



The Royal College of Pathologists

Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathology reporting of liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic carcinoma (2nd edition)

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NICE has accredited the process used by The Royal College of Pathologists to produce its Cancer Datasets and Tissue Pathways guidance. Accreditation is valid for 5 years from July 2012. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The cancer datasets published by The Royal College of Pathologists are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the document was prepared. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Approval of the dataset will be sought from the British Association for the Study of the Liver (BASL), the Pathology and Liver sections of the British Society of Gastroenterology (BSG) the Association of Upper Gastrointestinal Surgeons (AUGIS), and panels of specialised and general histopathologists acting on behalf of the College.

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 second edition of this dataset (2012) incorporates the changes to the classification of liver and bile duct cancers introduced in TNM 7th edition, 2009.¹ The section on intrahepatic cholangiocarcinoma is new in this version of the TNM classification. Gall bladder cancer was not previously covered by a College dataset and, since surgery for cancers of stage 1b (into the muscle wall) and above may require liver resection, they are now included here. Changes to the TNM staging of hepatocellular carcinoma and perihilar cholangiocarcinoma are also included. There is now harmonisation of cancer staging between TNM and WHO classification of tumours of the digestive system 4th edition 2010² and the American Joint Committee on Cancer 7th edition of the *Cancer Staging Manual*, 2010.³

The dataset has been reviewed by the Working Group for Cancer Services and was placed on the College website for consultation with the membership from 3 April to 1 May 2012. All comments received from the Working Group and membership have been addressed by the author to the satisfaction of the Chair of the Working Group and the Director of Publications.

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 Director of Professional Standards and are available on request.

2 Introduction

The primary purpose of this document is twofold:

- a. to define the set of data necessary for the uniform recording and staging of the core pathological features in liver cancer resection specimens
- b. 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. This will be of particular importance when the dataset is incorporated into the national cancer outcomes and services dataset (COSD).

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

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

- a. to provide prognostic information to clinicians and patients
- b. to select potential patients for future trials of adjuvant therapy
- c. to collect accurate data for cancer registration and epidemiology
- d. to allow correlation of resection specimens with preoperative imaging
- e. 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. Brief guidelines for reporting needle biopsy specimens of hepatic neoplasms are also included.

This second edition has been written shortly after the publication of the 4th edition of the WHO classification of tumours of the digestive system, which is based on a comprehensive recent literature review.² The staging system used is TNM7 (2009)/AJCC7 (2010).

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.

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 cancer (hepatocellular carcinoma [HCC] and intrahepatic or perihilar cholangiocarcinoma [CC]) and metastatic cancer (usually colorectal cancer liver metastasis [CRCLM]) is performed in a limited number of specialist centres in the UK. Patients with gall bladder cancer discovered following routine cholecystectomy should be referred to a specialist centre for consideration of further surgery. These guidelines cover all of these scenarios. They are not specifically intended for other types of tumour that may be resected, such as focal nodular hyperplasia, adenoma, primary sarcoma, 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.^{4,5}

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. TNM7, published in 2009, introduced separate TNM classifications for intrahepatic cholangiocarcinoma (previously classified in the same way as HCC) and perihilar cholangiocarcinoma. These are adopted in this revision of the RCPATH dataset. They largely match the AJCC staging classification, in which there is a helpful, more detailed description of the pathological staging criteria. Where these are discrepant (pN criteria for gall bladder and perihilar cancers) the TNM criteria are used. Perihilar cholangiocarcinomas 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.⁶

Core data items of tumour size, number, surgical margin, differentiation, vascular 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, gall bladder and CRCLM, this dataset is generic to all these scenarios in sections 3–8. Specific aspects for each tumour type are covered in detail in section 6, and there are five separate reporting proformas (HCC, intrahepatic CC, perihilar CC, gall bladder and CRCLM) in Appendix C, which share common macroscopic items but reflect the different microscopic items required for staging. Relevant references are included (hepatocellular carcinoma;^{7-23,24,25} cholangiocarcinoma;²⁶⁻³⁹ gall bladder cancer⁴⁰⁻⁴⁹ and metastatic colorectal carcinoma;⁵⁰⁻⁶⁰). See the WHO classification for a comprehensive recent reference list.²

3 Clinical information required on the specimen request form

The following information should be provided:

- 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 (R2 resection = macroscopic residual tumour, requires notification by the surgeon)
- details of any previous procedures or treatment such as radiofrequency ablation or trans-arterial chemo-embolisation (TACE), 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 fibrosis/cirrhosis in hepatocellular carcinoma; evidence of primary sclerosing cholangitis (PSC) in cholangiocarcinoma
- site(s) of any lymph nodes excised – in continuity with main specimen or submitted separately
- for patients with previous surgery (e.g. gall bladder bed resection following previously unsuspected carcinoma in cholecystectomy specimen), details of the previous surgical procedure and preferably a copy of the histology report.

For cholangiocarcinoma 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.

4 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 resection⁵⁹ 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.

