysplasia.

Distinct nodules within cirrhotic livers may show cytological atypia and an increase in the number of hepatic arteries. A spectrum of lesions exists from macro-regenerative nodules and focal nodular hyperplasia-like lesions, through low- and high-grade dysplastic nodules to early HCC. The agreed terminology used to describe these lesions is summarised in an international consensus document.[33] Appendix O describes the use of immunohistochemistry in the differential diagnosis of focal hepatocellular lesions in cirrhotic livers.

Recognition of early HCC is challenging and may be aided by immunohistochemistry for glypican-3 (although it is only expressed in about half of well-differentiated HCCs), glutamine synthetase and heat shock protein 70 (HSP70),[34–38] see Appendix O. At the time of writing this dataset, the criteria used for the diagnosis of dysplastic nodules in cirrhotic livers are still in evolution and therefore included as a non-core item in the dataset.

In liver without fibrosis/cirrhosis
The differential diagnosis of lesions composed of well differentiated/near normal hepatocytes in a non-cirrhotic liver is summarised in Appendix P, and includes FNH, HCA and well differentiated HCC. HCAs are further classified into subtypes based on genetic/molecular abnormalities. Each of the subtypes has an immunohistochemical phenotype which reflects their genetic abnormalities and can often be inferred from their morphological features.[39–41] Immunohistochemistry is important in the subtyping of HCAs, some of which have the potential to undergo malignant transformation. The subtypes are HNF1A mutated (H-HCA), inflammatory (I-HCA), beta-catenin mutated exon 3 (B^{ex3}-HCA), beta-catenin mutated exon 7/8 ($B^{ex7,8}$-HCA), sonic hedgehog HCA (sh-HCA), and unclassified when none of the above can be demonstrated. Of these, the B^{ex3}-HCA (~7% of HCA) are the subgroup associated with a risk of progression to HCC and the sh-HCA (~4% of HCA) are the subgroup related with increased bleeding risk, see Appendix P.[42,43]

The natural history and the risk of clinical bleeding and malignant transformation in relation to HCA subtypes are areas still under investigation.[44]

The specialised techniques for full classification of HCA are not widely available in the UK at the time of writing this dataset. Pragmatically, as a minimum, the use of immunohistochemistry for glutamine synthetase, amyloid A and beta catenin has been proposed to allow identification of the clinically important HCA types, inflammatory and beta-catenin activated HCA.[45,46]

It may not be possible, with currently available investigations, to differentiate between HCA and well differentiated HCC. For such lesions the diagnostic terms 'atypical hepatocellular adenoma-like neoplasm',[47] 'hepatocellular neoplasm of uncertain malignant potential'[48] or 'atypical hepatocellular neoplasm'[49] can be used.

Vascular invasion
Vascular invasion is an important prognostic factor.[50–52] For TNM pathological classification, vascular invasion is a component of the pT stage, rather than a separately designated V criterion. Stage pT2 includes any vascular invasion in HCC >20 mm (gross or microscopic involvement) but less than a main left or right or middle branch of the portal or hepatic vein. Such major vessel involvement is classified as pT4 in TNM8 (previously as pT3b). For HCC <20 mm vascular invasion is not associated with poorer prognosis.[17]

[Level of evidence A – Prognostic importance of vascular invasion.]

It is often difficult to determine whether nodules of HCC surrounded by fibrous tissue adjacent to the main tumour represent vascular invasion unless a part of the endothelised lumen is apparent. Vascular invasion may be suspected where the nodule is within a portal area, at the site appropriate to a portal vein branch, or by the presence of satellite nodules. These findings should prompt a thorough search for vascular invasion, which may be assisted by using histochemical (for elastic fibres) and/or immunohistochemical stains for endothelial markers. Vascular invasion is associated with an adverse prognosis when adjacent to but not within the tumour nodule.[53] Diagnosing vascular invasion is subject to observer variation.[54] For the purposes of TNM classification, when the tumour nodule is within a portal area at the site appropriate to a portal vein branch, vascular invasion is only confirmed if one can clearly identify the lumen and endothelium of a portal vein (personal communication: Professor LH Sobin, TNM Helpdesk). When the configuration of the tumour suggests it may have expanded and obliterated a vascular channel but the strict definition of vascular invasion provided by the TNM helpdesk is not met, record 'not identified'. For solitary tumours >20 mm, stage as pT2 only if there is convincing vascular invasion.

Satellite nodules have been shown to be prognostically important following liver resection[55] and liver transplantation for HCC.[56] However, there is no clear consensus concerning the definition of satellite nodules. In the recently published WHO classification and ICCR dataset, satellites are defined as occurring in close proximity to a single large dominant nodule, are often multiple, and usually within 2 cm of the main tumour.[3,4] Both satellitosis and intrahepatic venous dissemination are classified as multiple tumours, and are therefore equivalent for staging purposes (i.e. pT2, when no tumour is more than 50 mm).

[Level of evidence D – Prognostic importance of satellite nodules.]

Background liver disease

The prognosis following resection of HCC is strongly dependent on the presence and severity of underlying chronic liver disease, as assessed by, for example, the Child–Pugh score. Some staging systems incorporate a clinical assessment of functional hepatic status.[57] The Barcelona Liver Clinic Cancer (BCLC) staging system incorporates prognostic variables related to tumour status, liver function and health performance status and is recommended for prognostic prediction and treatment allocation.[58] The histology report should include information about the background liver, sampled as far from the tumour as possible to avoid peritumoural effects. The presence of hepatitis (viral or autoimmune), haemochromatosis, alcohol related liver disease and non-alcoholic fatty liver disease (NAFLD) should be recorded, as should both the stage of fibrosis and the nature and severity of inflammatory/metabolic disease. Because of its importance in prognosis,[9,57] the fibrosis stage of underlying chronic liver disease is regarded as a core data item. The aetiology may not always be known to the pathologist and is thus considered to be a non-core item.

[Level of evidence B – Prognostic importance of fibrosis stage.]

Preoperative ablative therapy

The effects of preoperative ablative therapy may be apparent macroscopically and/or histologically. This has been classified as complete, incomplete or absent in a consensus document.[59] Extensive tumour sampling is necessary to establish complete tumour ablation; tumours should be sampled entirely through their largest diameter if the tumour/nodule size is 20 mm or less. For every additional 10 mm, an additional section should be taken.[59] Viable areas are often recognisable macroscopically and block selection should be guided by this. Recording an impression of the proportion of the overall tumour that is viable may be helpful to oncologists, although its estimation is subjective.

Ablation of HCC may be attempted by using trans arterial chemo embolisation (TACE) or radiofrequency ablation (RFA) or other forms of direct ablation. TACE beads are usually evident in tissue sections in peritumoral tissue and elsewhere. RFA generally results in a wider field of tissue necrosis. Non-viable HCC at the centre of this may retain nuclear detail due to thermal fixation.[60,61]

5.3.2 Cholangiocarcinoma

As recently as 2002, in TNM6, the staging of intrahepatic CC was extrapolated from HCC. Recognition of the increasing evidence of different prognostic factors for intrahepatic CC[62] resulted in the introduction of a separate category for intrahepatic CC in TNM7. This has been further refined in TNM8, re-introducing size as a staging parameter, while removing the periductal infiltrating pattern which defined pT4 in the previous TNM7.[1,2]

In addition to the location of the CC, the Japanese classification according to the growth pattern into mass-forming, periductal infiltrating and intraductal papillary CC[63] has gained international recognition.[2] In general, mass-forming CC arises peripherally in the liver, and is covered in the section on intrahepatic cholangiocarcinoma. The periductal infiltrating pattern is characteristic of perihilar CC, which includes CC arising in right, left hepatic ducts up to the second division, and common hepatic duct proximal to the cystic duct. This growth pattern is also seen in some intrahepatic CC, where it is considered to arise from larger intrahepatic ducts.[64,65]

Intraductal papillary neoplasia of bile ducts (IPNB) is rare in Europe and North America and is the counterpart of intraductal papillary mucinous neoplasia in the pancreas.[66] CC arising from IPNB has a much more favourable prognosis than other CC. It should be reported using the perihilar CC dataset, as pTis if it occurs without invasion, or according to the depth of duct wall invasion. It may be associated with formation of a cystic tumour without ovarian-like stroma. This is to be distinguished from mucinous cystic neoplasm (previously hepatobiliary cystadenoma with ovarian-like stroma), a tumour that is seen only in female patients with a much lower incidence of malignant transformation.[64]

Intrahepatic cholangiocarcinoma

Tumour classification, staging and grading

This staging system applies to intrahepatic CC, combined HCC/CC and cholangiolocellular carcinoma. The AJCC Staging Manual states that it should also be used for primary neuroendocrine tumours of the liver.[2,3]

The 5th edition of the WHO classification recognises small duct and large duct sub-types of intrahepatic CC.[3] The large duct sub-type arises in the area and segmental intrahepatic ducts and usually has a periductal infiltrating growth pattern with or without a mass forming component. It is composed of columnar, often mucin secreting cells, and shares risk factors, precursor lesions, high frequency of perineural infiltration, molecular features and a poorer prognosis with perihilar CC.[3,64,65] Indeed for larger, central CC the actual site of origin is often obscure, second order bile ducts are within the liver, and distinction from perihilar CC may be impossible.[3,64] If in doubt, the staging for perihilar CC is the more appropriate one to use. This is highlighted in a recent review.[67]

Conversely, the small duct subtype is usually a peripherally located mass forming intrahepatic CC. It is composed of non-mucin producing cuboidal cells with ductular or cord-like pattern resembling cells of a ductular reaction. It is often densely sclerotic at the centre with a cellular periphery and expands around the portal areas which persist in its sclerotic interior.

The size of the tumour is now recognised to be prognostically important[68,69] with solitary tumours without vascular invasion divided into pT1a for tumours $\leq$50 mm and pT1b when >50 mm. Size is also important for correlation with preoperative imaging.

[Level of evidence C – Prognostic importance of tumour size.]

Staging also depends on the number of tumours (single or multiple) and vascular invasion; the presence of either or both constitute the criteria for stage pT2. The previous distinction between pT2a and b, separating vascular invasion from multiple tumours, is removed in TNM8.

For intrahepatic CC of both small and large duct sub-types, distinction from metastatic adenocarcinoma particularly from stomach or pancreas is based on the single or dominant intrahepatic mass and absence of a known extra-hepatic primary tumour. Currently available immunohistochemistry is not reliable in making this distinction.

Combined HCC/CC

These are primary liver carcinomas with unequivocal areas of both hepatocytic and cholangiocytic differentiation and should be staged as intrahepatic CC.[2,3] The diagnostic criteria for these tumours have been addressed by an international group, who recommend that diagnosis is based on morphological features on hematoxylin and eosin (H&E); these may optionally be supplemented by immunohistochemistry.[32] Sampling of macroscopically different areas in heterogeneous tumours is important to avoid underdiagnosis due to sampling error. The recognition of 'stem cell features' either by morphology or immunohistochemistry (see discussion in section 5.3.1) is no longer a diagnostic requirement. Despite a recent flurry of papers in this area, it remains a challenge for diagnostic histopathologists with dangers of both over and under diagnosis.[70,71]

This consensus terminology document[32] recognises two further rare patterns of primary liver carcinoma. Intermediate cell carcinoma is a monomorphic tumour composed of malignant cells that have features intermediate between hepatocytes and cholangiocytes, often in a desmoplastic stroma, and shows variable immunohistochemical positivity with markers of both. This tumour is regarded as a distinct subtype, which is neither HCC nor CC.

Cholangiolocellular carcinoma is composed of cuboidal cells arranged in anastomosing tubules, mimicking reactive bile ductules; like these structures they are often positive for CD56. Based on molecular evidence, this is a distinct form of biliary tumour,[72] which is regarded as a subtype of intrahepatic CC.

As well as the two main subtypes (large and small duct), further rare subtypes are listed within these two main categories in the WHO 2019 classification. Adenosquamous, squamous, mucinous, signet ring, clear cell, mucoepidermoid, lymphoepithelioma-like (Epstein–Barr virus associated) and sarcomatous intrahepatic CCs are regarded as variants of the large duct subtype. Intrahepatic CC with ductal plate malformation and cholangiolocellular carcinoma are considered to be variants of the small duct subtype.

Grading of CC can be based empirically on the degree of duct or gland formation and degree of cellular pleomorphism. Grade has been found to be a significant prognostic factor in a systematic review of 57 studies,[73] although there is no generally accepted specific grading system.

Integrity of liver capsule/bare area and presence of adherent tissues or other organs

Locally advanced intrahepatic mass-forming CCs invade through the liver capsule and directly into adjacent adherent organs. Perforation of the visceral peritoneum constitutes pT3 disease, and any roughened area of capsule over the tumour should be sampled for histology. However, pT3 tumours were not found to have an adverse prognosis compared with pT2.[68,69]

If there are adherent organs, histology of the site of adhesion is necessary to determine whether these are directly infiltrated by the CC, which is stage pT4 in TNM8 (previously this was also pT3).