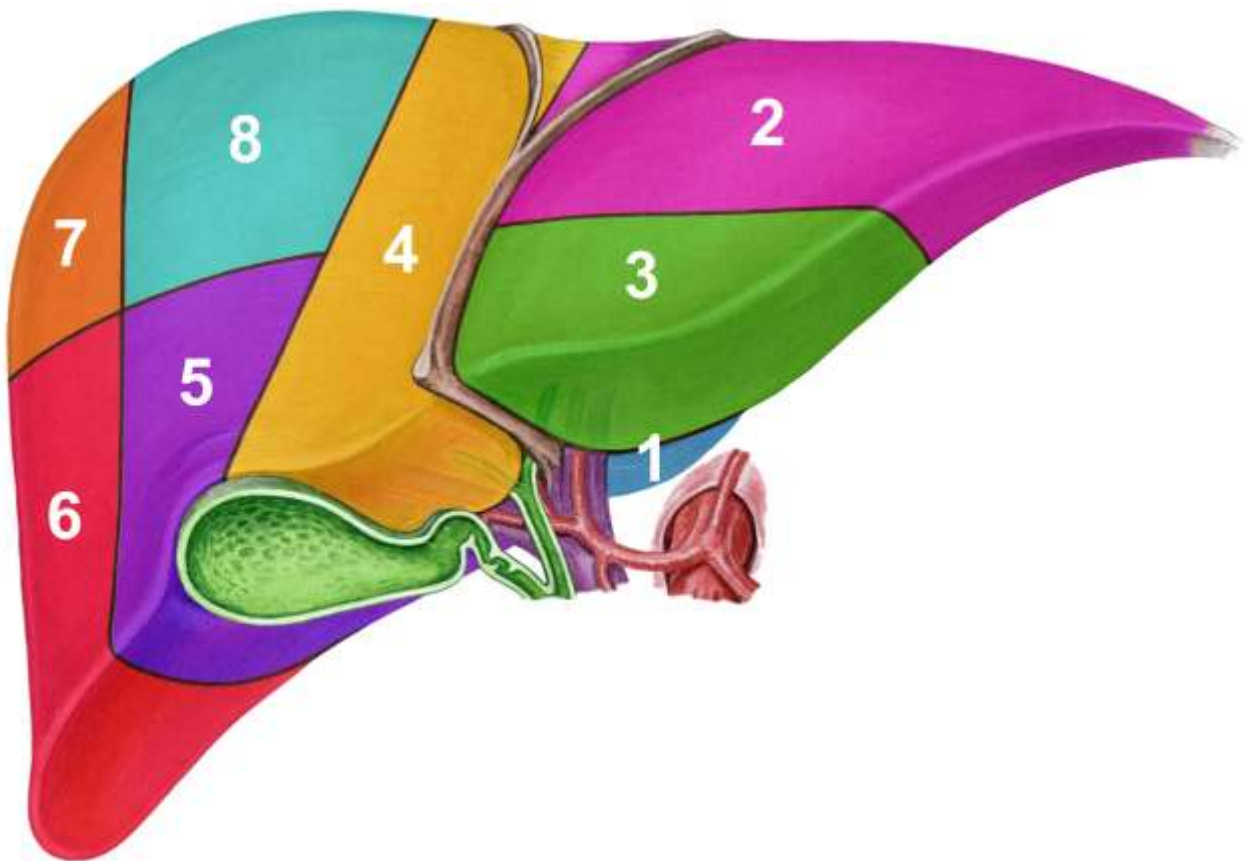


Figure 1: Segmentectomy specimens⁶¹ (reproduced with permission)

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

For perihilar cholangiocarcinomas (cholangiocarcinoma proximal to the junction of the cystic and common hepatic duct, see section 5.2), a length of extrahepatic duct will often 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 gall bladder 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 gall bladder bed is indicated for stage 1b cancers and above.⁴³ Biliary tree resection is undertaken if the cystic duct resection margin is involved. The gall bladder bed lies between segments 4b and 5, and either a limited resection of this area or a more radical resection may be performed with the aim of resecting any residual tumour and local lymph nodes.

5 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 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).
- 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.
- Gall bladder bed where there is adjacent intrahepatic tumour.
- Any site macroscopically suggestive of vascular or bile duct invasion.
- 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 hepatocellular carcinoma, 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 differentiation is related to prognosis (Evidence

level C).⁷⁻¹⁰ Deposits of metastatic colorectal cancer are often multiple, and do not require separate datasets for each deposit. A minimum of one block per tumour deposit is sufficient, although more should 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 cholangiocarcinoma (CC) specimens see section 5.2 below
- gall bladder – optional when this is macroscopically normal; for gall bladder cancer specimens see section 5.3 below
- the site of lymph nodes should be specified if known (hilar, hepatic artery, portal vein, cystic duct). More distant nodes (coeliac axis, periduodenal, periaortic) may be submitted separately by the surgeon. Large 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 cholangiocarcinoma.

5.1 Hepatectomy and segmentectomy specimens for intrahepatic tumours

(includes complete hepatectomy at transplant, hepatocellular carcinoma, intrahepatic cholangiocarcinoma and metastatic tumours)

Record the segments resected and the specimen weight after opening the gall bladder and rinsing out the bile. The specimen dimensions (antero-posterior, medio-lateral and supero-inferior) should also be measured, particularly in cases where much of the specimen is occupied by tumour. When included with the specimen, record the length of extrahepatic duct, number and site of lymph nodes, size and appearance of gall bladder

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 6.3.1 c) should be noted. The appearance of the background liver (normal, bile-stained, fibrotic/cirrhotic) should be

recorded. It is good practice to keep a photographic record of the macroscopic features of the specimen for use during 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.

5.2 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,²⁶ which was originally described as a small tumour at the confluence of right and left duct in patients presenting with obstructive jaundice, and tending to cause death by liver failure rather than dissemination. The terms 'perihilar' and 'hilar' are used variably in the literature, and for the purposes of cancer reporting, this dataset follows TNM in using 'perihilar' throughout.

The liver resection is handled as in section 5.1. 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 (Klatskin tumours), the distal 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 resection 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 opening³⁹ 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. Resection margin involvement may be at the proximal or distal duct resection 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 should be sought. This represents the peritoneal surface anteriorly and to the right, and a surgical plane posteriorly and to the left.

5.3 Gall bladder

Gall bladder cancer may be discovered during histopathological examination of routine cholecystectomy specimens. However, specimens from a previously known or suspected cancer may be resected *en bloc* with a portion of liver from the gall bladder bed, or submitted as a more extensive resection. The principles are the same for dissection of a gall bladder cancer that is resected in continuity with the contiguous liver.

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

Gall bladders should be opened longitudinally from the serosal surface to avoid disruption of the cystic duct margin and gall bladder bed margin in cholecystectomy specimens. For cholecystectomy specimens, ink the gall bladder 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 gall bladder, their macroscopic appearance (polypoid, ulcerating, plaque-like/infiltrative), whether on the free peritoneal or the hepatic side of the gall bladder, and depth of involvement including any adherent tissues.

For a staged liver resection following cholecystectomy with incidental carcinoma, the site of the gall bladder bed should be inked. Unless there is obvious extensive tumour, it is recommended that the entire gall bladder 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 cholangiocarcinoma.

5.4 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 three or more lymph nodes for primary intrahepatic and gall bladder cancers, and 15 lymph nodes for perihilar cholangiocarcinomas.¹ Regional lymph nodes are those in the hepaticoduodenal ligament: hilar, cystic duct, pericholedochal, hepatic artery, portal vein (see also section 6.3.2 b) for perihilar CC. More distant nodes, e.g. peri-aortic, coeliac, are occasionally resected and involvement of such nodes is classified as distant metastasis (M1); there is not a pN2 category in TNM7. Resections for metastatic colorectal cancer may also include lymph nodes if nodal metastasis is suspected at surgery.

6 Core data items

6.1 Clinical data

The following should be supplied:

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

6.2 Pathological data

The core data items are all those that are necessary for complete classification of the primary tumour stage according to TNM7, 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 6.3.

6.2.1 Macroscopic

This section is common to all three intrahepatic tumour dataset proformas; it is modified for perihilar CC and gall bladder 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 number and size
- presence of satellite lesions (regarded as multiple tumours for TNM staging)
- 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 cholangiocarcinoma: describe attached extrahepatic bile ducts, including length and site of any macroscopic abnormality
- for gall bladder 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.

6.2.2 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 6.3.

- Tumour type.
- Tumour differentiation.
- Minimum distance to resection margin (hepatic, and where appropriate bile duct or vascular) measured microscopically when less than 5 mm. Microscopic involvement (R1) is generally defined as a clearance of <1 mm.
- Invasion through liver capsule (Glisson's capsule).
- Vascular invasion including confirmation of macroscopic vessel invasion.
- Perineural invasion (cholangiocarcinoma).
- Effects of ablative or neoadjuvant therapy on tumour (if applicable).
- Background liver – presence and stage of fibrosis, and other chronic liver disease (see section 6.3.1 d below).
- Lymph node involvement (where appropriate); number of nodes with metastasis.

6.3 Specific information for individual tumours

6.3.1 HEPATOCELLULAR CARCINOMA

a) Tumour classification, staging and grading

Staging depends on the maximum size (\leq or $>$ 50 mm), number of tumours (single or multiple) and venous invasion. A solitary tumour of any size without vascular invasion is staged as pT1 and with vascular invasion (for definition see below) as stage pT2. Multiple tumours where none is greater than 50 mm diameter are also staged as pT2. Whilst 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 TNM7, stage pT3 is divided into two categories. For multifocal HCC where any individual lesion is more than 50 mm, the stage is pT3a. Stage pT3b is defined as any HCC where there is 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).

Tumour grade is also related to prognosis⁷⁻¹⁵ (Evidence level C). Grading has conventionally been divided into four categories based on nuclear features according to the 1954 classification of Edmondson and Steiner.¹⁴ This classification is also quoted in standard reference texts.^{4,5} A recent consensus document advocated a three-point grading system (well, moderately or poorly differentiated), with only the worst grade recorded in the final report. This is supported by the prognostic significance being in the separation of well- and poorly differentiated neoplasms.¹⁵ Grade 1 and 2 HCC of Edmondson and Steiner are combined as well-differentiated HCC in the three-point grading system. For practical purposes, well-differentiated HCCs are those where the tumour cells closely resemble hepatocytes such that the differential diagnosis is with dysplastic nodule (in cirrhosis) or adenoma (in non-cirrhotic livers). Poorly differentiated HCC are those where the hepatocellular nature of the tumour is not evident from the morphology.

Hepatocellular carcinomas are frequently heterogeneous and most are predominantly moderately differentiated. They should be graded according to the least differentiated area. Well-differentiated HCC is rarely seen in isolation except in small (<20 mm) tumours. 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 Appendix E1) or the presence of raised serum α fetoprotein (AFP). Rare histological variants of scirrhous, sarcomatoid and undifferentiated HCC are described in the WHO publication, and are associated with a poor prognosis.

The same staging system is used for the rare fibrolamellar type of hepatocellular carcinoma; this arises in young patients without background liver disease.

There is an increasing recognition of a morphological spectrum between HCC and intrahepatic cholangiocarcinoma, possibly reflecting that a significant number of these tumours arise from a common progenitor cell origin.^{16,17} Poorly differentiated HCCs that are CK19 positive but do not have morphological features of cholangiocarcinoma appear to have a poorer prognosis^{15,16} (Evidence level D), but at present are best regarded as hepatocellular carcinoma for staging and treatment purposes. Tumours that show mixed features of hepatocellular and cholangiocarcinoma are staged as for intrahepatic cholangiocarcinoma in TNM7. These include intrahepatic cholangiocarcinomas with 'hepatoid features' (e.g. showing

expression of AFP or hepatocyte specific antigen) and tumours with pure 'intermediate hepatobiliary phenotype' or cholangiolocellular carcinoma.

b) Premalignant changes, including small cell and large cell hepatocyte change

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, and this has been the subject of a recent consensus document.¹⁸ Recognition of early HCC is challenging, and may be aided by immunohistochemistry for HSP70, glypican-3 and glutamine synthetase.¹⁹⁻²¹ 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. Appendices D and E include a table of immunohistochemical markers used in the differential diagnosis of HCC in cirrhotic livers. Immunohistochemistry is also becoming important in the subtyping of liver cell adenomas; this area is outside the scope of the cancer dataset.²²

c) Vascular invasion

Vascular invasion is an important prognostic factor^{12,13} (Evidence level C). 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 (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 pT3b.

It is often difficult to determine whether nodules of hepatocellular carcinoma surrounded by fibrous tissue adjacent to the main tumour represent vascular invasion unless a part of the endothelialised lumen is apparent. Vascular invasion may be suspected where the nodule is within a portal area, at the site appropriate to a portal vein, or by the presence of satellite nodules. These findings should prompt a thorough search for vascular invasion. Diagnosing vascular invasion is subject to observer variation.²³ For the purposes of TNM classification, when the tumour nodule is within a portal area at the site appropriate to a portal vein, 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). Satellite nodules have been shown to be prognostically important following liver resection and liver transplantation for HCC (Evidence level D)^{24,25} and have recently been defined as "microscopic nodules of hepatocellular carcinoma separated from the tumour by an interval of non-tumoural liver parenchyma".²⁴ 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).

d) 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.^{7,8} 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,

haemochromatosis, alcoholic 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 (Evidence level C),⁷ 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.

e) 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 the recent consensus document.¹⁵ 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.¹⁵ Recording an impression of the proportion of the overall tumour that is viable may be helpful to oncologists, although its estimation is subjective.

6.3.2 CHOLANGIOCARCINOMA

In TNM6, the staging of intrahepatic cholangiocarcinoma (ICC) was extrapolated from HCC. Recognition of the increasing evidence of different prognostic factors for ICC resulted in the introduction of a separate category for ICC in TNM7.^{29,30} In TNM7, ICC is staged separately, recognising that its pathological behaviour and prognostic features are distinct from both HCC and perihilar cholangiocarcinoma.

In addition to the location of the CC, the Japanese classification according to the growth pattern into mass-forming, periductal infiltrating and intraductal papillary CC³² has gained international recognition.² In general, mass-forming CC arises peripherally in the liver, and is covered in section 6.3.2 a. The periductal infiltrating pattern is characteristic of perihilar CC, which includes CC arising in right, left and common hepatic ducts.

Intraductal papillary CC is rare in the West, and is the counterpart of intraductal papillary neoplasia in the pancreas.³⁶ It 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. In either case, if there is an invasive CC arising from the cystic lesion, the staging for perihilar cholangiocarcinoma dataset is appropriate.

a) Intrahepatic cholangiocarcinoma

i. Tumour classification, staging and grading

This staging system applies to intrahepatic CC, cholangiolocellular carcinoma and combined hepatocellular and cholangiocarcinoma (mixed hepatocellular/cholangio-cellular carcinoma). Classification of intrahepatic CC including the relationship of intrahepatic CC to HCC with progenitor phenotype, and the significance of the growth patterns of intrahepatic CC (including mass forming, periductal infiltrating, and mixed types) is a currently evolving area. This section of the dataset document should be used for peripheral mass-forming CC.

Intrahepatic CCs form an expansile tumour mass with obvious borders, and usually arise peripherally in the liver. The maximum diameter is readily determined. The size of the tumour

is not a staging criterion since prognosis is independent of size (Evidence level D),²⁹ however, it is important for correlation with preoperative imaging.