Regional lymph nodes

For right intrahepatic CC, the regional lymph nodes include the hilar (common bile duct, hepatic artery, portal vein and cystic duct), periduodenal and peripancreatic lymph nodes. For left intrahepatic CC, regional lymph nodes include hilar and gastrohepatic lymph nodes. The site of the node cannot be determined by the pathologist, unless specified by the surgeon. TNM8 recommends that six or more lymph nodes are included in a regional lymphadenectomy; however, if fewer nodes are received but are negative the classification should be pN0. For

either location of intrahepatic CC, spread to the coeliac and/or periaortic and caval lymph nodes represent distant metastases (M1).[1]

Background liver disease
Intrahepatic CC of small duct subtype has an association with cirrhosis of various causes, including chronic viral hepatitis.[74,75] Like HCC, this is an important prognostic feature in intrahepatic CC,[76] which should be recorded as a core item, in addition to the items required for TNM staging. PSC is a risk factor for the large duct subtype, as it is for perihilar CC.

Perihilar cholangiocarcinoma
Tumour classification, staging and grading
CCs of the large bile ducts are separated for TNM staging purposes into perihilar and distal groups. Perihilar CC are defined anatomically as those located proximal to the origin of the cystic duct, including the main right and left duct up to their second branch. These segmental ducts are associated with peribiliary glands; progenitor cells from these may be the origin on perihilar CC.[77] Because of the site and frequent invasion of adjacent liver these are resected with contiguous liver. Distal CCs are included in the dataset on pancreas, ampulla and extrahepatic bile ducts. Adenocarcinoma arising in the cystic duct is staged as for gallbladder cancer (see section 5.3.3).

Staging depends on the depth of invasion through the bile duct wall and involvement of surrounding adipose tissue (pT2a), adjacent hepatic parenchyma (pT2b) or major vessels (pT3 and 4). Size, small vessel involvement and invasion of adjacent organs, other than the liver, are not staging criteria. The distinction between stage pT1 and pT2 is based on invasion through the bile duct wall into surrounding adipose or liver tissue and must be determined microscopically. Stage pT3 refers to unilateral involvement of branches of the main right or left hepatic artery or portal vein, while pT4 tumours with involvement of bilateral structures would usually be considered inoperable in the UK.

Tumour size
Tumour size is measured for correlation with preoperative imaging but does not affect tumour staging. The extent of tumour infiltration is often difficult to determine macroscopically. There may be extensive fibrosis of the bile ducts related to cholangitis or stenting, while tumour infiltration within the duct wall is characteristically diffuse and concentric and often extends beyond the macroscopic extent of involvement. It is best to measure the maximum extent of the tumour macroscopically and confirm the size histologically. If the duct is serially sliced up to the point flush with the liver surface at the porta hepatis, knowledge of the thickness of each slice (i.e. length of extrahepatic duct/number of slices) will allow the approximate dimension of the tumour to be derived from the number of slices involved. Often perihilar CCs have an intrahepatic extension that is measured in slices of the hepatectomy, once the extrahepatic part of the ducts has been dissected.

Microscopic features
Perihilar CC characteristically has a periductal infiltrating growth pattern, often associated with abundant fibroblastic stroma. Grading of perihilar CCs is on a three-tier system, based on the degree of glandular differentiation, mucin production, mitotic activity and nuclear features, and for heterogeneous tumours is based on the least differentiated area. Differentiation was a prognostic feature in a meta-analysis of operable cases.[78]

[Level of evidence B – Prognostic importance of histological differentiation.]

Perineural infiltration is also common and is a poor prognostic factor in some series.[79]

Uncommon histological patterns listed in the WHO classification include intestinal type, foveolar type, mucinous, signet ring cell, clear cell, hepatoid, invasive micropapillary, and rare types include squamous cell, adenosquamous, sarcomatous and undifferentiated carcinomas.[3]

Vascular invasion of main portal vein or hepatic artery branches refers to the first order branch (e.g. main left or right portal vein). Infiltration into the vessel wall is categorised as invasion whether or not there is tumour in the lumen, since this staging parameter is important in relation to the operability rather than predictor of dissemination.[80] Unlike HCC and intrahepatic CC, microscopic invasion of small vessels is not a staging parameter.

Lymph node metastases

Hilar lymph nodes are characteristically large (up to 40 mm) in chronic biliary disease, and node size does not predict metastasis. CC metastases are frequently microscopic and in the subcapsular sinus, and so unless a metastasis is macroscopically visible, the whole of the node(s) should be sliced and embedded. Micrometastasis found only by immunohistochemistry has been shown not to affect prognosis.[81]

Correct lymph node staging requires a lymphadenectomy of 15 or more lymph nodes, which is rarely performed in the UK. A smaller lymph node yield with no metastasis is still classified as pN0. pN1 tumours have regional lymph node metastasis involving 1–3 perihilar and pericholedochal nodes in the hepatoduodenal ligament. Four or more involved nodes are classified as pN2 in TNM8. These nodes are usually included in the main resection specimen. Periaortic, pericaval, superior mesenteric artery, or coeliac artery lymph nodes are sometimes also submitted as separate specimens; metastases in these nodes are regarded as distant metastases for TNM staging (pM1).

Background liver disease

The presence and severity of any underlying liver disease should be documented. This may include changes related to PSC, which is an important risk factor for perihilar CC. However, these must be distinguished from the secondary effects of biliary obstruction upstream from the CC. Periportal copper associated protein, which provides evidence of chronic biliary obstruction, is frequently present in patients with perihilar CC who do not have underlying PSC.

Precursor and in situ lesions

These lesions should be sought and recorded as non-core items using the new terminology of flat biliary intraepithelial neoplasia (BilIN), previously biliary dysplasia, or intraductal papillary neoplasia (IPNB) for macroscopically visible papillary lesions. This classification brings biliary terminology into line with the equivalent pancreatic counterparts.[66] For a description of morphological features of BilIN, please see the table on page 273 of the WHO classification.[3]

5.3.3 Cancer of the gallbladder

Tumour classification and staging

Over 50% of gallbladder cancers are discovered incidentally in routine cholecystectomy specimens.[8,82] Clinical risk factors include gallstones, anomalous pancreatobiliary duct junction and polyps.[83] The incidence of carcinoma in routine cholecystectomy specimens is 0.25–0.89% in a recent systematic review,[8] and since the cancer may be inapparent macroscopically, routine sampling of all gallbladders is necessary, as described in *Tissue Pathways for Gastrointestinal and Pancreatobiliary Pathology*.[84] This view was reinforced by a recent paper.[85]

The same terminology of BilIN is now also used for gall bladder flat or micropapillary dysplasia. High grade BilIN is equivalent to carcinoma in situ. When BilIN is identified in a routine cholecystectomy, the question arises how many additional blocks need to be taken. A recent study concluded that if high grade BilIN is identified on routine sections, the whole gall bladder should be blocked, but if low-grade BilIN is identified one extra block per cm should be taken. No additional sections are required if intestinal metaplasia but not BilIN was present in the initial sections. Patients with BilIN who had clear cystic duct margins did not develop progressive disease even if BilIN was present elsewhere.[86]

Macroscopically, gallbladder cancers are usually flat, firm and poorly defined.[3] Suspicious gallbladders should be thoroughly sampled, and the discovery of high grade intra-epithelial neoplasia, either flat (BilIN) or polypoid, in routine cholecystectomy specimens is an indication for more extensive sampling to exclude carcinoma.[83]

Gallbladders with hyalinising cholecystitis, in which a dense paucicellular fibrosis replaces the gallbladder wall, sometimes with focal calcification (incomplete porcelain gallbladder) have a significant risk of macroscopically inapparent adenocarcinoma and should be thoroughly sampled.[87]

Patients with incidental gallbladder cancer should be referred to the hepatobiliary cancer centre MDT. Further resection of the gallbladder bed is indicated for patients with stage pT1b and pT2 carcinoma,[8,88] dependent on the age and performance status of the patient. This includes resection of the biliary tree if the cystic duct resection margin is involved, along with local lymphadenectomy.

In patients with gallbladder cancer detected on pre-operative imaging, en bloc resection is undertaken, with at least adjacent gallbladder bed, and with resection of the biliary tree along with periportal and coeliac lymphadenectomy. The extent of surgery depends on the primary tumour and fitness of the patient, ranging from resection of the gall bladder and adjacent liver bed, up to formal extended right hepatectomy for patients with locally advanced gall bladder cancer on preoperative imaging but without distant metastasis.[88] For staged (further) resection of liver/gallbladder bed following the diagnosis of carcinoma in a routine cholecystectomy specimen, the pathological staging will require information from the original cholecystectomy. This report and, wherever possible, review of the slides are therefore necessary for completion of the gall bladder cancer reporting proforma.

Staging depends on the depth of invasion through the gallbladder wall and involvement of the peritoneal surface, adjacent liver, other organs or major vessels. The important distinction between stage pT1a and pT1b is determined by invasion of the muscle layer of the gall bladder wall. pT2 tumours extend beyond the outer limit of the smooth muscle and in TNM8 are divided into pT2a for involvement of perimuscular connective tissue on the serosal side with no involvement of the peritoneal surface, and pT2b for invasion of the perimuscular connective tissue on the hepatic side with no invasion of the liver. Compared with pT2a tumours, those on the hepatic aspect have a higher rate of perineural and vascular invasion and lymph node metastasis and are associated with a poorer prognosis.[89] Perforation of the visceral serosa or direct invasion of the liver and/or one other adjacent organ or structure constitutes pT3. Tumours clinically staged as T4 (invasion of main portal vein or hepatic artery or of two or more extrahepatic organs/structures) would usually be considered inoperable in the UK.

Distinction between stage pT1a and more advanced cancer that may require further surgery is therefore of central importance, although is poorly reproducible.[3,90] This rests on the maximum depth of infiltration into or beyond the muscle wall, and careful consideration is required during staging in evaluating inflammation with associated atypia, involvement of Rokitansky–Aschoff sinuses, and Lushka's ducts in the gallbladder bed. The five-year survival rate of patients with early gallbladder cancer (pT1) is over 85% but patients with Rokitansky–Aschoff sinus involvement had a lower survival rate than those with no involvement.[90] Although uncommon, in cases of adenomyomatous hyperplasia, ductal structures may be present in perineural spaces mimicking invasion by tumours.[91] Other diagnostic pitfalls that may mimic malignancy are when extracellular mucin deposits contain free-floating benign epithelium or are adjacent to Rokitansky–Aschoff sinuses showing dysplastic changes.[92] For these reasons, gallbladder histology from cases with incidental early gallbladder adenocarcinoma should be reviewed centrally in the context of the hepatobiliary MDT meeting.

Most gallbladder adenocarcinomas are of biliary type. There is a wide range of other less common types including intestinal-type, mucinous, clear cell, poorly cohesive/signet ring cell,

adenosquamous and squamous, gastric foveolar type, adenosquamous carcinoma, carcinosarcoma, sarcomatoid hepatoid and undifferentiated.[3]

In situ and precursor lesions

The finding of precursor lesions should prompt further sampling to exclude associated malignancy. Precursor lesions include flat biliary intra-epithelial neoplasia and intracholecystic papillary neoplasms (ICPN). Polyps >10 mm have traditionally been termed 'adenoma' but this term is now restricted to pyloric gland adenoma composed of pyloric or Brunner's type glands, which has a much lower risk of associated malignancy.[93,94] Most pyloric gland polyps are smaller and considered to represent metaplastic change.

The terminology of ICPN is now recommended for all other polyps >10 mm.[3,95] Gallbladder cancers with polypoid papillary areas need to be distinguished from ICPNs that resemble their pancreatic equivalents, with delicate papillary growth.[94] They may be multifocal and may or may not be associated with more extensive BilIN. Four morphological patterns of ICPN are recognised (biliary, gastric, intestinal and oncocytic); however, mixed components are frequent, and all are classified together as ICPN.

Associated invasive adenocarcinoma has been reported to occur in over half[95] and factors associated with invasive malignancy are the extent of high-grade dysplasia, papillary growth pattern and biliary cell lineage, but not size. The invasive component may be elsewhere in the gallbladder, so the whole specimen should be embedded. The importance of recognising co-existing precursor lesions has been emphasised.[96]

Lymph node metastases

A regional lymphadenectomy specimen will ordinarily include 6 or more lymph nodes, including the cystic duct, hepatic hilum, coeliac and superior mesenteric artery nodes. A smaller lymph node yield with no metastasis is still classified as pN0. pN1 tumours have regional lymph node metastasis involving 1–3 nodes; involvement of 4 or more regional nodes is now classified a pN2 in TNM8, while more distant nodes are M1.

Neuroendocrine tumours of the gallbladder

NENs of the gall bladder are rare and there is no separate TNM staging system for them; they should be staged as for other gall bladder cancers.[3] The classification as neuroendocrine tumour (NET) grades 1, 2 and 3 and neuroendocrine carcinoma (NEC) of large cell and small cell types matches that of NENs elsewhere in the digestive tract,[3] as described in the dataset for reporting NENs of the gastro-enteropancreatic tract.[97]

For NETs, the risk of malignant behaviour largely depends on size, with tumours >20 mm having increased invasion into the liver and risk of metastasis.[3] Prognostic factors for NETs are complete resection and patient age.[98] The prognosis for NEC is very poor, as most cases are disseminated at presentation. NEC is frequently mixed with adenocarcinoma; in these cases, the NEC component is the primary driver of behaviour and management and should be included in the report.[3] Mixed neuroendocrine–non-neuroendocrine tumours of the gall bladder have also been described.[99]

5.3.4 Metastatic carcinoma

Most liver resections are performed for CRCLM. There are often multiple deposits in one or more specimens, for example a segmental resection and some smaller non-anatomical resections. When multiple, one dataset proforma can be used to encompass all specimens. Occasionally metastases from other primary sites are resected, and the same principles apply for reporting these. If the tumour histology is not characteristic of the clinically proposed primary site, comparison with previous histology from the primary resection if available, and/or immunohistochemistry to investigate the site of origin would be indicated. Molecular studies (e.g. for KRAS, NRAS, BRAF and microsatellite instability for CRC) have usually been previously conducted on the primary tumour; occasionally the clinician may request these on the metastatic tumour.

The report should document the site, size and appearance of each tumour in a way that allows correlation with preoperative imaging. Prognosis after liver resection is related to both the stage of the primary colorectal carcinoma and to features of the liver resection[98,100–103] of which the number of tumours >3, margin status, and size of the largest lesion are important. This is recognised in a clinical score predicting recurrence after resection, which combines these factors from the liver resection with clinical parameters (disease free interval after primary surgery >1 year, serum carcinoembryonic antigen (CEA) level >200, extrahepatic disease) and pN stage of the primary resection.[104] The clearance at the surgical margin is a predictor of overall survival and of recurrence within the liver, with a margin <1 mm being associated with poorer outcomes;[100–106] this is not affected by the use of chemotherapy.[106,107] Hilar lymph node involvement may also be prognostically important.[108]

Recent reviews have described additional pathological factors associated with recurrence and/or survival.[109–112] These include venous and lymphatic invasion; the presence of any vascular invasion should be recorded as a core item; however, distinguishing lymphatic and small blood vessels requires immunohistochemistry but, since both appear to be prognostic, this distinction is not a requirement for routine reporting. Perineural and bile duct invasion have not been shown to have a consistent prognostic effect.

These reviews also describe tumour growth pattern characteristics that have an independent association with outcome. These include the presence or absence of a fibrous pseudocapsule and the histological growth pattern defined as desmoplastic, pushing or replacement.[109–111] Consensus guidelines for scoring the growth patterns have been produced.[113] However, since the growth pattern can be difficult to assess reproducibly and is affected by prior chemotherapy, it is currently regarded as a non-core item.

Effects of neoadjuvant therapy

Preoperative chemotherapy may result in partial or complete response of CRCLM; this may occur without evidence of a response on imaging.[114] Chemotherapy may have been given at some point in the past for the primary tumour, or in the neoadjuvant setting to downstage disease prior to metastasis resection. Areas of ‘dirty’ necrosis surrounded by a garland of adenocarcinoma cells are usually present in metastatic colorectal carcinoma especially at the centre of the tumour, regardless of chemotherapy. Tumour response to chemotherapy is characterised by reduced viable carcinoma associated with intratumoural fibrosis, which may dominate over necrosis.[115,116] Histopathological response correlates with five-year overall survival.[116] A histological response with minimal or no remaining carcinoma is associated with an improved prognosis, while absence of significant response is a poor prognostic feature.[114] The response can be recorded in a manner equivalent to that of the primary CRC, and for convenience the same descriptors are used here as in the colorectal dataset,[117] namely no viable cancer cells/rare small groups of viable cells/residual cancer with evident regression/no evident tumour regression. There is often also a histiocyte response, and/or isolated mucin lakes within dense fibrous tissue. Where there are multiple deposits, the response to therapy may vary among them and so histological sampling of each is recommended.

Background liver disease

The presence and severity of any changes in the uninvolved liver should be noted. For example, fatty liver disease is common as obesity and alcohol misuse are risk factors for CRC and may have an adverse impact on liver function if a large resection is undertaken. Chemotherapy may also cause injury to the background liver. This varies with the agent used. In several studies, oxaliplatin has been shown to induce sinusoidal obstruction syndrome (SOS) in about 50% patients, while irinotecan may contribute to steatosis and steatohepatitis.[118–121]

SOS can evolve into nodular regenerative hyperplasia (NRH) with the potential complication of portal hypertension. Chemotherapy-associated liver injury persists for a long time following chemotherapy. SOS and NRH regress nine months after chemotherapy, whereas steatosis

and steatohepatitis persist.[122] A qualitative estimate of the severity of these chemotherapy-related changes can be included,[118–120] although involvement is often heterogeneous, and its assessment is subjective.

6 Non-core data items

Non-core data items in College datasets are defined as those that are:

- preferences of individual laboratories
- items for clinical research
- supplementary information that may contribute to management or treatment decisions in individual cases.

Examples of these are included in this dataset and are considered to represent good practice but are not data that are required for TNM staging. These data items may be subject to observer variation. Some may become core data items in future.

These items would normally be included in the text of the report, or as locally agreed additions to the dataset proforma report:

- WHO histological subtype of tumour
- immunohistochemistry – includes K19 for HCC, and K7/20 and CDX2 for CRCLM that lacks characteristic morphology. Molecular studies for CRCLM not already available on the primary tumour.
- presence of fibrous pseudocapsule surrounding tumour (HCC and CRCLM) and growth pattern for CRCLM
- as appropriate, the presence of premalignant lesions: large or small cell change (dysplasia), dysplastic hepatocellular nodules, or BilIN (biliary dysplasia)
- background liver disease – aetiology and severity. This is important in both primary liver cancer and in resection of CRCLM; while the fibrosis stage is a core dataset item, further details of the aetiology and severity of background chronic liver disease are considered non-core items in view of their dependence on adequate clinical information and subjectivity in their assessment.

Molecular data:

- at the time of writing, molecular testing for FGFR2 fusion is recommended for cholangiocarcinoma patients eligible for treatment. It is likely that further testing will be approved by NICE, and this is an evolving field. Please refer to the national test directory for current recommendations.
- these tests are performed on biopsy material. Therefore, for a targeted tumour biopsy where cholangiocarcinoma is in the differential diagnosis, it is important to minimise immunohistochemistry for tumour diagnosis to conserve adequate tissue for future genetic tests.

7 Diagnostic coding and staging

The TNM 8 stage criteria for each tumour type covered in this dataset are summarised in Appendix A. The TNM subsets can be converted to the International Stage Groupings (TNM 8), although this may require additional clinical data, e.g. presence of distant metastases (see Appendix A).

The site and histological diagnosis should be coded using SNOMED-CT (Appendix C).

8 Additional histological investigations to aid tumour diagnosis

The use of ancillary immunohistochemical and histochemical investigations in liver tumour diagnosis is described in Appendices N–R. These may be of particular relevance in reporting targeted needle core biopsies of focal lesions (see section 10):

Appendix O−P: Immunohistochemical markers in the diagnosis of HCC:

Appendix O: Immunohistochemical markers helpful in distinguishing well differentiated HCC from dysplastic nodules in cirrhotic livers

Appendix P: Immmunohistochemical markers helpful in the classification of HCA and identifying risk of malignancy.

Appendix Q−R: Immunohistochemical markers helpful in the differential diagnosis of liver cancers:

Appendix Q: tumours that resemble HCC

Appendix R: tumours with morphological features of adenocarcinoma – table reproduced from the Royal College of Pathologists dataset for cancer of unknown primary.

Appendix S: Other special stains that may be useful for the differential diagnosis of liver biopsies containing tumour.

9 Reporting frozen sections

The commonest indication for hepatobiliary frozen section is for the diagnosis of focal subcapsular liver lesions – usually to distinguish metastasis from benign lesions such as bile duct adenoma or von Meyenburg complexes (microhamartomas). Frozen sections are often requested during surgery for perihilar CC including bile duct transection margins and enlarged lymph node, suspected to contain metastasis.

Inflammatory conditions including PSC, Mirizzi syndrome (inflammatory mass around gallbladder neck mimicking malignant bile duct stricture) and IgG4 cholangitis may closely mimic perihilar CC on imaging. Similarly, inflammatory disease of gallbladder such as xanthogranulomatous cholecystitis may mimic carcinoma of gallbladder both radiologically and at the time of surgery. Although specimens may be sent for intra-operative diagnosis and a positive result for malignancy is useful, frozen section cannot reliably exclude malignancy since small, early tumours may be associated with an extensive inflammatory response.

The practice of laparoscopic assessment of patients with suspected perihilar CC with biopsy of suspicious lymph nodes, peritoneal or subcapsular liver deposits reduces the need for intra-operative diagnosis by frozen section and has been shown to be clinically effective.[12]

[Level of evidence D – Laparoscopic assessment with biopsy avoids need for intra-operative frozen section.]

Frozen section is rarely required during surgery for intrahepatic primary or metastatic carcinoma.

10 Reporting of needle core biopsy specimens for the investigation of focal lesions

Targeted needle core biopsies are commonly obtained during the investigation of focal liver lesions detected by ultrasound scanning or other imaging. Outside hepatology centres, these may outnumber medical liver biopsies. The following section of these guidelines for handling

and reporting is therefore included in both the tissue pathways and the liver biopsy section of The Royal College of Pathologists' liver cancer dataset.[123]

Targeted liver biopsies from focal lesions are taken:

- for the diagnosis of suspected **metastatic malignancy**, especially in the context of malignancy of unknown origin. The Royal College of Pathologists' dataset on malignancy of unknown origin describes a stepwise approach recommended for the immunohistochemical investigation of these biopsies.[124]

or

- for the diagnosis of suspected **primary liver neoplasm** in the following situations:
  - in normal or non-cirrhotic liver where imaging shows features suggesting HCA or HCC, or CC
  - in the context of advanced stage chronic liver disease/cirrhosis where the diagnosis of a focal lesion cannot be made from its imaging characteristics
  - for some patients with radiological features of advanced HCC, which is not amenable to curative treatment, histological confirmation of the diagnosis may be required prior to considering systemic treatment options.

It should be noted that hepatobiliary surgeons advise against needle biopsy to confirm a diagnosis of CRCLM where future surgical excision may be an option because of the risk of chest wall recurrence at the biopsy site, as a consequence of seeding.

[Level of evidence D – Risk of chest wall recurrence following biopsy of CRCLM.][125]

The diagnosis in these cases is made on the basis of imaging and the appropriate clinical setting.

For cirrhotic patients under surveillance for HCC, diagnostic biopsy is recommended for lesions >10 mm which do not show characteristic imaging features of HCC using specific radiological techniques.[126] The assessment of dysplasia and neoplasia can be challenging in this context and biopsies are normally taken in hepatology centres, with availability of ancillary immunohistochemical stains, which can help to clarify the diagnosis.

10.1 Specimen submission

The request form should clearly indicate that the biopsy is from a focal lesion. It should include the size and intrahepatic site (segment) of the lesion targeted with other relevant clinical information such as a previous history of malignant disease and imaging findings and specify whether primary or metastatic disease is suspected. It is often helpful if the operator indicates on the request form if there is doubt or difficulty achieving successful targeting of the lesion.

Unlike medical liver biopsies, there is no minimum recommended specimen size. The risk of complications is higher for targeted tumour biopsies and an 18-gauge needle is usually used.[127] A small biopsy containing diagnostic tumour tissue can still be regarded as adequate, although such samples may not contain sufficient tissue for full immunohistochemical evaluation, and a considered stepwise approach to investigation is especially important where tissue is limited. If the biopsy is small and fragmented, consideration may be given to embedding tissue in separate blocks to maximise the number of tissue sections available.

10.2 Sectioning and staining

Initially, one or two shallow levels stained with H&E should be examined; if two levels are cut, intervening unstained sections should be kept on slides suitable for immunohistochemistry. Once the presence of lesional tissue is confirmed, further investigations may be requested based on the tumour morphology and clinical circumstances. If no tumour tissue is seen

initially, deeper levels should be requested before reporting a biopsy as being negative for tumour.

The possibility that the biopsy is from a well-differentiated hepatocellular lesion (FNH, HCA, well-differentiated HCC or focal fatty change/sparing) should be considered if hepatocellular tissue is present without normal architectural landmarks (portal tracts and hepatic veins). The interpretation of well differentiated hepatocellular lesions is complex and challenging, particularly in small needle biopsy specimens. A range of immunohistochemical stains may be used to further characterise these lesions (see Appendix O and P), not all of which may be available outside of hepatology centres.

Alternatively, the biopsy may show abnormalities due to an adjacent focal lesion. If there is no lesional tissue present, the report should indicate that additional biopsies/investigations are required for diagnosis.