Staging depends on the number of tumours (single or multiple) and vascular invasion. Unlike HCC, vascular invasion (any size of vessel, pT2a) is distinguished from multiple tumours (pT2b, with or without vascular invasion). Tumour perforating the visceral peritoneum or direct infiltration of adjacent organs constitutes pT3 disease. The periductal infiltrating pattern, when associated with a tumour mass, indicates late-stage disease with a poorer prognosis and is classified as pT4 in TNM7. If the tumour is entirely of periductal infiltrating pattern, consideration should be given as to whether it arises in a main right or left duct; if so, it should be staged as perihilar CC.

Intrahepatic CC typically has a microacinar glandular pattern with central sclerosis, and 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 contributory.

Most intrahepatic CCs are adenocarcinomas. Rare variants listed in the WHO classification include adenosquamous, squamous, mucinous, signet ring, clear cell, mucoepidermoid, lymphoepithelioma-like (EBV associated) and sarcomatous intrahepatic CCs.

ii. 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.

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

iv. Background liver disease

Intrahepatic CC has an association with cirrhosis of various causes including chronic viral hepatitis,^{37,38} and this is emerging as an important feature in intrahepatic CC.

b) Perihilar cholangiocarcinoma

i. Tumour classification, staging and grading

Cholangiocarcinomas 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, and because of the frequent invasion of adjacent liver are resected with contiguous liver. Distal cholangiocarcinomas are included in the dataset on pancreas, ampulla and extrahepatic bile ducts. Adenocarcinoma arising in the cystic duct is staged as for gall bladder cancer (see section 6.3.3). Because of the complexity and rarity of resection for perihilar CC, central registration with much more detailed surgical and staging data has recently been proposed.⁶

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. Size and 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.

ii. 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 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.³⁷ 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 cholangiocarcinomas have an intrahepatic extension that is measured in slices of the hepatectomy, once the extrahepatic part of the ducts has been dissected.

iii. Microscopic features

Grading of cholangiocarcinomas applies to those with a pure or predominant adenocarcinoma pattern; well-differentiated tumours are relatively common and associated with a favourable prognosis in some series;³¹ perineural infiltration is also common and is a poor prognostic factor.³³ Uncommon variants listed in the WHO classification include intestinal type adenocarcinoma, squamous cell, adenosquamous, clear cell, mucinous, and spindle cell.

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.⁶

iv. Lymph node metastases

Hilar lymph nodes are characteristically large (up to 40 mm) in chronic biliary disease, and node size does not predict metastasis. Cholangiocarcinoma metastases are frequently microscopic and subcapsular, and so unless metastasis is macroscopically visible, the whole of the node(s) should be sliced and embedded. Micrometastasis found only by immunohistochemistry has not been shown to affect prognosis.³⁵

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 nodes along the cystic duct, common bile duct, hepatic artery and portal vein, likely to be included in the main resection specimen. Periaortic, pericaval, superior mesenteric artery, or coeliac artery lymph nodes would normally be submitted as separate specimens; metastases in these nodes are regarded as distant metastases for TNM staging (pM1).

v. 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 without underlying PSC.

vi. Precursor and *in situ* lesions

These lesions should be sought and recorded as non-core items using the new terminology of flat BillN, (biliary intraepithelial neoplasia, previously biliary dysplasia) This classification brings biliary terminology into line with the equivalent pancreatic counterparts.^{2,36}

6.3.3 CANCER OF THE GALL BLADDER

a) Tumour classification and staging

Staging depends on the depth of invasion through the gall bladder 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 without involving any of the following structures: peritoneal surface, adjacent liver, extra-hepatic organ. Involvement of the latter 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.

About 50% of gall bladder cancers are discovered incidentally in cholecystectomy specimens performed routinely for gall stone disease, etc. Macroscopically suspicious gall bladders should be thoroughly sampled, and the discovery of intra-epithelial neoplasia (dysplasia) in routine cholecystectomy specimens is an indication for more extensive sampling to exclude early carcinoma. Patients with incidental gall bladder cancer should be referred to the hepatobiliary cancer centre MDT. The evidence base for selecting patients for further surgery is currently inconclusive and cases should be evaluated on an individual basis.^{43,44} For recent data on the prognosis of early stage gall bladder cancer, see reference 45.

For stage 2 and stage 1b tumours, current surgical practice is to undertake a further surgical resection of the gall bladder bed or more extensive segmental resection, for example of segments 4b and 5 or more, and with resection of the biliary tree if the cystic duct resection margin is involved 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 right trisectionectomy for patients with locally advanced gall bladder cancer on preoperative imaging but without distant metastasis.

Distinction between stage pT1a and more advanced cancer that may require further surgery is therefore of central importance. 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 gall bladder bed. The five-year survival rates of patients with early gall bladder cancer (pT1) is over 85% but patients with Rokitansky-Aschoff sinus involvement had a lower survival rate than those with no involvement (Evidence level D).⁴⁶ Although uncommon, in cases of adenomyomatous hyperplasia, ductal structures may be present in perineural spaces mimicking invasion by tumours.⁴⁷ 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.⁴⁸ For these reasons, gall bladder histology should be reviewed centrally in the context of the hepatobiliary MDT meeting.

Most gall bladder adenocarcinomas are of biliary type. Other less common types include intestinal type, gastric foveolar type, adenosquamous carcinoma, carcinosarcoma, cribriform carcinoma, clear cell adenocarcinoma, mucinous, signet ring cell, squamous cell and undifferentiated carcinomas.²

For staged (further) resection of liver/gall bladder 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.

b) *In situ* and precursor lesions

The finding of precursor lesions should prompt further sampling to exclude associated malignancy. Precursor lesions include polypoid adenomas, flat biliary intra-epithelial neoplasia and intracystic papillary neoplasms. Adenomas are classified into pyloric-gland, intestinal, foveolar and biliary types). BillIN is classified into three grades. BillIN grade 1 and 2 are found in association with chronic cholecystitis, and is of no established clinical significance. If BillIN3 is found, multiple sections should be taken to exclude invasive carcinoma.

Intracystic papillary neoplasia in the gall bladder is the counterpart of intraductal papillary neoplasia in the bile ducts and pancreas.

c) Lymph node metastases

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 nodes along the cystic duct, common bile duct, hepatic artery and portal vein, likely to be included in the main resection specimen.

d) Neuroendocrine tumours of the gall bladder

Neuroendocrine tumours of the gall bladder are rare. They are not included in the dataset for endocrine tumours of the GI tract including pancreas, and there is no separate TNM staging system for them; they should be staged as for other gall bladder cancers. The proportion of small cell carcinomas relative to well-differentiated tumours (carcinoid tumours) is higher than at other sites in the GI tract. Prognosis varies with differentiation, tumour size and stage (Evidence level D).⁴⁹ About 50% of gall bladder carcinoid tumours are confined to the gall bladder at diagnosis. Currently the data items in the gall bladder dataset can be used for gall bladder carcinoid tumours.

6.3.4 METASTATIC CARCINOMA

Most liver resections are performed for metastatic colorectal carcinoma. There are often multiple deposits. Occasionally metastases from other primary sites are resected, and the same principles apply for reporting these.

The report should document the site, size and appearance of each lesion in a way that allows correlation with preoperative imaging. Such metastases represent haematogenous spread in

TNM stage IV, Dukes' stage D colorectal carcinoma. Prognosis is related to both the stage of the primary colorectal carcinoma and to features of the liver resection⁵⁰⁻⁵³ particularly tumour number and clearance at the surgical margin.⁵¹ The observation of microscopic vascular invasion around the tumour is also prognostically relevant in several studies.⁴⁸ Hilar lymph node involvement may also be prognostically important (Evidence level D).⁵⁴

a) Effects of neoadjuvant therapy

Preoperative chemotherapy may result in partial or complete response of the adenocarcinoma. Chemotherapy may have been adjuvant following colectomy for the primary tumour, or neoadjuvant 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.^{55,56} Assessment is equivalent to that of the primary colorectal lesion, and for convenience the same descriptors are used in the dataset. 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.

b) 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 is a risk factor for colorectal cancer 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 in about 50% patients, while irinotecan may contribute to steatohepatitis.⁵⁷⁻⁶⁰

Sinusoidal obstruction syndrome can evolve into nodular regenerative hyperplasia with the potential complication of portal hypertension. A qualitative estimate of the severity of these chemotherapy-related changes can be included,^{57,59} although involvement is often heterogeneous.

7 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. The non-core items are largely specific for tumour type and are considered in more detail in section 9.

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

- WHO subtype of tumour
- immunohistochemistry – includes CK19 for HCC and CK7/20 for metastatic CRC that lacks characteristic morphology
- presence of fibrous pseudocapsule surrounding tumour (HCC and metastatic colorectal carcinoma)
- as appropriate, the presence of premalignant lesions: large or small cell hepatocyte change (dysplasia), dysplastic hepatocyte nodules, or biliary intra-epithelial neoplasia (BillIN/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.

8 Diagnostic coding and staging

The TNM 7 stage for each tumour type covered in this dataset is shown in Appendix A. The TNM subsets can be converted to the International Stage Groupings (TNM 7), 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 T and M codes (Appendix B). The SNOMED P code can be used to indicate surgical procedure according to local practice.

9 Specific aspects of individual tumours not covered elsewhere

The use of ancillary immunohistochemical and histochemical investigations in liver tumour diagnosis is described in Appendices D, E and F:

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

Appendix E: Immunohistochemical markers helpful in the differential diagnosis of liver cancers:

E1: tumours that resemble HCC

E2: tumours with morphological features of adenocarcinoma (from NICE Guideline *Diagnosis and management of metastatic malignant disease of unknown primary origin*, July 2010).

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

10 Reporting frozen sections

Most hepatobiliary specimens for frozen section are required during surgery for perihilar CC and are sent in the following circumstances:

- resection margin of bile duct
- enlarged lymph node, suspected to contain metastasis

- focal subcapsular liver lesion for diagnosis – usually to distinguish metastasis from benign lesions such as bile duct adenoma or von Meyenburg complexes.

Inflammatory conditions including PSC, Mirizzi syndrome (inflammatory mass around gall bladder neck mimicking malignant bile duct stricture) and IgG4 disease may closely mimic perihilar cholangiocarcinoma 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 cholangiocarcinoma, with biopsy of suspicious lymph nodes, peritoneal or subcapsular liver deposits reduces the need for intra-operative diagnosis by frozen section.

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

11 Reporting of needle biopsy specimen

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 guidelines for handling and reporting are therefore also included in the tissue pathway document on liver biopsies.

It should be noted that most hepatobiliary surgeons advise against needle biopsy to confirm a diagnosis of metastatic colorectal carcinoma or hepatocellular carcinoma where future surgical excision may be an option because of the risk of upstaging the disease.⁶² The diagnoses in these cases are made on the basis of imaging and the appropriate clinical setting.

11.1 Specimen submission

The request form should indicate that the biopsy is from a focal lesion and should also include other relevant clinical information such as a previous history of malignant disease or imaging results.

Unlike medical liver biopsies, there is no minimum recommended specimen size. A biopsy containing diagnostic tumour tissue can be regarded as adequate, although small samples may not contain sufficient tissue for full immunohistochemical evaluation.

11.2 Sectioning and staining

Initially one or two shallow levels stained with H&E should be examined. The pathologist can then determine whether tumour is present and what further investigations are required based on the morphology of the tumour in the biopsy and clinical circumstances.

11.3 Further investigations

Discussion with the clinician at an early stage is recommended if the presence of tumour is confirmed 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 clinical management decisions.

Immunohistochemical evaluation is usually required to investigate the nature of the tumour. The selected panel of markers will be tailored for each individual biopsy depending on the tumour morphology any clinically suggested site of origin for metastatic disease, the amount of tissue available in the biopsy, and for the exclusion of potentially treatable disease.

The guidelines from the National Institute for Health and Clinical Excellence (NICE) for investigating patients who present with metastatic carcinoma of unknown primary origin recommend the use of immunohistochemistry to investigate the likely primary site of origin.⁶³ In patients with a biopsy showing a malignancy of unknown origin a simple panel of immunohistochemistry tests is essential to exclude melanoma, lymphoma or sarcoma.

For biopsies that show carcinoma of trabecular or hepatoid pattern in which the morphological differential is with primary HCC, immunohistochemistry is often helpful (see Appendix D).

For biopsies that show features of adenocarcinoma, the use of immunohistochemistry is specifically addressed in the NICE recommendations as follows:

“Use a panel of antibodies comprising CK7, CK20, TTF-1, PLAP, ER (women only) and PSA (men only) in all patients with adenocarcinoma of unknown origin. Use additional immunohistochemistry to refine the differential diagnosis, guided by the results of the panel of antibodies in the previous recommendation and the clinical picture.”

Appendix 2 of the NICE guidelines consists of two tables of immunohistochemistry in metastatic carcinoma; first a table of the various combinations of CK7 and CK 20 according to primary sites, and second a table of frequency of positivity for individual markers CK7,CK20, ER, PR, TTF-1 and PSA in 13 primary sites. These are reproduced in Appendix E. Further markers can be used depending on the clinical circumstances; in particular placental alkaline phosphatase (PLAP) is a useful marker for germ cell tumours, some of which have the appearance of adenocarcinoma. The clinical evidence base for these recommendations is included in the NICE guidelines.⁶³ A wider range of immunohistochemical markers is described in an earlier evidence-based study by Dennis *et al.*⁶⁴

Other special stains may also be useful. These include PAS and PAS-diastase for the distinction between hepatocellular and glandular neoplasms, and reticulin staining for the differential diagnosis of dysplastic and neoplastic hepatocellular lesions. See Appendix F for a guide to special stains.