10.3 Further investigations

In the presence of tumour, early access to further information from clinical discussion or from reviewing the electronic patient record is recommended to guide the immunohistochemical investigations. For example, details of a previous history of primary malignancy may have been omitted from the request form or from imaging studies. If the patient is extremely ill, a tissue diagnosis of malignancy may be sufficient to allow immediate clinical management decisions.

Immunohistochemical evaluation is usually required to investigate the nature of the tumour. The selected panel of markers will depend upon tumour morphology, any clinically suggested site of primary origin, past medical history, the amount of tissue available in the biopsy and, in certain circumstances, trying to identify tumours which may respond to a specific form of chemotherapy. However, when there is a history of previous malignancy or radiological features of a primary tumour, a compatible morphology is often sufficient without immunohistochemistry, especially where previous histology is available for review.

Histological work up of a potentially primary liver lesion has a different strategy from the differential diagnosis of metastatic disease; this possibility should be considered before requesting a panel of immunohistochemistry routinely used for diagnosing metastatic adenocarcinoma.

Other special stains may also be useful. These include PAS and PAS diastase for the distinction between hepatocellular and other neoplasms, and reticulin staining for the differential diagnosis of dysplastic and neoplastic hepatocellular lesions. See Appendix S for a guide to special stains in tumour biopsies, other than immunostains.

10.3.1 Metastatic malignancy

When the clinical suspicion and/or initial morphology is suggestive of metastatic disease, the RCPath *Dataset for cancer of unknown primary and malignancy of unknown primary origin* should be followed.[124] This document provides a detailed stepwise approach to the diagnosis and will not be considered further here.

10.3.2 Primary liver lesions

When a primary liver lesion is suspected on imaging, and/or the biopsy has a morphological pattern of a ‘solid organ’ carcinoma (liver, kidney, adrenal, thyroid, pancreatic acinar cell or neuroendocrine carcinoma) the next step depends on whether or not the patient has advanced stage chronic liver disease. In addition to the solid organ carcinomas listed in the *Dataset on cancer of unknown primary and malignancy of unknown primary origin*, pancreatic acinar cell carcinoma may mimic HCC histologically and be associated with raised AFP; immunohistochemistry for trypsin should be considered to investigate for this.

For a patient with no history, clinical or imaging signs of chronic liver disease, the choice of immunohistochemistry will depend on whether:

- the lesion is clearly malignant histologically and the differential diagnosis lies between a primary hepatic neoplasm (HCC or cholangiocarcinoma) and metastatic carcinoma (10.3.2.1 below)
- the lesion is clearly hepatocellular and the differential diagnosis lies between a benign hepatocellular lesion (HCA or FNH) and well-differentiated HCC (see below).

Immunohistochemistry for the diagnosis of primary liver malignancy in a patient without advanced stage chronic liver disease

For biopsies that show carcinoma of trabecular or hepatoid pattern in which the morphological differential is between primary HCC and metastatic carcinoma, immunohistochemistry is often helpful. Appendix Q summarises the immunohistochemistry useful in this situation. Most HCCs are positive for Hepatocyte Specific Antigen (HSA)/ HepPar1. Poorly differentiated HCC may be HepPar1 negative but is more often positive for AFP (serum levels may be raised and/or tumour cells immunopositive). Glypican 3 is an alternative oncofetal antigen expressed in most HCCs but also in some other tumours. Arginase 1 has been claimed to be the most specific/sensitive marker to demonstrate hepatocellular differentiation.[128] Canalicular staining for CD10, CD13, bile salt export pump (BSEP) or polyclonal CEA can be useful second line indicators of hepatocellular differentiation.

Immunohistochemistry for the diagnosis of well differentiated hepatocellular lesions in a patient without advanced stage chronic liver disease

The classification of well differentiated/histologically benign focal hepatocellular lesions based on morphology and immunohistochemistry is summarised in Appendix O (dysplastic nodules in cirrhotic liver) and Appendix P (FNH, HCA in non-cirrhotic liver) and has been discussed above (Section 5.3.1). These lesions are biopsied for diagnosis to determine if resection is indicated, in particular if there is an HCA of subtype with risk of malignant transformation or bleeding.

FNH can usually be diagnosed on the basis of imaging and only requires biopsy diagnosis if it lacks typical features.

The classification of HCA is still evolving, with the recent additions of sonic hedgehog mutated adenoma (which has a high risk of haemorrhage) and the molecular classification of beta catenin mutated adenomas based on the mutated exon, which correlates with degree of risk of malignant transformation. However, molecular techniques required are not generally available in the UK where current practice is to classify the lesion as inflammatory, steatotic, beta-catenin activated or unclassified HCA based on morphology and immunohistochemistry.[36,45,129,130]

Well differentiated HCC can be very difficult to distinguish from HCA on biopsy.[36] Deficiency of reticulin (although reticulin may be lost in steatotic areas) or hepatocyte plates >2 cells thick, positivity for glypican 3, diffuse positivity for glutamine synthetase (also seen in beta-catenin activated HCA), or nodule-in- nodule appearance are features concerning for HCC. The term ‘hepatocellular neoplasm of uncertain malignant potential (HUMP)’ has been proposed for lesions with some suspicion of malignant transformation but which lack definitive features, based on resection specimens.[48] The morphological atypia in these lesions is focal and therefore may be absent from biopsies (reticulin loss, cytological atypia or pseudogland formation).

Other terms which have been used to describe these difficult to classify lesions include ‘atypical hepatocellular adenoma-like neoplasms’ and 'atypical hepatocellular neoplasms’.[47,49,131] In addition to morphological criteria, other features used to identify atypical lesions at increased risk of malignancy include genetic abnormalities (beta catenin gene (*CTTNB1*) activation) or an unusual clinical context (male, female age >50 or <15 years).

Immunohistochemistry for the diagnosis of focal lesions in a patient with advanced chronic liver disease/cirrhosis

Patients with known advanced chronic liver disease/cirrhosis who are eligible for treatment of liver malignancy are usually enrolled into a surveillance programme. Lesions identified by ultrasound are further investigated with MRI and/or CT in order to establish a diagnosis of HCC. The Liver Imaging Reporting and Data System (LIRADS) classification is commonly used for this assessment.[132] If the diagnosis is uncertain and important for therapeutic decision, a biopsy is recommended (EASL guidelines).[126] In this situation the differential diagnosis lies between a large regenerative nodule, dysplastic nodule and early/well-differentiated HCC. For further details, see *Guidelines on the use of liver biopsy in clinical practice* from the British Society of Gastroenterology, Royal College of Radiologists and Royal College of Pathologists.[133]

Focal lesions detected in patients with cirrhosis are diagnosed based on imaging characteristics according to the LIRADS, in which the likelihood of a lesion being HCC is scored on a scale of 1 to 5, where 1 is definitely benign and 5 is definitely malignant.[132] Such lesions may be biopsied when the radiology score is inconclusive (LIRADS 4) and the diagnosis is important for patient management, or to confirm the diagnosis in patients undergoing radiofrequency ablation. Such lesions represent a continuum of neoplastic progression, and there may be intra-lesional variation; a definitive diagnosis may not be possible from a biopsy.

Immunohistochemistry useful in this situation includes glutamine synthetase, glypican 3 and HSP70. Positivity for at least two of these favours HCC.[35] Abnormality or loss of reticulin and an infiltrative growth pattern may enable a definite diagnosis of HCC to be made, although the latter is rarely seen in biopsies. Diffuse positivity of the sinusoidal endothelium for CD34 corresponds to ‘capillarisation of sinusoids’ in arterialised hepatocellular lesions and can provide useful confirmation that the lesion identified on imaging has been sampled; however, it does not distinguish between high grade dysplastic nodule and well differentiated HCC. Other features supportive for a diagnosis of malignancy are a high Ki67 labelling index compared with non-lesional liver and positive staining for AFP, although the latter is rarely seen in small well-differentiated HCCs.

10.4 Report content

The report should include the following:

- the clinical information received with the biopsy
- a macroscopic description, including biopsy size
- the presence or absence of tissue from the focal lesion, and of non-lesional liver tissue (hepatocytes, bile ducts) as histological confirmation that the specimen is indeed from the liver
- a morphological description of the lesion
- the results of any additional stains carried out, including immunohistochemistry
- a comment on the non-lesional liver, if sufficient is included
- a definite diagnosis of the focal lesion where possible, or a discussion of the differential diagnosis. This would include a discussion of tumours compatible with or excluded by immunohistochemistry
- a concise, single-line summary to conclude the report
- an appropriate SNOMED code
- a record (including names) of any intra-departmental consultation, outside referral for second opinion and/or discussion with clinician that has contributed to the histopathology

report. This may be achieved by adding a supplementary report when the diagnosis is later refined or revised as a result of discussion at a clinical meeting or outside review.

10.5 Biliary cytology

Investigation of patients with biliary strictures suspicious of malignancy may include brush cytology or tiny endoscopic 'spy bite' biopsies obtained from within the duct during endoscopic retrograde cholangiopancreatography (ERCP). The material for cytology should be processed in accordance with the Royal College of Pathologists' *Tissue pathways for diagnostic cytopathology*, section 3.1.4.[134] Interpretation may be complicated by the presence of inflammatory changes, especially if there is also a stent or history of PSC.[135] Review of brush cytology together with small SpyBite biopsies can include the sensitivity and specificity of either technique used alone.[136] Endoscopic ultrasound fine needle aspiration cytology for perihilar strictures has a lower detection rate than for distal CC and is not recommended due to risk of tumour dissemination.[137] Ancillary techniques, such as fluorescence in situ hybridisation, next generation sequencing, proteomics and liquid biopsy may enhance assessment made by conventional cytopathology in the future,[136] but are not currently in common usage in the UK.

11 Criteria for audit

Turnaround time of pathology reports should also be audited. The recommended minimum standard for diagnostic biopsy and cytology is 90% authorised within five working days from the date of specimen receipt in the histopathology laboratory.

The recommended minimum standard for surgical resection cases is 90% authorised within ten working days from the date of specimen receipt in the histopathology laboratory. The date of receipt is day zero. Any case that is authorised at any time on day five (biopsy/cytology) or ten (surgical resection) meets this standard; those authorised thereafter do not.

Interim reports are encouraged if cases are referred for second opinions. In this event, date of authorisation of the first report is considered for turnaround time analysis. Turnaround times should be analysed by case and not by individual specimen

Liver resection in the UK is now undertaken in a limited number of specialist centres. The overall aim of the dataset is to ensure a common approach to data collection among pathologists at different centres. National audit would then have the potential to identify best practice, which would lead to improvements in clinical management and outcome of patients with primary liver cancer. Successful implementation of the dataset would enable central collation of data to facilitate comparison and sharing of experience among centres. To this end, the core items of the dataset are included in the COSD dataset.

The changes consequent on moving from TNM7 to TNM8 are shown in the table Appendix B, to assist in comparison of reports which cover more than one TNM staging system; TNM8 has been in use in the UK since January 2018.

Clinical audit among hepatobiliary cancer centres could include aspects of surgical practice and use of adjuvant therapies. Operable primary hepatobiliary cancer is rare in the UK, and audit of the stage-related outcomes of different surgical procedures across cancer centres has the potential to generate an evidence base to support surgical decision making and improve outcomes.

Aspects of the dataset that could be audited within pathology departments include audit of the completeness of recording of all data items in histopathology reports.

Audit within the multidisciplinary team could include audit of imaging/pathology correlation especially in liver transplant patients, including frequency of incidental HCC in explant

specimens not previously detected by imaging, and image detected tumours which could not be identified in the resection specimen.[138]

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Appendix A TNM classification

This appendix lists the TNM classifications for HCC, intrahepatic CC, perihilar CC and gallbladder carcinoma. There should be histological confirmation of the disease and separation of cases by histological type.

The pT, pN and pM categories correspond to the T, N and M categories.

Primary tumour (pT)

Hepatocellular carcinoma

pT0		No evidence of primary tumour
pT1	pT1a	Solitary tumour 20 mm or less in greatest dimension with or without vascular invasion
	pT1b	Solitary tumour more than 20 mm in greatest dimension without vascular invasion
pT2		Solitary tumour with vascular invasion more than 20 mm dimension **or** multiple tumours, none more than 50 mm in greatest dimension
pT3		Multiple tumours any more than 50 mm in greatest dimension
pT4		Single or multiple tumour(s) of any size involving a major branch of the portal or hepatic vein or tumour(s) with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder **or** with perforation of visceral peritoneum

Intrahepatic cholangiocarcinoma (ICC), combined HCC/ICC, cholangiolocellular carcinoma and NEN

pT0		No evidence of primary tumour
pTis		Carcinoma in situ (intraductal tumour)
pT1	pT1a	Solitary tumour 50 mm or less in greatest dimension without vascular invasion
	pT1b	Solitary tumour more than 50 mm in greatest dimension without vascular invasion
pT2		Solitary tumour with intrahepatic vascular invasion **or** multiple tumours, with or without vascular invasion
pT3		Tumour perforating the visceral peritoneum
pT4		Tumour or involving the local extra hepatic structures by direct invasion

Perihilar cholangiocarcinoma

pT0		No evidence of primary tumour
pTis		Carcinoma in situ, high grade BilIN
pT1		Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
pT2	pT2a	Tumour invades beyond the wall of the bile duct to surrounding adipose tissue
	pT2b	Tumour invades adjacent hepatic parenchyma
pT3		Tumour invades unilateral branches of the portal vein or hepatic artery
PT4		Tumour invades the main portal vein or its branches bilaterally **or** the common hepatic artery **or** unilateral second-order biliary radicals with contralateral portal vein **or** hepatic artery involvement

Gallbladder carcinoma

pT0		No evidence of primary tumour
pTis		Carcinoma in situ, high grade BilIN
pT1	pT1a	Tumour invades lamina propria
	pT1b	Tumour invades muscular layer
pT2	pT2a	Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa
	pT2b	Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver
pT3		Tumour 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 extra-hepatic bile ducts
PT4		Tumour invades main portal vein or hepatic artery **or** invades two or more extrahepatic organs or structures.