If no tumour tissue is seen in the initial sections, deeper levels should be requested before reporting a negative biopsy. The possibility that the biopsy is from a well-differentiated hepatocellular lesion (focal nodular hyperplasia, liver cell adenoma, well-differentiated hepatocellular carcinoma or focal fatty change/sparing) should be considered. 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.

11.4 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 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 background 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
- an appropriate SNOMED code.

11.5 Biliary cytology

Investigation of patients with biliary strictures suspicious of malignancy may include brush cytology during ERCP. Ideally the material should be placed into transport medium for liquid-based cytology (LBC). The literature indicates that better results are achieved with this approach than with direct smears prepared at the bedside.⁶⁵ Interpretation may be complicated by the presence of inflammatory changes, especially if there is also a stent or history of PSC.⁶⁶ New techniques such as FISH and digital image analysis⁶⁷ are being developed as enhancements to conventional cytopathology.

12 Criteria for audit of the dataset

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.

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 and of margin positivity rates.

Audit activity specifically related to the College's Key Performance Indicators (KPIs) in pathology:

1. Percentage of hepatobiliary multidisciplinary meetings supported by the input of a consultant histopathologist.
2. Electronic communication with cancer registries and audit of histopathology clinical opinions, using SNOMED or SNOMED-CT topography, morphology and procedure codes.
3. Documentation in original histology report of MDM or other histopathological review and discussion of any alterations to the report as a result of this quality-assurance process.

4. The percentage of cancer resection cases that were reported using template or proforma including College cancer dataset information.
5. Percentage of diagnostic biopsies reported, confirmed and authorised within seven days of biopsy.
6. Interpretive EQA scheme membership as a minimum by the lead consultant histopathologist responsible for hepatobiliary cancer reporting. (KPI suggested CPA standard).

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Appendix A TNM classification

This appendix lists the TNM classifications for hepatocellular carcinoma, intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and gall bladder 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.

Hepatocellular carcinoma

- pT0 No evidence of primary tumour
- pT1 Solitary tumour without vascular invasion
- pT2 Solitary tumour with vascular invasion or multiple tumours , none more than 5 cm in greatest dimension
- pT3a Multiple tumours, any more than 5 cm
- pT3b Single or multiple tumours of any size involving a major branch of the portal vein or hepatic vein
- pT4 Tumour(s) with direct invasion of adjacent organs other than the gall bladder or with perforation of visceral peritoneum.

Intrahepatic cholangiocarcinoma

- pT0 No evidence of primary tumour
- pTis Carcinoma *in situ* (intraductal tumour)
- pT1 Solitary tumour without vascular invasion
- pT2a Solitary tumour with vascular invasion
- pT2b Multiple tumours, with or without vascular invasion
- pT3 Tumour perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
- pT4 Tumour with periductal invasion (periductal growth pattern).

Perihilar cholangiocarcinoma

- pT0 No evidence of primary tumour
- pTis Carcinoma *in situ*
- pT1 Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
- 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 main portal vein or its branches bilaterally; or the common hepatic artery; or the biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement.

Gall bladder carcinoma

- pT0 No evidence of primary tumour
- pTis Carcinoma *in situ*
- pT1a Tumour invades lamina propria
- pT1b Tumour invades muscular layer
- pT2 Tumour invades perimuscular connective tissue; no invasion beyond serosa or into 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.

N – Regional lymph nodes – all tumour sites

- pNx Regional lymph nodes cannot be assessed
- pN0 No regional lymph node metastases. Histological examination of a regional lymphadenectomy specimen will ordinarily include three or more lymph nodes for HCC, ICC and 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
- pN1 Regional lymph node metastasis.

M – distant metastasis

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 – for hepatocellular carcinoma

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Stage grouping – for intrahepatic cholangiocarcinoma

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Stage grouping for perihilar cholangiocarcinoma

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage II	T2a,b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1,T2,T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Stage grouping for gall bladder carcinoma

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

Appendix B SNOMED T and M codes

T56000	Liver
T56020	Left lobe of liver
T56010	Right lobe of liver
T56110	Intrahepatic bile duct
T58000	Extrahepatic bile duct
T57000	Gall bladder
Epithelial tumours: hepatocellular	
M81703	Hepatocellular carcinoma
M81713	Hepatocellular carcinoma, fibrolamellar variant
M81803	Combined hepatocellular-cholangiocarcinoma
Epithelial tumours: biliary	
M81482	Biliary intra-epithelial neoplasia, grade 3 (BillIN 3)
M85032	Intraductal papillary neoplasm with high grade intra-epithelial neoplasia
M84702	Mucinous cystic neoplasm with high grade intra-epithelial neoplasia
M81603	Intrahepatic cholangiocarcinoma
M85033	Intraductal papillary neoplasm with associated invasive carcinoma
M84703	Mucinous cystic neoplasm with associated invasive carcinoma
M81623	Perihilar cholangiocarcinoma (Klatskin tumour)
M81403	Adenocarcinoma (gall bladder, extrahepatic ducts)
M82463	Neuroendocrine carcinoma
M81406	Metastatic adenocarcinoma

Appendix C Reporting proformas

This appendix comprises the following suite of reporting proformas:

- C1 Liver resection: hepatocellular carcinoma
- C2 Intrahepatic cholangiocarcinoma
- C3 Perihilar cholangiocarcinoma
- C4 Gall bladder +/- liver resection for gall bladder cancer
- C5 Liver resection: colorectal cancer metastasis.

Appendix C1 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-posteriormm, medio-lateralmm, 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 Yes No If yes, diameter of vessel involvedmm
Specify which vessel is involved: main left portal vein/main right portal vein/hepatic vein
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 type (specify).....
Tumour grade/differentiation by worst area: Well Moderate Poor
Tumour cells present at margin Yes No
If margin is clear: is clearance >10 mm: Yes No
If no, minimum distance to marginmm
Macroscopic vascular invasion confirmed: Yes No
Microscopic vascular invasion identified: Yes No
Evidence of response to preoperative treatment: Yes No If yes, complete incomplete

Background liver

Fibrosis None present
If present: Not bridging
Bridging
Bridging with nodules
Complete cirrhosis

Aetiology

Hepatitis B
Hepatitis C
Autoimmune hepatitis
Haemochromatosis
Alcohol
NAFLD
Not known
Other.....

Number of lymph nodes examined:

Number with metastases:

Comments/additional information

Pathological staging pT..... pN.....

PT0 No tumour identified

pT1 Solitary without vascular invasion

pN0 No lymph node metastases

pT2 Solitary with vascular invasion or multiple ≤ 50 mm

pN1 Lymph node metastases

pT3a Multiple, any ≥ 50 mm

pT3b Involvement of major branch of portal or hepatic vein

pT4 Invades adjacent organs (other than gall bladder) or perforates peritoneum

Signature of pathologist

Date/...../.....