Regional lymph nodes (pN)

Hepatocellular carcinoma/intrahepatic cholangiocarcinoma

pNx	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases
pN1	Regional lymph node metastasis

Histological examination of a regional lymphadenectomy specimen will ordinarily include six or more lymph nodes for ICC, there is no recommended number of nodes for HCC. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Perihilar cholangiocarcinoma/gall bladder carcinoma

pNx	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases
pN1	Metastasis to 1–3 regional nodes
pN2	Metastasis to 4 or more regional nodes

Histological examination of a regional lymphadenectomy specimen will ordinarily include six or more lymph nodes for gall bladder cancer, and 15 lymph nodes for Perihilar CC. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Distant metastasis (pM)

The only pM code that can be assigned by the pathologist is pM1 – it is not possible to ascertain the absence of distant metastases.

pM1	Distant metastasis

This includes metastasis to non-regional lymph nodes, including periaortic, pericaval, superior mesenteric artery and/or coeliac artery lymph nodes.

Stage grouping

Hepatocellular carcinoma

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Intrahepatic cholangiocarcinoma

Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Perihilar cholangiocarcinoma

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a, b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
Stage IVB	Any T	Any N	M1

Gallbladder carcinoma

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0

Stage IB	T1b	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1, T2, T3	N1	M0
Stage IVA	T4	N0, N1	M0
Stage IVB	Any T	N2	M0
	Any T	Any N	M1

Appendix B Summary of changes in TNM staging criteria between TNM 6, 7 and 8

Hepatocellular carcinoma

	TNM6 2002	TNM7 2010	TNM8 2018
pT1	Single, no vascular invasion	Single, no vascular invasion	pT1a single, <2 cm +/- vascular invasion
			pT1b single, >2 cm, no vascular invasion
pT2	Single with vascular invasion or multiple <5 cm	Single with vascular invasion or multiple, none >5 cm	Single >2 cm with vascular invasion. or multiple, none >5 cm
pT3	Multiple >5 cm or involves major branch of portal or hepatic vein	pT3a multiple tumours any more than 5 cm	Multiple tumours any more than 5 cm
		pT3b tumour involving major branch of portal or hepatic vein	
pT4	Direct invasion of adjacent organs other than GB or perforates visceral peritoneum		Involves major branch of portal or hepatic vein, or direct invasion of adjacent organs (except GB) or perforates visceral peritoneum
pN1	Regional nodes +ve		Sample $\geq$3 nodes

Intrahepatic cholangiocarcinoma

	TNM6 2002 = hepatocellular carcinoma	TNM7 2010 ICC now has separate TNM	TNM8 2018
pTis		Carcinoma in situ	Inc. high grade BilIN
pT1	Single, no vascular invasion	Single, no vascular invasion	Single, no vascular invasion pT1a <5 cm pT1b >5 cm
pT2	Single with vascular invasion or multiple <5 cm	pT2a single with vascular invasion	Single with vascular invasion. or multiple +/- vascular invasion
		pT2b multiple +/- vascular invasion	
pT3	Multiple >5 cm or involves major branch of portal or hepatic vein	Perforates visceral peritoneum or invades local extra-hepatic structures	Perforates visceral peritoneum

pT4	Direct invasion of adjacent organs other than GB or perforates visceral peritoneum	Tumour with periductal growth pattern	Invades local extra-hepatic structures
pN1	Regional nodes +ve Sample ≥3 nodes		Sample ≥6 nodes

Perihilar cholangiocarcinoma

	TNM6 2002 **= extrahepatic ducts**	**TNM7 2010**	**TNM8 2018**
pTis	Carcinoma in situ		Inc. high grade BilIN/IPNB
pT1	Ductal wall	Confined to wall	
pT2	Beyond ductal wall	pT2a into surrounding adipose tissue	
		pT2b into adjacent hepatic parenchyma	
pT3	Liver, GB, pancreas or unilateral vessels	Unilateral branch of portal vein (PV) or hepatic artery (HA)	
pT4	Other adjacent organs or main vessels	Main PV or bilateral branches, or common HA or second order biliary radicals with contralateral PV or HA	
pN1	Regional nodes +ve	Regional nodes +ve	pN1 1–3 nodes +ve pN2 >3 nodes +ve Sample 15 nodes

Gallbladder carcinoma

	TNM6 2002 **= hepatocellular carcinoma**	**TNM7 2010**	**TNM8 2018**
pTis	Carcinoma in situ		Inc. high grade BilIN/ICPN
pT1	pT1a invades lamina propria pT1b invades muscle		
pT2	Invades perimuscular connective tissue – no extension beyond visceral peritoneum or into liver		Invades perimuscular connective tissue – no extension beyond visceral peritoneum or into liver
			pT2a peritoneal side pT2b hepatic side
pT3	Perforates visceral peritoneum and/or invades liver and/or one other adjacent organ		
pT4	Invades main PV or HA or ≥2 extrahepatic organs		
pN1	Regional nodes +ve		Sample ≥6 nodes

	Sample ≥3 nodes	

Appendix C Liver primary and metastatic carcinoma SNOMED coding

Topographical codes	SNOMED-RT	SNOMED CT terminology	SNOMED CT Code
Liver	T62000	Liver structure (body structure)	10200004
Left lobe of liver	T62020	Structure of left lobe of liver (body structure)	69842003
Right lobe of liver	T62010	Structure of right lobe of liver (body structure)	48521005
Intrahepatic bile duct	T62110	Intrahepatic biliary tract structure (body structure)	90140006
Extrahepatic bile duct	T64000	Extrahepatic duct structure (body structure)	16014003
Gall bladder	T63000	Gallbladder structure (body structure)	28231008

Morphological codes	SNOMED-RT	SNOMED CT terminology	SNOMED CT Code
Epithelial tumours: hepatocellular			
Hepatocellular carcinoma	M81703	Hepatocellular carcinoma (morphologic abnormality)	25370001
Hepatocellular carcinoma, fibrolamellar variant	M81713	Hepatocellular carcinoma, fibrolamellar (morphologic abnormality)	15619004
Epithelial tumours: biliary			
Biliary intra-epithelial neoplasia, high grade	M81482	Glandular intraepithelial neoplasia, grade III (morphologic abnormality)	128640002
Intraductal papillary neoplasm with high grade intra-epithelial neoplasia	M85032	Noninfiltrating intraductal papillary adenocarcinoma (morphologic abnormality)	30566004
Mucinous cystic neoplasm with high grade intra-epithelial neoplasia	M84702	Mucinous cystadenocarcinoma, non-invasive (morphologic abnormality)	128900005
Intrahepatic cholangiocarcinoma	M81603	Cholangiocarcinoma (morphologic abnormality)	70179006

Combined hepatocellular-cholangiocarcinoma	M81803	Combined hepatocellular carcinoma and cholangiocarcinoma (morphologic abnormality)	52178006
Intraductal papillary neoplasm with associated invasive carcinoma	M85033	Intraductal papillary adenocarcinoma with invasion (morphologic abnormality)	64524002
Mucinous cystic neoplasm with associated invasive carcinoma	M84703	Mucinous cystadenocarcinoma (morphologic abnormality)	79143006
Perihilar cholangiocarcinoma (Klatskin tumour)	M81623	Klatskin's tumor (morphologic abnormality)	6492006
Adenocarcinoma (gall bladder, extrahepatic ducts)	M81403	Adenocarcinoma, no subtype (morphologic abnormality)	35917007
Neuroendocrine carcinoma	M82463	Neuroendocrine carcinoma (morphologic abnormality)	55937004
Metastatic adenocarcinoma	M81406	Adenocarcinoma, metastatic (morphologic abnormality)	4590003

Procedure
Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

ICD codes – include specific codes for intrahepatic and perihilar cholangiocarcinoma.[139]

Appendix D Reporting proforma for liver resection: hepatocellular carcinoma

Surname: ..... Forenames: ..... Date of birth: .....
Sex: ..... CHI/NHS no: ..... Hospital: .....
Hospital no:..... Date of receipt:..... Date of reporting: .....
Report no: ..... Pathologist: ..... Surgeon: .....

Gross description

Type of specimen:
Segmental resection □ List segments (if known): ……
Non-anatomic (wedge) resection □ Site/segment of origin: ……
Hepatectomy (at transplant) □

Specimen weight……g

For segmental resections, specimen dimensions:
antero-posterior ……mm, medio-lateral ……mm, supero-inferior……mm

Number of tumours present. …… List maximum tumour diameters (up to largest 4): ……mm
Satellite tumour(s) present: Yes □ No □
Distance from nearest hepatic resection margin: ……..mm

Macroscopic involvement of vessels: Main left portal vein □ Main right portal vein □ Hepatic vein □ Vessel not specified □
No macroscopic involvement □ Diameter of vessel involved ……mm
Liver capsule intact and smooth Yes □ No □
Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ …….....…..
Lymph node(s) received Yes □ No □

Histology
Tumour type: HCC NOS □ Fibrolamellar carcinoma □ Other histological subtype □ (If Other, specify)…….....
Tumour grade/differentiation by worst area: Well □ Moderate □ Poor □
Tumour cells present at excision margin: Yes □ No □
If no, distance to resection margin: <1 mm □ 1–10 mm □ state distance: ……mm >10 mm □
Macroscopic vascular invasion confirmed: Yes □ No □
Microscopic vascular invasion identified: Present □ Not identified □
Evidence of response to preoperative treatment: Yes, complete □ Yes, incomplete □ No □ Not applicable □
Best block of tumour for molecular testing: ……..

Background liver

Insufficient for assessment □

Fibrosis	None present	□	**Aetiology**		
If present:			Hepatitis B	□	
	Portal/periportal	□	Hepatitis C	□	
	Sinusoidal/pericellular	□	Autoimmune hepatitis	□	
	Both portal & sinusoidal	□	Haemochromatosis	□	
	Bridging	□	Alcohol	□	
	Bridging with nodules	□	NAFLD	□	
	Complete cirrhosis	□	Not known	□	
			Other	□	(If Other, specify) .....

Number of lymph nodes examined: …….. Number of lymph nodes with metastases: …….

Comments/additional information

Pathological staging pT…….. pN…….

pT0 No tumour identified

pT1a Solitary tumour ≤20 mm with or without vascular invasion

pT1b Solitary tumour >20 mm without vascular invasion

pT2 Solitary tumour >20 mm with vascular invasion, or multiple tumours, none >50 mm

pT3 Multiple tumours, any >50 mm

pT4 Tumour(s) invade a major branch of the portal or hepatic vein or with direct invasion of adjacent organs (includes diaphragm but not gall bladder) or perforates visceral peritoneum

pN0 No lymph node metastases

pN1 Lymph node metastases

Signature of pathologist ……..... Date …./…./……..

SNOMED-CT codes …….

Appendix E Reporting proforma for liver resection: intrahepatic cholangiocarcinoma

Surname: ..... Forenames: ..... Date of birth: .....
Sex: ..... CHI/NHS no: ..... Hospital: .....
Hospital no:..... Date of receipt:..... Date of reporting: .....
Report no: ..... Pathologist: ..... Surgeon: .....

Gross description

Type of specimen:

Segmental resection □ List segments (if known): ……
Non-anatomic (wedge) resection □ Site/segment of origin: ……
Hepatectomy (at transplant) □

Specimen weight……g

For segmental resections, specimen dimensions:
antero-posterior ……mm, medio-lateral ……mm, supero-inferior……mm

Number of tumours present. …… List maximum tumour diameters: ……mm
Satellite tumour(s) present: Yes □ No □
Distance from nearest hepatic resection margin: ……..mm

Macroscopic involvement of vessels: Main left portal vein □ Main right portal vein □ Hepatic vein □ Vessel not specified □
No macroscopic involvement □ Diameter of vessel involved ……mm
Liver capsule intact and smooth Yes □ No □
Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ ……..…..
Lymph node(s) received Yes □ No □

Histology

Tumour type: Cholangiocarcinoma NOS □
Subtype large duct □ Small duct □ Combined HCC/CC □ Cholangiolocellular □
Other histological subtype □ (If other, specify)……..……
Tumour grade/differentiation: Well □ Moderate □ Poor □
Tumour cells present at resection margin: Yes □ No □
If no, distance to resection margin: <1 mm □ 1–10 mm □ state distance: ……mm >10 mm □
Macroscopic vascular invasion confirmed: Yes □ No □
Microscopic vascular invasion identified: Present □ Not identified □
Perineural invasion identified: Present □ Not identified □
Best block of tumour for molecular testing: ……..

Background liver

Insufficient for assessment □

Fibrosis	None present	□	**Aetiology**		
If present:			Hepatitis B	□	
	Portal/periportal	□	Hepatitis C	□	
	Sinusoidal/pericellular	□	Autoimmune hepatitis	□	
	Both portal & sinusoidal	□	Haemochromatosis	□	
	Bridging	□	Alcohol	□	
	Bridging with nodules	□	NAFLD	□	
	Complete cirrhosis	□	Not known	□	
			Other	□	(If Other, specify) .....

Number of lymph nodes examined: …….. Number of lymph nodes with metastases: …….

Comments/additional information

Pathological staging pT…….. pN…….

pTis Carcinoma in situ

pT1a Solitary tumour ≤50 mm without vascular invasion

pT1b Solitary tumour >50 mm without vascular invasion

pT2 Solitary with intrahepatic vascular invasion **or** multiple tumours, with or without vascular invasion

pT3 Tumour perforating the visceral peritoneum.

pT4 Tumour involves local extra hepatic structures by direct invasion

pN0 No lymph node metastases

pN1 Lymph node metastases

Signature of pathologist ……..... Date …./…./……..

SNOMED-CT codes

ICD 11 code: intrahepatic cholangiocarcinoma: 2C12.10

Appendix F Reporting proforma for liver resection: perihilar cholangiocarcinoma

Surname: ..... Forenames: ..... Date of birth: .....

Sex: ..... CHI/NHS no: ..... Hospital: .....

Hospital no:..... Date of receipt:..... Date of reporting: .....

Report no: ..... Pathologist: ..... Surgeon: .....

Gross description

Type of specimen: Segmental resection List segments (if known): ……

Non-anatomic (wedge) resection □ Site/segment of origin: ……

Length of attached extrahepatic bile duct …….mm

Specimen weight……g

For segmental resections, specimen dimensions:

antero-posterior ……mm, medio-lateral ……mm, supero-inferior……mm

Ducts involved: Right main duct □ Left main duct □ Confluence of ducts □ Common hepatic duct □

Direct invasion of liver Yes □ No □

Maximum tumour size ……..mm

Distance from nearest hepatic resection margin ……..mm

Distance from bile duct transection margin …….mm

Hepatic metastases present Yes □ No □

Liver capsule intact and smooth Yes □ No □

Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ ……..……..

Lymph node(s) received Yes □ No □

Portal vein or first left or right branch included? Yes □ No □

Histology

Tumour type: Cholangiocarcinoma NOS □ Arising from IPNB □ Arising from mucinous cystic neoplasm □

Other histological type □ If other, please specify…….…….

Tumour grade/differentiation (adenocarcinoma): Well □ Moderate □ Poor □

Tumour cells present at hepatic resection margin Yes □ No □

Tumour cells present at main duct transection margin Yes □ No □

Tumour cells present at circumferential dissection or peritoneal margin Yes □ No □ Not applicable □

If margin is clear: distance to resection margin: <1 mm □ 1–10 mm □ state distance …..mm >10 mm □

Indicate closest margin: Hepatic □ Main duct □ Circumferential dissection or peritoneal □

Invasion of lumen or wall of main left / right portal vein / hepatic artery Present □ Not identified □

Which vessel? .....

Microscopic vascular invasion identified: Present □ Not identified □
Perineural invasion identified: Present □ Not identified □
Best block of tumour for molecular testing: ……..

Background liver disease: None □ Primary sclerosing cholangitis □ Other □

If other, please specify……

Number of regional lymph nodes examined: …….. Number regional lymph nodes with metastases: …….

Comments/additional information

Pathological staging for hilar cholangiocarcinoma:pT…….. pN…….

pTis Carcinoma in situ, high grade *BilIN* / IPNB

pT1 Tumour confined to bile duct with extension up to the muscle layer or fibrous tissue

pT2a Tumour invades beyond wall of the bile duct into surrounding adipose tissue

pT2b Tumour invades adjacent hepatic parenchyma

pT3 Tumour invades unilateral branches of portal vein or hepatic artery

pT4 Tumour invades the main portal vein or its branches bilaterally **or** the common hepatic artery **or** unilateral second order biliary radicals with contralateral portal vein or hepatic artery involvement.

pN0 No regional lymph node metastases

pN1 Metastasis to 1–3 regional nodes

pN2 Metastasis to 4 or more regional nodes

(Record non-regional lymph node metastases as pM1)

Signature of pathologist ……..... Date …./…./……..

SNOMED-CT codes

ICD 11 code: perihilar cholangiocarcinoma: 2C18.0

Appendix G Reporting proforma for liver resection: gallbladder cancer

Surname: ..... Forenames: ..... Date of birth: .....
Sex: ..... CHI/NHS no: ..... Hospital: .....
Hospital no:..... Date of receipt:..... Date of reporting: .....
Report no: ..... Pathologist: ..... Surgeon: .....

Gross description

Type of specimen: Cholecystectomy (cancer not previously suspected) □
En bloc gall bladder and liver □ List liver segments resected :…….....….
Staged liver resection □ List liver segments resected :….....…….
Previous gall bladder report reviewed □ Slides reviewed □ pT stage ……
Previous report not available □

Gall bladder

Dimensions: Length:……mm Width:……mm Maximum wall thickness:……mm
Mucosal aspect of tumour: Papillary/exophytic □ Plaque/infiltrative □
Location of tumour: Peritoneal side □ Hepatic side □ Both or not assessable □
Maximum dimension of tumour …….mm
Gall stones present? Yes □ No □
Length of cystic duct ……..mm Other bile ducts resected? Yes □ No □

Liver resections:

Specimen weight……g
Specimen dimensions: Antero-posterior ……mm Medio-lateral ……mm Supero-inferior……mm
Direct invasion of liver Yes □ No □
If yes: depth of liver invasion .....mm Distance from nearest hepatic resection margin ……..mm
Hepatic metastases present Yes □ No □
Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ …….....…..
Lymph node(s) received Yes □ No □
Includes non-regional nodes? Yes □ No □

Histology

Tumour grade/differentiation (adenocarcinoma): Well □ Moderate □ Poor □
Other histological type □ (specify)…….....….

Depth of invasion

Lamina propria □ Muscular layer □ Beyond muscle □

Perforates serosa □ Invades liver □

Invades other organs Yes □ No □ If yes, which…….....

Cystic duct: Involved □ BilIN □ No BilIN □

Other ducts resected Yes □ No □ If yes: involved by dysplasia/BilIN: Yes □ No □

Tumour cells present at any resection margin: Yes □ No □

Indicate which margin: Hepatic □ Bile duct □ Other □ If other please state which …….

If margins are clear: distance to resection margin L <1 mm □ 1–10 mm □ state distance: ……..mm >10 mm □

Microscopic vascular invasion identified: Present □ not identified □

Perineural invasion identified: Present □ not identified □

Best block of tumour for molecular testing: ……..

Number of lymph nodes examined: …….. Number of lymph nodes with metastases: …….

Comments/additional information

Pathological staging: gall bladder carcinoma pT…….. pN……

PTis Carcinoma in situ, high grade BiliN / ICPN

pT1a Tumour invades lamina propria

pT1b Tumour invades muscular layer

pT2a Tumour invades perimuscular connective tissue on the peritoneal side with no extension to the serosa

pT2b Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver

pT3 Tumour 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 extra-hepatic bile ducts.

pT4 Tumour invades the main portal vein or hepatic artery or invades 2 or more extrahepatic organs or structures

pN0 No regional lymph node metastases

pN1 Metastasis to 1–3 regional lymph node pN2 metastasis to 4 or more regional nodes. (Record non-regional lymph node metastases as pM1)

Signature of pathologist ……..... Date …./…./……..

SNOMED-CT codes

Appendix H Reporting proforma for liver resection: colorectal carcinoma metastasis

Surname: ..... Forenames: ..... Date of birth: .....

Sex: ..... CHI/NHS no: ..... Hospital: .....

Hospital no:..... Date of receipt:..... Date of reporting: .....

Report no: ..... Pathologist: ..... Surgeon: .....

Gross description

Number of specimens received …..

Type of specimen: Segmental resection □ List segments (if known): ……

Non-anatomic (wedge) resection □ Site/segment of origin: ……

List if several …….

Specimen weight (all specimens combined) ……g

For segmental resections, specimen dimensions (largest specimen):

antero-posterior ……mm, medio-lateral ……mm, supero-inferior……mm

Number of tumours present. …… Satellite tumour(s) present: Yes □ No □

List maximum diameters for up to four largest tumours : ……mm, ……mm, ……mm, ……mm

Distance from nearest hepatic resection margin of nearest tumour: ……..mm

Liver capsule intact and smooth Yes □ No □

Invasion of adherent or adjacent organ Yes □ No □ If yes, which organ …….....…..

Lymph node(s) received Yes □ No □

Histology

Tumour grade/differentiation: Well/ moderate □ Poor □

Tumour cells present at resection margin: Yes □ No □

If no, distance to resection margin: <1 mm □ 1–10 mm □ state distance: ……..mm >10 mm □

Microscopic vascular invasion identified Present □ not identified □

Neoadjuvant therapy given Yes □ No □ Not known □

If yes: no residual tumour cells □ rare small groups of viable cells □

residual cancer cells with evident regression □ no evident tumour regression □

Best block of tumour for molecular testing: ……..

Background liver

Normal □ Steatosis □ Chronic liver disease with fibrosis □ Sinusoidal obstruction syndrome □

Comments/additional information

Appendix I Reporting proforma for liver resection: hepatocellular carcinoma in list format

Element name	Values	Implementation notes
Gross description		
Type of specimen	Single selection value list: • Segmental resection • List segments (if known) Non-anatomic (wedge) resection – Site/segment of origin: • Hepatectomy (at transplant)	Specify 'List segments (if known) if segmental resection is selected. Specify 'Site/segment of origin' if non-anatomic (wedge resection is selected).
Specimen weight	Integer	State specimen weight in grams (g)
For segmental resections, specimen dimensions:	• Integer (antero-posterior (mm)) • Integer (medio-lateral (mm)) • Integer (supero-inferior (mm))	
Number of tumours present	Integer	
List maximum tumour diameters (up to largest four):	Integer (mm)	Up to four separate values
Satellite tumour(s) present:	Single selection value list: • Yes • No	
Distance from nearest hepatic resection margin: (mm)	Integer (mm)	
Macroscopic involvement of vessels	Multiple selection value list: • Main left portal vein • Main right portal vein • Hepatic vein • Vessel not specified • No macroscopic involvement	
Diameter of vessel involved (mm)	Integer (mm)	Leave blank if 'Macroscopic involvement of vessels = No macroscopic involvement'
Liver capsule intact and smooth	Single selection value list: • Yes • No	
Invasion of adherent organ or adjacent organ	Single selection value list:	

	• Yes • No	
If yes, which organ	Free text	Leave blank if 'Invasion of adherent organ or adjacent organ = No'
Lymph node(s) received	Single selection value list: • Yes • No	
Histology		
Tumour type	Single selection value list: • HCC NOS • Fibrolamellar carcinoma • Other histological subtype	
If other specify	Free text	Enter value if 'Tumour type = Other histological subtype'
Tumour grade/differentiation by worst area:	Single selection value list: • Well • Moderate • Poor	
Tumour cells present at excision margin	Single selection value list: • Yes • No	
If no, distance to resection margin	Single selection value list: • <1 mm • 1–10 mm • >10 mm	
State distance	Number (mm)	If 'Distance to resection margin = 1–10 mm, state distance in mm'
Macroscopic vascular invasion confirmed	Single selection value list: • Yes • No	
Microscopic vascular invasion identified	Single selection value list: • Present • Not identified	
Evidence of response to preoperative treatment	Single selection value list: • Yes, complete • Yes, incomplete • No • Not applicable	
Best block of tumour for molecular testing	Free text	
Background liver	Single selection value list: • Insufficient for assessment	

Fibrosis	Single selection value list: • None present If present: • Portal/periportal • Sinusoidal/pericellular • Both portal & sinusoidal • Bridging • Bridging with nodules • Complete cirrhosis	
Aetiology	Multiple selection value list: • Hepatitis B • Hepatitis C • Autoimmune hepatitis • Haemochromatosis • Alcohol • NAFLD • Not known • Other	
Other	Free text	Please specify if 'Aetiology = Other'
Number of lymph nodes examined	Integer	
Number of lymph nodes with metastases	Integer	
Comments/additional information	Free text	
Pathological staging pT	Free text pT0 No tumour identified pT1a Solitary tumour <20 mm with or without vascular invasion pT1b Solitary tumour >20 mm without vascular invasion pT2 Solitary tumour >20 mm with vascular invasion, or multiple tumours, none >50 mm pT3 Multiple tumours, any >50 mm pT4 Tumour(s) invade a major branch of the portal or hepatic vein or with direct invasion of adjacent organs (includes diaphragm but not gall bladder) or perforates visceral peritoneum	Enter values for pT and pN (e.g. pT1a)

Pathological staging pN	pN0 No lymph node metastases pN1 Lymph node metastases	
SNOMED-CT codes	May have multiple codes. Look up from SNOMED tables.	