SNOMED codes

pT

M

Appendix C2 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-posteriormm, medio-lateralmm, 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 Yes No If yes, diameter of vessel involvedmm
Specify which vessel is involved: main left portal vein/main right portal vein/hepatic vein
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: Mass-forming Periductal infiltrating Intraductal papillary
Other histological type (specify).....
Tumour grade/differentiation: Well Moderate Poor
Tumour cells present at margin Yes No
If margin is clear: is clearance >10 mm: Yes No
If no, minimum distance to marginmm
Macroscopic vascular invasion confirmed: Yes No
Microscopic vascular invasion identified Yes No
Perineural invasion identified: Yes No

Background liver

Fibrosis None present
If present: Not bridging
Bridging
Bridging with nodules
Complete cirrhosis

Aetiology

Hepatitis B
Hepatitis C
Autoimmune hepatitis
Haemochromatosis
Alcohol
NAFLD
Not known
Other.....

Number of lymph nodes examined:

Number with metastases:

Comments/additional information

Pathological staging pT..... pN.....

pTis Carcinoma *in situ*

pT1 Solitary without vascular invasion

pN0 No lymph node metastases

pT2a Solitary with vascular invasion

pN1 Lymph node metastases

pT2b Multiple, with or without vascular invasion

pT3 Invades adjacent organs/perforates peritoneum

pT4 Tumour with periductal invasion

Signature of pathologist

Date/...../.....

SNOMED codes

pT

M

Appendix C3 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 ductmm
Specimen weight.....g
For segmental resections, specimen dimensions:
antero-posteriormm, medio-lateralmm, supero-inferior.....mm
Ducts involved: Right main duct Left main duct Confluence of ducts Common hepatic duct
Direct invasion of liver
Maximum tumour sizemm
Distance from nearest hepatic resection marginmm
Distance from bile duct resection marginmm
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: Periductal infiltrating Intraductal papillary Cystic component
Tumour grade/differentiation (adenocarcinoma): Well Moderate Poor
Other histological type (specify).....
Tumour cells present at hepatic margin Yes No
Tumour cells present at main duct resection margin Yes No n/a
Tumour cells present at circumferential/peritoneal margin Yes No n/a
If margin is clear: is clearance >10 mm: Yes No
If no, minimum distance to marginmm
Main portal vein/hepatic artery invasion of wall Yes No
Which vessel?

Microscopic vascular invasion identified: Yes No
Perineural invasion identified: Yes No
Background liver disease: None Primary sclerosing cholangitis Other

Number of regional lymph nodes examined: Number with metastases:

Comments/additional information

Pathological staging for hilar cholangiocarcinoma: pT..... pN.....
pTis Carcinoma *in situ* pN0 No lymph node metastases
pT1 Tumour confined to bile duct pN1 Lymph node metastases
pT2a Tumour invades beyond wall into fibroadipose tissue (Record non-regional lymph node metastases as pM1)
pT2b Tumour invades hepatic parenchyma
pT3 Tumour invades unilateral branches of portal vein/hepatic artery
pT4 Bilateral main vessel/duct involvement

Signature of pathologist **Date** .../.../.....

SNOMED codes pT M

Appendix C4 Reporting proforma for liver resection: gall bladder 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

Gall bladder

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

Liver resections:

Specimen weight.....g
 Specimen dimensions: Antero-posteriormm Medio-lateralmm Supero-inferior.....mm
 Direct invasion of liver Yes No
 If yes: depth of liver invasionmm Distance from nearest hepatic resection marginmm
 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): Other histological type (specify).....

Well Moderate Poor

Depth of invasion

Lamina propria (pT1a) Muscular layer (pT1b) Beyond muscle (pT2)
 Perforates serosa (pT3) Invades liver (pT3)
 Invades other organs Yes No If yes, which.....

Cystic duct: Involved Dysplasia/BilIN No dysplasia/BilIN
Other ducts resected Yes No If yes: involved by dysplasia/BilIN: Yes No

Tumour cells present at any resection margin: Yes No
If margin is clear: is clearance >10 mm: Yes No
If no: minimum distance to marginmm
Microscopic vascular invasion identified: Yes No

Perineural invasion identified: Yes No

Number of lymph nodes examined: Number with metastases:

Comments/additional information

Pathological staging: gall bladder carcinoma pT..... pN.....
pTis Carcinoma *in situ* pN0 no lymph node metastases
pT1a Tumour invades lamina propria pN1 regional lymph node metastases
pT1b Tumour invades muscular layer (Record non-regional lymph node metastases as pM1)
pT2 Tumour invades perifibromuscular connective tissue
pT3 Tumour perforates serosa/invades liver/one other organ
pT4 Tumour invades ≥ 2 extrahepatic organs or main portal vein/hepatic artery

Signature of pathologist **Date** / /

SNOMED codes pT M

Appendix C5 Reporting proforma for liver resection: colorectal cancer 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 liver specimens received
Type of specimen: Segmental resection List segments:
Non-anatomic (wedge) resection Site/segment(s) of origin:
List if several.....

Specimen weight (all specimens combined)g
For segmental resections, specimen dimensions (largest specimen):
antero-posteriormm, medio-lateralmm, supero-inferior.....mm

Number of tumours present..... Satellite lesions present Yes No

List maximum diameters for up to four largest tumoursmm, mm,mm,mm
Distance from hepatic resection margin of nearest tumourmm

Liver capsule intact and smooth Yes No
Invasion of adherent adjacent tissue Yes No
Lymph nodes(s) received Yes No

Histology

Tumour grade/differentiation

Well/moderately differentiated Poorly differentiated
For tumour closest to margin: tumour cells present at margin Yes No
If margin is clear: is clearance >10 mm: Yes No If no: minimum distance to marginmm

Microscopic vascular invasion identified: Yes No
Neoadjuvant therapy given: Yes No Not known
Response to neoadjuvant therapy: Yes No
If yes: No residual tumour cells/mucus lakes only Minimal residual tumour No marked regression
Number of lymph nodes examined: Number with metastases:

Background liver

Normal Steatosis Chronic liver disease with fibrosis Other.....

Comments/additional information

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

SNOMED codes pT M

Appendix D Immunohistochemical markers helpful in distinguishing well-differentiated HCC from dysplastic nodules in cirrhotic livers¹⁹

Antibody	Staining pattern	Differential HCC <i>versus</i> dysplastic nodule	Normal/other
CK7/19	Cytoplasmic	Absent around tumour cells of stromal invasion	Highlights preserved ductular reaction in pseudo-invasion
Glypican 3	Cytoplasmic, membranous, canalicular	+ve in HCC, more often in less differentiated, <10% HGDN	Regenerating hepatocytes, melanocytic lesions
HSP70	Nucleus and cytoplasm	+ve in HCC, more often in well differentiated, <10% HGDN	+ve hepatobiliary cells of ductular reaction
Glutamine synthetase (GS)	Diffuse strong cytoplasmic	+ve in HCC, more often in less well differentiated, 14% HGDN	+ve perivenular hepatocytes, maplike in FNH, diffuse +ve in b-catenin activated sub-type of liver cell adenoma
Combination of GS, glypican 3, and HSP70	Any two of these positive – sensitivity 72%, specificity 100% for HCC (20)		
CD34	Sinusoidal endothelium	Progressive increase through LGDN, HGDN, HCC	Periportal/periseptal sinusoids More +ve in arterialised lesions – FNH and adenoma
PCNA/Ki67	Nuclear	Progressive increase through LGDN, HGDN, HCC	Regenerating hepatocytes in hepatitis, etc.
afetoprotein	Cytoplasmic	Serum marker, patchy in less well-differentiated HCC, <50% poorly differentiated HCC are positive	Negative in normal Metastatic hepatoid malignancies may be positive

Key

LGDN = low grade dysplastic nodule

HGDN = high grade dysplastic nodule

FNH = focal nodular hyperplasia

Appendix E Immunohistochemical markers helpful in the differential diagnosis of liver cancers

Appendix E1

Tumours that resemble HCC: support HCC

Antibody	% in HCC	Comments
HepPar1	86	Well differentiated, rarer in metastasis
AFP	37	Poorly differentiated, usually also seropositive
pCEA	75	Canalicular pattern specific for HCC, cytoplasmic non-specific
CD10	61	Canalicular, clearer than pCEA
CAM5.2	90	If CK7-ve, suggests HCC due to CK8 and 18 in HCC
Care with: PGP – 87% HCC+ve TTF1 – 63% HCC cytoplasmic +ve (depends on reagent), 0% nuclear +ve		

Tumours that resemble HCC: support metastasis

Antibody	% in HCC	Comments
mCEA	3	Positive in adenocarcinoma including cholangiocarcinoma
S100, HM45	0	Differential <i>versus</i> melanoma
Vimentin, RCC	7, 0	Differential <i>versus</i> renal cell carcinomas
Synaptophysin, CD56	9,14	Differential <i>versus</i> neuroendocrine carcinoma
CK7, CK20	15, 9	Metastatic adenocarcinoma Useful in conjunction with CAM5.2, see above
CK19	<10	Differential <i>versus</i> cholangiocarcinoma Positivity is poor prognostic marker in HCC

Appendix E2 Immunohistochemical investigations for liver biopsies containing metastatic tumour: tumours with morphological features of adenocarcinoma

These tables are transcribed directly from Appendix 2 of *Diagnosis and management of metastatic malignant disease of unknown primary origin, Full Guideline* (July 2010), developed for NICE by the National Collaborating Centre for Cancer.

Combining CK7 and CK20

	CK7+CK20+	CK7+CK20-	CK7-CK20+	CK7-CK20-
Oesophagus	81	12	0	6
Ovary mucinous	74	23	3	0
Urothelium	61	21	4	14
Pancreas	55	36	4	4
Stomach	48	25	20	6
Biliary	33	62	5	0
Endometrium	9	92	0	0
Salivary gland	0	100	0	0
Ovary non-mucinous	6	91	0	3
Breast	6	86	1	6
Lung	9	85	0	6
Colon	11	1	79	9
Kidney	0	9	0	91
Prostate	1	9	11	79

The figures in each box represent the percentage of tumours of a particular type that is positive for that particular CK7/CK20 combination.

The squares are a grey scale, with black being 100% and white 0%.

Row totals do not always sum to 100% as not all studies reported all possible combinations of CK7 and CK20.

Individual antibodies

	CK7	CK20	ER	PR	TTF-1	PSA
Biliary	81	33	4	29	0	Hash
Breast	83	7	63	43	0	0
Colon	16	88	2	20	0	0
Endometrium	85	5	31	100 [†]	0	3
Kidney	9	2	3	8	0*	0*
Lung	85	13	5	21	85	0
Oesophagus	50	29	0	100 [†]	0	0
Ovary	73	23	53	32	1	2
Pancreas	95	32	0	2	1	0
Prostate	11	14	10	0*	9	91
Salivary gland	100*	50*	25*	25*	0	Hash
Stomach	49	37	0	5	1	3
Urothelium	74	72	Hash	Hash	Hash	0

The figures in each square represent the percentage of a particular tumour type that is positive for each of the six antibodies.

The squares are a grey scale with black being 100% and white 0%.

Hash boxes indicate no data available.

Sparse data (N<5).

Appendix F 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	Presence of luminal PAS-D positive material and/or cytoplasmic mucin vacuoles favours a diagnosis of adenocarcinoma. Hepatocellular carcinomas may contain PAS-diastase positive globules (e.g. α -1-antitrypsin).
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. liver cell adenoma, focal nodular hyperplasia). Reticulin fibres usually reduced or absent in hepatocellular carcinoma (but may be focally retained in some well differentiated HCCs).

NOTE: Adenocarcinoma includes primary cholangiocarcinoma as well as metastatic adenocarcinoma.

Appendix G Summary table – explanation of levels of evidence

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

Level of evidence	Nature of evidence
A	<p>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</p> <p>or</p> <p>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.</p>
B	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
C	<p>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</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix H AGREE monitoring sheet

The Cancer Datasets of the Royal College of Pathologists comply with the AGREE standards for good quality clinical guidelines (www.agreecollaboration.org). The sections of this dataset that indicate compliance with each of the AGREE standards are indicated in the table.

AGREE standard	Section of dataset
SCOPE AND PURPOSE	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The clinical question(s) covered by the guidelines is (are) specifically described	introduction
3 The patients to whom the guideline is meant to apply are specifically described	introduction
STAKEHOLDER INVOLVEMENT	
4 The guideline development group includes individuals from all the relevant professional groups	foreword
5 The patients' views and preferences have been sought	Not applicable *
6 The target users of the guideline are clearly defined	Introduction
7 The guideline has been piloted among target users	Foreword
RIGOUR OF DEVELOPMENT	
8 Systematic methods were used to search for evidence	Introduction
9 The criteria for selecting the evidence are clearly described	Introduction
10 The methods used for formulating the recommendations are clearly described	Introduction
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword
12 There is an explicit link between the recommendations and the supporting evidence	Throughout
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	4–11
16 The different options for management of the condition are clearly presented	Throughout
17 Key recommendations are easily identifiable	6
18 The guideline is supported with tools for application	Appendices
APPLICABILITY	
19 The potential organisational barriers in applying the recommendations have been discussed	Foreword
20 The potential cost implications of applying the recommendations have been considered	Foreword
21 The guideline presents key review criteria for monitoring and/audit purposes	12
EDITORIAL INDEPENDENCE	
22 The guideline is editorially independent from the funding body	Foreword
23 Conflicts of interest of guideline development members have been recorded	Foreword

* The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised the Director of Communications that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.