Appendix J Reporting proforma for liver resection: intrahepatic cholangiocarcinoma in list format

Element name	Values	Implementation notes
Gross description		
Type of specimen	Single selection value list: • Segmental resection – List segments (if known) • Non-anatomic (wedge) resection – Site/segment of origin: • Hepatectomy (at transplant)	Specify 'List segments (if known) if segmental resection is selected. Specify 'Site/segment of origin' if non-anatomic (wedge resection is selected).
Specimen weight	Integer	State specimen weight in grams (g)
For segmental resections, specimen dimensions:	• Integer (antero-posterior (mm)) • Integer (medio-lateral (mm)) • Integer (supero-inferior (mm))	
Number of tumours present	Integer	
List maximum tumour diameters	Integer (mm)	Up to four separate values
Satellite tumour(s) present:	Single selection value list: • Yes • No	
Distance from nearest hepatic resection margin: (mm)	Integer (mm)	
Macroscopic involvement of vessels	Multiple selection value list: • Main left portal vein • Main right portal vein • Hepatic vein • Vessel not specified • No macroscopic involvement	
Diameter of vessel involved (mm)	Integer (mm)	Leave blank if 'Macroscopic involvement of vessels = No macroscopic involvement'
Liver capsule intact and smooth	Single selection value list: • Yes • No	
Invasion of adherent organ or adjacent organ	Single selection value list: • Yes • No	

If yes, which organ	Free text	Leave blank if 'Invasion of adherent organ or adjacent organ = No'
Lymph node(s) received	Single selection value list: • Yes • No	
Histology		
Tumour type	Single selection value list: • Cholangiocarcinoma NOS • Subtype large duct • Small duct • Combined HCC/CC • Cholangiolocellular • Other histological subtype (specify)	If 'other' selected, specify
If other specify	Free text	Enter value if 'Tumour type = Other histological subtype'
Tumour grade/differentiation	Single selection value list: • Well • Moderate • Poor	
Tumour cells present at resection margin	Single selection value list: • Yes • No	
If no, distance to resection margin	Single selection value list: • <1 mm • 1–10 mm • >10 mm	
State distance	Number (mm)	If 'Distance to resection margin = 1–10 mm, state distance in mm'
Macroscopic vascular invasion confirmed	Single selection value list: • Yes • No	
Microscopic vascular invasion identified	Single selection value list: • Present • Not identified	
Perineural invasion identified	Single selection value list: • Present • Not identified	
Best block of tumour for molecular testing	Free text	

Background liver	Single selection value list • Insufficient for assessment	
Fibrosis	Single selection value list • None present If present: Single selection value list • Portal/periportal • Sinusoidal/pericellular • Both • Bridging • Bridging with nodules • Complete cirrhosis	
Aetiology	Multiple selection value list: • Hepatitis B • Hepatitis C • Autoimmune hepatitis • Haemochromatosis • Alcohol • NAFLD • Not known • Other	Free text – if 'Other' is selected
Other	Free text	Please specify if 'Aetiology = Other'
Number of lymph nodes examined	Integer	
Number of lymph nodes with metastases	Integer	
Comments/additional information	Free text	
Pathological staging pT	Free text pTis Carcinoma in situ pT1a Solitary tumour ≤50 mm without vascular invasion pT1b Solitary tumour >50 mm without vascular invasion pT2 Solitary with intrahepatic vascular invasion **or** multiple tumours, with or without vascular invasion pT3 Tumour perforating the visceral peritoneum. pT4 Tumour involves local extra hepatic structures by direct invasion	Enter values for pT and pN
Pathological staging pN	pN0 No lymph node metastases	

	pN1 Lymph node metastases	
SNOMED-CT codes	May have multiple codes. Look up from SNOMED tables.	
ICD 11 code:	**Intrahepatic cholangiocarcinoma: 2C12.10**	

Appendix K Reporting proforma for liver resection: perihilar cholangiocarcinoma in list format

Element name	Values	Implementation notes
Gross description		
Type of specimen	Single selection value list: • Segmental resection – List segments (if known) • Non-anatomic (wedge) resection – Site/segment of origin	Specify 'List segments (if known) if segmental resection is selected. Specify 'Site/segment of origin' if non-anatomic (wedge resection is selected)
Specimen weight	Integer	State specimen weight in grams (g)
For segmental resections, specimen dimensions:	• Integer (antero-posterior (mm)) • Integer (medio-lateral (mm)) • Integer (supero-inferior (mm))	
Ducts involved:	Multiple selection value list: • Right main duct • Left main duct • Confluence of ducts • Common hepatic duct	
Direct invasion of liver	Single selection value list: • Yes • No	
Maximum tumour size	Integer (mm)	
Distance from nearest hepatic resection margin	Integer (mm)	
Distance from bile duct transection margin	Integer (mm)	
Hepatic metastases present	Single selection value list: • Yes • No	
Liver capsule intact and smooth	Single selection value list: • Yes • No	
Invasion of adherent or adjacent organ	Single selection value list: • Yes • No	
If yes, which organ	Free text	Please specify if 'Invasion of adherent or adjacent organ = Yes'
Lymph node (s) received	Single selection value list:	

	• Yes • No	
Portal vein or first left or right branch included?	Single selection value list: • Yes • No	
Histology		
Tumour type	Single selection value list: • Cholangiocarcinoma NOS • Arising from IPNB • Arising from mucinous cystic neoplasm • Other histological type	
Specify	Free text	Enter value if 'Tumour type = Other histological type'
Tumour grade/differentiation (adenocarcinoma):	Single selection value list: • Well • Moderate • Poor	
Tumour cells present at hepatic resection margin	Single selection value list: • Yes • No	
Tumour cells present at main duct transection margin	Single selection value list: • Yes • No	
Tumour cells present at circumferential dissection or peritoneal margin	Single selection value list: • Yes • No • Not applicable	
If margin is clear: distance to closest resection margin:	Single selection value list: • <1 mm • 1–10 mm (if yes, state distance (mm) • >10 mm	Specify in millimetres (mm)
State distance	Number (mm)	State distance if 'distance to resection margin = 1–10 mm'
Indicate closest margin:	Single selection value list: • Hepatic • Main duct • Circumferential dissection or peritoneal	
Main portal vein/hepatic artery invasion of wall	Single selection value list: • Yes	If 'Yes', specify

	• No	
If yes, which vessel?	Free text	Specify if 'Main portal vein/hepatic artery invasion of wall = Yes'
Microscopic vascular invasion identified	Single selection value list • Present • Not identified	
Perineural invasion identified	Single selection value list • Present • Not identified	
Best block of tumour for molecular testing	Free text	
Background liver disease	Single selection value list • None • Primary sclerosing cholangitis • Other (specify)	If other is selected, specify
Other	Free text	Specify if 'Background liver disease = Other'
Number of regional lymph nodes examined:	Integer	
Number of regional lymph nodes with metastases:	Integer	
Comments/additional information	Free text	
Pathological staging pT	Free text (Enter values for pT, pN) pTis Carcinoma in situ, high grade BilIN pT1 Tumour confined to bile duct with extension up to the muscle layer or fibrous tissue pT2a Tumour invades beyond wall of the bile duct into surrounding adipose tissue pT2b Tumour invades adjacent hepatic parenchyma pT3 Tumour invades unilateral branches of portal vein or hepatic artery pT4 Tumour invades the main portal vein or its branches bilaterally **or** the common hepatic artery **or** unilateral second order biliary radicals with contralateral portal vein or hepatic artery involvement.	

	pN0 No regional lymph node metastases pN1 Metastasis to 1–3 regional nodes pN2 Metastasis to 4 or more regional nodes	
Pathological staging pN	pN0 No regional lymph node metastases pN1 Metastasis to 1–3 regional nodes pN2 Metastasis to 4 or more regional nodes	Record non-regional lymph node metastases as pM1
SNOMED-CT codes	May have multiple codes. Look up from SNOMED tables.	
ICD 11 code:	**Perihilar cholangiocarcinoma: 2C18.0**	

Appendix L Reporting proforma for liver resection: gallbladder cancer in list format

Element name	Values	Implementation notes
Gross description		
Type of specimen	Single selection value list: • Cholecystectomy (cancer not previously suspected) • En bloc gall bladder and liver • List liver segments resected • Staged liver resection • List liver segments resected • Previous gall bladder report reviewed • Slides reviewed • pT stage • Previous report not available	Specify if 'List liver segments resected', and/or 'pT stage' is selected
Gall bladder		
Dimensions:	• Integer (length (mm)) • Integer (width (mm)) • Integer (maximum wall thickness (mm))	
Mucosal aspect of tumour:	Single selection value list: • Papillary/exophytic • Plaque/infiltrative	
Location of tumour:	Single selection value list: • Peritoneal side • Hepatic side • Both or not assessable	
Maximum dimension of tumour	Size in mm	
Gall stones present?	Single selection value list: • Yes • No	
Length of cystic duct	Integer (mm)	
Other bile ducts resected?	Single selection value list: • Yes • No	
Liver resections		
Specimen weight	Integer (g)	
Specimen dimensions:	• Integer (antero-posterior (mm)) • Integer (medio-lateral (mm)) • Integer (supero-inferior (mm))	
Direct invasion of liver	Single selection value list:	

	• Yes • No	
If yes: depth of liver invasion	Integer (mm)	Only applicable if 'Direct invasion of liver = yes'
Distance from nearest hepatic resection margin	Integer (mm)	
Hepatic metastases present	Single selection value list: • Yes • No	
Invasion of adherent or adjacent organ	Single selection value list: • Yes • No	
If yes, which organ	Free text	Specify if 'Invasion of adherent or adjacent organ = Yes'
Lymph node(s) received	Single selection value list: • Yes • No	
Includes non-regional lymph nodes?	Single selection value list: • Yes • No	Leave blank if 'Lymph node(s) received = No'
Histology		
Tumour grade/differentiation (adenocarcinoma):	Single selection value list • Well • Moderate • Poor • Other histological type (specify)	
Other histological type (specify)	Free text	If 'Other histological type' selected', specify
Depth of invasion		
	Single selection value list • Lamina propria • Muscular layer • Beyond muscle • Perforates serosa • Invades liver	If 'Invades other organs' 'Yes' is selected, specify
Invades other organs	Single selection value list: • Yes • No	
If yes, which	Free text	Specify if 'Invades other organs = Yes'
Cystic duct	Single selection value list • Involved • BillN	

	• No BillN	
Other ducts resected	Single selection value list • Yes • No	If 'Yes' applicable, select additional value
Involved by dysplasia/BillN	Single selection value list • Yes • No	Leave blank if 'Other ducts resected = No'
Tumour cells present at any resection margin:	Single selection value list • Yes • No	
Indicate which margin:	Single selection value list • Hepatic • Bile duct • Other	Leave blank if 'Tumour cells present at any resection margin = No'
If other, please state which	Free text	Specify if 'Indicate which margin = Other'
If margins are clear: distance to resection margin	Single selection value list • <1 mm • 1–10 mm (state distance in mm) • >10 mm	
State distance	Number (mm)	If '1–10 mm' is selected, specify in millimetres (mm)
Microscopic vascular invasion identified	Single selection value list • Present • Not identified	
Perineural invasion identified	Single selection value list • Present • Not identified	
Best block of tumour for molecular testing:	Free text	
Number of lymph nodes examined	Integer	
Number of lymph nodes with metastases	Integer	
Comments/additional information	Free text	
Pathological staging: pT	Free text (Enter values for pT, pN) pTis Carcinoma in situ, high grade BiliN pT1a Tumour invades lamina propria pT1b Tumour invades muscular layer pT2a Tumour invades perimuscular connective tissue on the	

	peritoneal side with no extension to the serosa pT2b Tumour invades perimuscular connective tissue on the hepatic side with no extension into the liver pT3 Tumour 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 extra-hepatic bile ducts. pT4 Tumour invades the main portal vein or hepatic artery or invades 2 or more extrahepatic organs or structures	
Pathological staging: pT	pN0 No regional lymph node metastases pN1 Metastasis to 1−3 regional lymph node pN2 metastasis to 4 or more regional nodes.	(Record non-regional lymph node metastases as pM1)
SNOMED-CT codes	May have multiple codes. Look up from SNOMED tables.	

Appendix M Reporting proforma for liver resection: colorectal carcinoma metastasis in list format

Element name	Values	Implementation notes
Gross description		
Number of specimens received	Integer	
Type of specimen		
Type of specimen	Multiple selection value list: • Segmental resection – List segments (if known) • Non-anatomic (wedge) resection – Site/segment of origin: – List if several	Specify 'List segments (if known) if segmental resection is selected. Specify 'Site/segment of origin' if non-anatomic (wedge resection is selected),
Specimen weight	Integer	State specimen weight in grams (g)
For segmental resections, specimen dimensions:	• Integer (antero-posterior (mm)) • Integer (medio-lateral (mm)) • Integer (supero-inferior (mm))	
Number of tumours present	Free text	
Satellite tumour(s) present:	Single selection value list • Yes • No	
List maximum diameters for up to four largest tumours	Integer (mm)	Up to four values
Distance from nearest hepatic resection margin of nearest tumour	Integer (mm)	
Liver capsule intact and smooth	Single selection value list • Yes • No	
Invasion of adherent or adjacent organ	Single selection value list • Yes • No	
If yes, which organ	Free text	Please specify if 'Invasion of adherent or adjacent organ = Yes'
Lymph node(s) received	Single selection value list • Yes	

	• No	
Histology		
Tumour grade/differentiation	Single selection value list • Well/moderate • Poor	
Tumour cells present at resection margin:	Single selection value list • Yes • No	
If no, distance to resection margin:	Single selection value list • <1 mm • 1–10 mm (state distance in mm) • >10 mm	
State distance	Number (mm)	Specify if distance to resection margin 1–10 mm
Microscopic vascular invasion identified	Single selection value list • Present • Not identified	
Neoadjuvant therapy given	Single selection value list • Yes • No • Not known	
If yes:	Single selection value list: • No residual tumour cells • Rare small groups of viable cells • Residual cancer cells with evident regression • No evident tumour regression	Specify if “Neoadjuvant therapy given = Yes”
Best block of tumour for molecular testing	Free text	
Background liver	Single selection value list • Normal • Steatosis • Chronic liver disease with fibrosis • Sinusoidal obstruction syndrome	
Comments/additional information	Free text	
SNOMED-CT codes	May have multiple codes. Look up from SNOMED tables.	

Appendix N Morphological subtypes of hepatocellular carcinoma – relative frequency and key histological features[3]

For illustrative photographs of subtypes, please see WHO Classification of Tumours.[3]

HCC subtype	Relative frequency	Key morphological features
Steatohepatitic	5–20%	>50% tumour shows histological features of steatohepatitis with steatotic and ballooned neoplastic cells, Mallory–Denk bodies, intra-tumoral inflammation and pericellular fibrosis
Clear cell	3–7%	>80% of the tumour with clear cell morphology due to intracytoplasmic glycogen; may have steatotic neoplastic cells
Macrotrabecular massive	5%	>50% of the tumour with macrotrabecular growth pattern; trabeculae ≥10 cell-thick
Scirrhous	4%	>50% of the tumour shows dense fibrosis
Chromophobe	3%	Neoplastic cells have light or clear cytoplasm; generally mild nuclear pleomorphism with focal areas of marked nuclear atypia; scattered microscopic pseudocysts
Fibrolamellar	1%	Large eosinophilic neoplastic cells with large vesicular nuclei and prominent nucleoli; usually numerous intracytoplasmic pale and/or hyaline bodies; neoplastic cells positive for K7 and CD68; dense lamellar intratumoural fibrosis; non-cirrhotic background liver
Neutrophil-rich	<1%	Numerous neutrophils diffusely infiltrating within the tumour; may have focal sarcomatoid morphology
Lymphocyte-rich	<1%	Dense intratumoural lymphoid cell infiltrates; lymphocytes outnumber neoplastic cells in most areas

Appendix O Immunohistochemical markers helpful in distinguishing well differentiated hepatocellular carcinoma from dysplastic nodules in cirrhotic liver[20]

Antibody	Staining pattern	Differential HCC versus dysplastic nodule	Normal/other
K7/K19	Cytoplasmic/ membranous	Highlights ductular reaction in portal tracts and fibrous septa surrounding dysplastic nodules. Absent around tumour cells in stromal invasion of portal tracts and/or fibrous septa in early HCC	Highlights preserved ductular reaction in pseudo-invasion
Glypican 3	Cytoplasmic, membranous, canalicular	Positive in HCC, more often in less differentiated, <10% HGDN	Regenerating hepatocytes, melanocytic lesions
HSP70	Nucleus and cytoplasm	Positive in HCC, more often in well differentiated, <10% HGDN	Positive hepatobiliary cells of ductular reaction
Glutamine synthetase (GS)	Diffuse strong cytoplasmic	Positive in HCC, more often in less well differentiated, 14% HGDN	Positive in perivenular hepatocytes, map-like in FNH, diffuse positive in beta-catenin activated sub-type of HCA
Combination of GS, glypican 3, and HSP70	Any two of these positive – sensitivity 72%, specificity 100% for HCC (30,51)		
CD34	Sinusoidal endothelium	Progressive increase through LGDN, HGDN, HCC	Periportal/periseptal sinusoids May also be positive in benign arterialised lesions such as FNH and HCA
a-fetoprotein (AFP)	Cytoplasmic	Serum marker, patchy in well-differentiated HCC, <50% poorly differentiated HCC are positive	Negative in normal Metastatic hepatoid carcinomas may be positive

Abbreviations

LGDN = low grade dysplastic nodule
HGDN = high grade dysplastic nodule
HCC = hepatocellular carcinoma
HCA = hepatocellular adenoma
FNH = focal nodular hyperplasia

Appendix P Benign focal hepatocellular lesions in non-cirrhotic liver: morphology and immunophenotype[39–42,45–49]

Lesion	Clinicopathological features	Immunopheno-type	Genetic alteration
Focal nodular hyperplasia (FNH)	Central scar with abnormal vessels, fibrovascular septa with ductular reaction and inflammation	'Map-like' staining pattern for glutamine synthetase (GS)	Polyclonal
Inflammatory hepatocellular adenoma (HCA) (I-HCA)	Sinusoidal dilatation away from arterioles (telangiectasia) Ductular reaction (FNH-like) Inflammation Mild steatosis may also be present Some associated with metabolic syndrome/ alcohol excess and steatosis in background liver; can be multiple	Serum amyloid A C-reactive protein (both of these are occasionally diffusely positive in non-lesional liver, in which case they are non-informative within the lesion)	Oncogene-induced inflammation JAK/STAT pathway (IL-6/STAT3 activation) Up to 10–20% may also be beta-catenin mutated
HNF 1a inactivated (H-HCA)	Marked steatosis (rare in men; commonest type in women – can be multiple)	Lack of normal cytoplasmic staining for liver fatty acid binding protein (LFABP)	HNF1a inactivation
Beta catenin mutated (b-HCA)	May show cytological atypia, pseudoglandular formation Increased risk of malignant transformation (up to 40%)	Diffuse staining for GS Beta-catenin nuclear expression (usually sparse cells only)	Wnt/beta-catenin Further characterised by exon 3 or 7/8 mutations. Increased risk of malignant transformation confined to exon 3 mutated lesions
Sonic hedgehog HCA (shHCA)	High risk of haemorrhage	Diffuse expression of argininosuccinate synthase 1 (ASS1)	*INHBE-GLI1* fusion
Unclassified	Usually solitary	No abnormalities	

Abbreviations

FNH Focal nodular hyperplasia
LFABP Liver fatty acid binding protein
HNF-1a Hepatocyte nuclear factor 1 alpha
JAK/STAT Janus kinase – signal transducer and activator of transcription
IL-6/STAT3 Interleukin-6/signal transducer and activator of transcription

Appendix Q Immunohistochemistry for the differential diagnosis of liver biopsies containing tumour

Tumours that resemble hepatocellular carcinoma (HCC): support HCC

This table provides more detail on the identification of HCC than is included in the cancer of unknown primary dataset.[140]

Antigen	% in HCC	Comments
HSA/HepPar1	86	Well/moderately differentiated, rarer in metastasis. Granular staining pattern. Can be seen with hepatoid adenocarcinoma metastasis
Arginase-1	>85%	More sensitive than HepPar1, especially for poorly differentiated HCC[140]
Canalicular antigen expression	60−80	Demonstration of biliary canaliculi between tumour cells with antibodies such as polyclonal CEA, CD10, CD13 and BSEP, as available. Diffuse staining is non-specific
AFP	37	Poorly differentiated, usually also seropositive and very focal. Complements HepPar and canalicular stains, which tend to stain better differentiated HCC
pCEA	75	Canalicular pattern is specific for HCC. Cytoplasmic staining is non-specific
CD10	61	Canalicular pattern is clearer than with pCEA. It is less sensitive than CD13
CAM5.2	90	If K7 negative, suggests HCC owing to the presence of K8/18 in HCC
Glutamine synthetase	50-69%	+ve if >50% tumour cells with strong immunoreactivity[35,38,141]
Glypican 3	>70	Staining may be weak/focal in well-differentiated HCC. It is not a hepatocyte-specific marker, more an oncofoetal antigen, so it can be seen with a number of non-HCC malignancies
Note: PGP 9.5 – 87% HCC positive; 9% synaptophysin positive, CD56 14%. TTF1 – 93% HCC cytoplasmic positive, 0% nuclear positive; stains normal liver but depends on antibody clone (hepatocyte staining with clone 8G7/G3/130).[142] K19 stains a minority of HCC and is associated with a poorer prognosis. Glutamine synthetase diffusely stains some HCC but also stains beta-catenin activated hepatocellular adenoma. Glypican 3 – 14% of gastrointestinal and pancreatic metastatic liver carcinomas positive[143] HCC: Hepatocellular carcinoma		

Tumours that resemble HCC: support metastasis

Antibody	% in HCC	Comments
mCEA	3	Positive in adenocarcinoma including cholangiocarcinoma
S100, HM45	0	Differential versus melanoma
Vimentin, RCC	7, 0	Differential versus renal cell carcinomas
Synaptophysin, CD56	9, 14	Differential versus neuroendocrine carcinoma
K7, K20	10–34, 9	Metastatic adenocarcinoma Useful in conjunction with CAM5 2, see above K7 +ve in most fibrolamellar carcinomas
CDX2	5	Positivity favours GI tract origin[144]
K19	<10	Differential versus cholangiocarcinoma Positivity is poor prognostic marker in HCC

Appendix R Immunohistochemical investigations for liver biopsies containing metastatic tumour: tumours with morphological features of adenocarcinoma

The table below is transcribed from the RCPath *Dataset for histopathological reporting of cancer of unknown primary (CUP) and malignancy of unknown primary origin (MUO)*.[124] Permission is only granted for the publication of this specific document and any new document or review document will require a reapplication for permission.

Table 6: IHC markers commonly used for prediction of primary site in adenocarcinomas

	PSA, PAP or NKX3.1	TTF1 or Napsin A	GCDFP-15, mamma-globin or GATA3	WT1 or PAX8	ER	CA125	Meso-thelin	CK 7	CDX2 and/or CK20
Prostate	+	-	-	-	-	-	-	-	-
Lung	-	+	-	-	-	-/+	-/+	+	-
Breast	-	-	+/-	-	+/-	-/+	-	+	-
Ovary serous	-	-	-	+	+/-	+	+	+	-
Ovary mucinous	-	-	-	-	-/+	-/+	-/+	-/+	-/+
Pancreas	-	-	-	-	-	+/-	+/-	+	-/+
Stomach	-	-	-	-	-	-	-/+	+/-	-/+
Colon	-	-	-	-	-	-	-	-/+	+

+ = 90% or more +/- = 50–90% -/+ = 10–50% - = 10% or less

Please refer to the above dataset for other guidance on the investigation of cancer of unknown primary origin**.**

Appendix S Other special stains that may be useful for the differential diagnosis of liver biopsies containing tumour

Stain	Comment
Periodic acid Schiff (PAS)	Glycogen commonly present in hepatocellular neoplasms, rarely in adenocarcinoma
PAS-diastase (PAS-D)	Presence of luminal PAS-D positive material and/or cytoplasmic mucin vacuoles favours a diagnosis of adenocarcinoma. HCC may contain PAS-D positive intracytoplasmic globules (e.g. α-1-antitrypsin) or PAS-D positive luminal material in pseudoglandular/adenoid pattern
Perls	Bile retains green colour and may be more easily recognised than in an H&E-stained section. Presence of intracellular or canalicular bile pigment favours diagnosis of hepatocellular neoplasm
Reticulin	Normal reticulin fibre content retained in dysplastic nodules and benign hepatocellular lesions (e.g. HCA, FNH) Reticulin fibres usually reduced or absent in HCC (but may be focally retained in some well differentiated HCCs.) Reticulin fibres may be reduced in areas of steatosis, including steatotic HCA

Note: Adenocarcinoma includes CC as well as metastatic adenocarcinoma.

Appendix T Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix U AGREE guideline monitoring sheet

The Cancer Datasets of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this Dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	3–10
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	3–10
16 The different options for management of the condition or health issue are clearly presented	3–10
17 Key recommendations are easily identifiable	3–10
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword