



The Royal College of Pathologists

Pathology: the science behind the cure

Standards and Datasets for Reporting Cancers

Dataset for liver resection specimens and liver biopsies for primary and metastatic carcinoma

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1 INTRODUCTION

These guidelines describe the core data that should be provided in histopathological reports of liver resection specimens. Brief guidelines for reporting needle biopsy specimens of hepatic neoplasms are also included. Liver resection for primary liver cancer (hepatocellular carcinoma and intrahepatic or hilar cholangiocarcinoma) is performed in a limited number of specialist centres in the UK, while resection for metastatic colorectal carcinoma is more widely performed. These guidelines cover all three of these scenarios. They are not specifically intended for other types of tumour that may be resected, such as focal nodular hyperplasia, primary sarcoma, 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.^{1,2}

For primary tumours, the core items of information are those required to derive the TNM staging of the resected tumour,³ and others which may be of prognostic significance. Core data items of tumour size, number, surgical margin, vascular invasion, lymph node status and background liver disease are important in tumour staging and have been found to be prognostic factors in hepatocellular carcinoma⁴⁻¹² cholangiocarcinoma¹³⁻¹⁸ and metastatic colorectal carcinoma.¹⁹⁻²²

There is less evidence about the prognostic importance of pathological features of primary liver cancer than those of other sites for three reasons – publications are based on relatively small series (compared with other cancer sites) of resectable primary liver tumours; results from the far East may not translate to Western experience, and survival may be more related to the severity of background chronic liver disease than to tumour biology.

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

- to provide prognostic information to clinicians and patients
- to provide accurate data for cancer registration
- to allow correlation of resection specimens with pre-operative imaging
- to allow the accurate and equitable comparison of surgical practice in different units.

2 CLINICAL INFORMATION REQUIRED ON SPECIMEN REQUEST FORM

This includes the type of operative procedure, segments resected, site of tumour with description of imaging findings and whether this has been a potentially complete resection or whether there is known residual tumour. Details of any previous treatment such as radiofrequency ablation or tumour embolisation (for hepatocellular carcinoma) or neo-adjuvant chemotherapy (for metastatic adenocarcinoma) should be provided, as should information about background chronic liver disease, i.e. aetiological factors for fibrosis/cirrhosis in hepatocellular carcinoma; evidence of PSC in cholangiocarcinoma. Site(s) of any lymph nodes excised – in continuity with main specimen or submitted separately. For cholangiocarcinoma specimens it is helpful if the surgeon can identify and label the bile duct resection margin(s).

3 TYPE OF SPECIMEN

Liver tumours are resected by either segmental resection, following the planes of whole liver segments defined by intra-operative ultrasound, or non-anatomical (wedge) resection, for

small accessible sub-capsular lesions.²³ The dataset should also be applied to total hepatectomy specimens from patients undergoing liver transplantation when there is tumour present.

Segmentectomy procedures result in sizable resection specimens; the surgeon should state the segments included as this may not always 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.

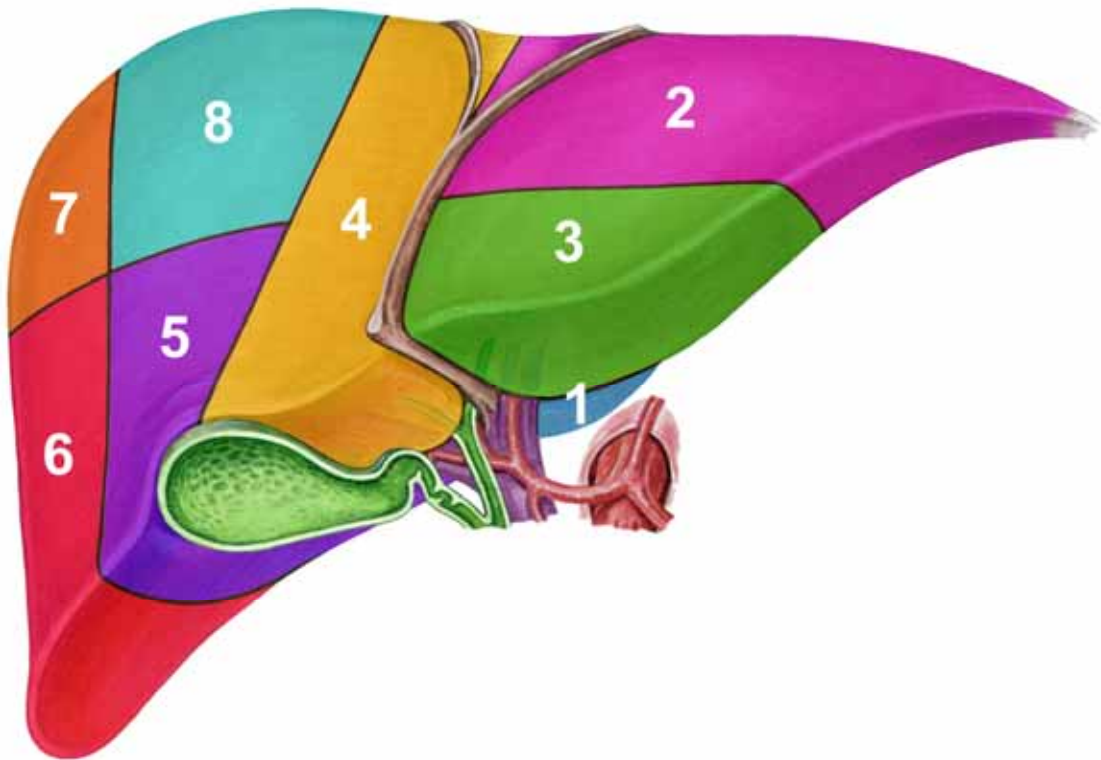


Figure 1 Segmentectomy specimens

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

For hilar cholangiocarcinomas, a length of extrahepatic duct will be resected in continuity with the right or left trisectionectomy specimen; bile duct carcinomas confined to the extrahepatic ducts (extrahepatic cholangiocarcinoma) may be resected without hepatectomy, and should be reported as described in the minimum dataset for the histopathological reporting of pancreatic, ampulla and bile duct carcinoma.

4 SPECIMEN HANDLING

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, while the specimen hardening by fixation facilitates accurate slicing. If fresh tumour is to be obtained, this can be done either by slicing the specimen fresh, 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.

For complex cases, knowledge of findings on pre-operative imaging is very helpful.

5 GROSS DESCRIPTION

5.1 Hepatectomy and segmentectomy specimens

Record the segments resected and the specimen weight (after opening the gall bladder and rinsing 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 in the specimen, record the length of extrahepatic duct, number and site of lymph nodes and size and appearance of gall bladder (when present).

The specimen should be sliced at right angles to the parenchymal resection plane, and by preference in the horizontal plane to facilitate correlation with pre-operative cross-sectional imaging. Slices should be a maximum of 1cm thickness; finer slicing can be achieved using a bacon slicer, but is not necessary for routine practice. The minimum size of tumours detectable by imaging is in the order of 5mm.

Record the number, site, maximum diameter, and distance from hepatic margin of the tumours. For multiple tumours, the sites should be recorded in the text of the report in such a way that allows correlation with pre-operative imaging. For example, this can conveniently be recorded by numbering the horizontal slices from the top, and stating the slices and approximate segments for each tumour. Deposits of metastatic colorectal cancer are often multiple, and do not require separate datasets for each tumour. The presence of satellite nodules (tumours <10mm diameter, in the vicinity of a larger tumour) and 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, which can be used during MDT meetings.

The specimen should be carefully inspected for macroscopically apparent vascular invasion, and any suspected vascular invasion should be sampled for histological confirmation. This is specifically important for the staging of hepatocellular carcinomas.

5.2 Hilar cholangiocarcinoma

For resections of hilar cholangiocarcinoma (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 the structures, e.g. with a coloured tie. The resection

margins of these ducts may be submitted separately by the surgeon, with or without a request for frozen section.

Examination of the biliary tree can be achieved by longitudinal opening²⁴ or serial transverse sections, according to the preference of the pathologist. These approaches give different emphasis on reported characteristics, with longitudinal opening allowing precise measurement of the mucosal extent of the tumour, while completely embedded 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.

Lymph nodes – specimens may include lymph nodes, either separately dissected by the surgeon, or at the liver hilum. Resections for metastatic colorectal cancer generally do not include lymph nodes.

6 BLOCK SELECTION

All specimens – blocks to include:

- tumour margin with adjacent liver tissue (for microscopic vascular invasion)
- nearest resection margin (when this is close enough to the tumour to be included in the block)
- liver capsule where there is subjacent tumour and overlying adherent tissue or macroscopic capsular invasion.
- gall bladder bed where there is adjacent intrahepatic tumour
- any site macroscopically suggestive of vascular or bile duct invasion
- background liver (taken as far as possible from the tumour).

The number of tumour blocks will depend on tumour type but should include samples from areas of differing macroscopic appearance in heterogeneous tumours. For metastatic carcinoma, a minimum of 1 block per tumour is sufficient, although more should be taken in patients who have had neoadjuvant chemotherapy, and especially if initial blocks show no viable tumour. For hepatocellular carcinoma, a minimum of 3 tumour blocks is recommended, because tumour heterogeneity is common and differentiation is related to prognosis.

Samples can also be taken from the following sites (includes tissues that are not present in all specimens):

- hilum (to include large vessels)
- hepatic vein margin (if tumour nearby)
- gall bladder (optional when this is macroscopically normal).
- resection margins of the extrahepatic biliary tree (when included)
- lymph nodes (for large nodes without macroscopic involvement, serially sliced and all embedded).

7 CORE DATA ITEMS

7.1 Macroscopic

- Type of specimen
- Specimen weight
- Specimen dimensions (antero-posterior, medio-lateral and superior-inferior)
- Tumour number and size
- Distance from resection margin(s)
- Macroscopic evidence of vascular invasion
- Integrity of liver capsule/bare area and presence of adherent tissues (e.g. diaphragm) or other organs
- Appearance of background liver.

7.2 Microscopic

- Tumour type
- Tumour differentiation
- Resection margin (hepatic, and where appropriate bile duct, vascular, circumferential)
- Vascular invasion
- Perineural invasion (cholangiocarcinoma)
- Background chronic liver disease (for primary hepatic neoplasms – type and fibrosis stage)
- Lymph node involvement (where appropriate).

8 NON-CORE DATA ITEMS

8.1 Microscopic

- WHO type of tumour (for HCC)
- Effects of ablative or neoadjuvant therapy on tumour (if applicable)
- Presence of fibrous capsule (HCC and metastatic colorectal carcinoma)
- Presence of satellite lesions
- As appropriate, the presence of large or small cell dysplasia (change) or biliary dysplasia
- Background liver disease (for metastatic hepatic neoplasms).

9 NOTES ON RECORDING CORE AND NON-CORE ITEMS.

9.1 Hepatocellular carcinoma

9.1.1 Tumour classification and grading:

Tumour differentiation (Edmondson and Steiner)^{1,25} but not histological pattern²⁶ (trabecular, acinar, solid) is related to prognosis. Hepatocellular carcinomas are frequently heterogeneous and most are predominantly grade 2 or 3. Grade 1 hepatocellular carcinoma closely resembles normal liver, and is rarely seen in isolation except in small (<2cm) tumours. Grade 4 HCC is

not morphologically recognizable as HCC, and its diagnosis depends on adjacent better-differentiated tumour or immunohistochemistry/raised serum alpha feto-protein.

Rare types of hepatocellular carcinoma include tumours showing evidence of both hepatocellular and cholangiolar differentiation (mixed hepatocellular-cholangiocarcinoma)^{27,28} and fibrolamellar carcinoma. Other unusual variants include mixed classical/fibrolamellar pattern, spindle cell HCC etc.¹

9.1.2 Vascular invasion

Microscopic vascular invasion is an important prognostic factor;¹⁰⁻¹² tumours with microscopic vascular invasion are stage pT2.

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 should prompt a thorough search for vascular invasion. However, for proper classification for TNM purposes, where the tumor 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).

9.1.3 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 e.g. Child-Pugh score, and some staging systems incorporate a clinical assessment of functional hepatic status.⁴⁻⁶ The histology report should include information about the background liver, sampled as far from the tumour as possible to avoid peritumoral effects. This will include both the stage of fibrosis and the nature and severity of inflammatory/metabolic disease.

9.1.4 Pre-operative ablative therapy

The effects of pre-operative ablative therapy may be apparent macroscopically and/or histologically. Recording an impression of the proportion of the overall tumour that is viable may be helpful to oncologists, although its estimation is subjective and not a core item in the dataset.

9.2 Metastatic carcinoma

Most liver resections are performed for metastatic colorectal carcinoma; there are often multiple deposits. The report should document the site, size and appearance of each in a way that allows correlation with pre-operative imaging. Such metastases represent haematogenous spread in TNM stage IV, Dukes' stage D colorectal carcinoma. Prognosis is related to the stage of the primary colorectal carcinoma, and to tumour number and clearance at surgical margin;²⁰ the observation of microscopic vascular invasion around the tumour is also prognostically relevant in several studies.¹⁹ This dataset also conforms to the histopathology section of the BSG guidelines for resection of colorectal cancer liver metastases.²⁹

9.2.1 Effects of neoadjuvant therapy.

Pre-operative chemotherapy may result in partial or complete response of the adenocarcinoma. Areas of 'dirty' necrosis surrounded by a garland of adenocarcinoma cells are frequently present in metastatic colorectal carcinoma especially at the centre of the tumour, regardless of neoadjuvant treatment. Tumour necrosis due to chemotherapy is not

confined to the centre of the lesion, and is usually recognisable by a histiocyte response, and/or isolated mucin lakes within dense fibrous tissue. Where there are multiple deposits, the response to therapy may vary among and so histological sampling of each is recommended.

9.2.2 Background liver disease

Where liver tissue not adjacent to the tumour is available, the presence and severity of any changes in the uninvolved liver should be noted. This may include fatty liver disease (which may have an adverse impact on liver function if a large resection is undertaken) or chemotherapy-induced sinusoidal lesions.³⁰

9.3 Cholangiocarcinoma

9.3.1 Tumour size

Intrahepatic cholangiocarcinoma usually forms an expansile tumour mass with obvious border and the maximum dimension is readily determined.

For hilar cholangiocarcinoma, the extent of tumour infiltration may be 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.²⁴ 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. Some hilar cholangiocarcinomas have an intrahepatic extension that is measured in slices of the hepatectomy, once the hilar ducts have been dissected.

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.¹³ Uncommon variants include adenosquamous, clear cell, and spindle cell; biliary cystadenocarcinoma can also be recorded in this section.

9.3.2 Lymph node metastases

Hilar lymph nodes are characteristically large (up to 40mm) 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. A regional lymphadenectomy specimen will ordinarily include 3 or more lymph nodes.³ Micro-metastasis found only by immunohistochemistry does not affect prognosis.¹⁷

9.3.3 Background liver disease

Where appropriate, the presence and severity of any underlying liver disease should be documented. This may include changes related to sclerosing cholangitis, which is an important risk factor for hilar cholangiocarcinoma. Cases of peripheral cholangiocarcinoma are increasingly linked to other chronic liver disease, especially chronic viral hepatitis.³²

10 DIAGNOSTIC CODING

TNM coding (6th edition) and SNOMED coding are recommended – see Appendices A and B.

11 REPORTING OF NEEDLE BIOPSY SPECIMENS

Targeted needle core biopsies are commonly obtained in the investigation of focal liver lesions detected by ultrasound scanning or other imaging. Outside hepatology centres, these often 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 would 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.³³ These diagnoses are made on the basis of imaging and 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 by 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 tissue in the biopsy and clinical circumstances.

11.3 Further investigations

Discussion with the clinician at an early stage is recommended, once the presence of tumour has been confirmed, in order to guide the immunohistochemical investigations. For example, there may be a previous history of primary malignancy that was omitted from the request form or relevant information 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 panel of markers chosen will be tailored individually for each biopsy, depending on the tumour morphology, any clinically suggested site of origin for metastatic disease, the amount of tissue available in the biopsy, and to exclude potentially treatable disease. See Appendix D for guide to immunohistochemistry.^{34,35}

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 E for 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.

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APPENDIX A TNM CLASSIFICATION

The classification is intended primarily for hepatocellular carcinoma. It may also be used for cholangio- (intrahepatic bile duct) carcinoma of the liver. There should be histological confirmation of the disease and division of cases by histological type.

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

T – Primary tumour

- pTx Primary tumour cannot be assessed
- pT0 No evidence of primary tumour
- pT1 Solitary tumour without vascular invasion
- pT2 Solitary tumour with vascular invasion or multiple tumours , none more than 5cm in greatest dimension
- pT3 Multiple tumours more than 5cm or tumour involving a major branch of the portal or hepatic vein(s)
- pT4 Tumour(s) with direct invasion of adjacent organs other than the gall bladder or with perforation of visceral peritoneum

For hilar cholangiocarcinoma, the classification for staging extrahepatic bile duct carcinoma is appropriate.

- pTx Primary tumour cannot be assessed
- pT0 No evidence of primary tumour
- pTis Carcinoma in situ
- pT1a Tumour invades subepithelial connective tissue
- pT1b Tumour invades fibromuscular layer
- pT2 Tumour invades perifibromuscular connective tissue
- pT3 Tumour invades adjacent structures (liver, gall bladder) and/or unilateral tributaries of the portal vein (right or left) or hepatic artery (right or left).
- PT4 Tumour invades any of the following: main portal vein or its tributaries bilaterally, common hepatic artery, or other adjacent structures.

N – Regional lymph nodes

- pNx Regional lymph nodes cannot be assessed.
- pN0 No regional lymph node metastases. Histological examination of a regional lymphadenectomy specimen will ordinarily include 3 or more lymph nodes. 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

- PMx Distant metastasis cannot be assessed.
- pM0 No distant metastasis
- pM1 Distant metastasis.

Stage grouping for intrahepatic tumours

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

Stage grouping for hilar cholangiocarcinoma

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1,T2,T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	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
M81703	Hepatocellular carcinoma
M81403	Primary adenocarcinoma (with T56110 or T58000)
M81623	Hilar cholangiocarcinoma (Klatskin tumour)
M81803	Combined hepatocellular/cholangiocarcinoma
M81406	Metastatic adenocarcinoma

APPENDIX C PROFORMA REPORTS

Please see the proformas on the following pages:

- Dataset for liver resection: hepatocellular carcinoma histopathology report
- Dataset for liver resection: cholangiocarcinoma histopathology report
- Dataset for liver resection: colorectal cancer metastasis histopathology report.

DATASET FOR LIVER RESECTION: Hepatocellular carcinoma histopathology report

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

Gross description and core macroscopic items

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:

Distance from nearest hepatic resection margin:mm

Macroscopic involvement of vessels	yes <input type="checkbox"/>	no <input type="checkbox"/>	If yes, diameter of vessel involvedmm
Invasion of adherent adjacent organ	yes <input type="checkbox"/>	no <input type="checkbox"/>	If yes, which organ
Liver capsule intact and smooth	yes <input type="checkbox"/>	no <input type="checkbox"/>	
Lymph node(s) received	yes <input type="checkbox"/>	no <input type="checkbox"/>	

Histology: core microscopic items

Tumour grade by worst area (Edmondson):
 grade 1 grade 2-3 grade 4 Fibrolamellar carcinoma
 Mixed hepatocellular-cholangiocarcinoma
 Other histological type (specify).....

Tumour cells present at margin yes no
 If no: margin >10mm or minimum distance to marginmm

Macroscopic vascular invasion confirmed	yes <input type="checkbox"/>	no <input type="checkbox"/>
Microscopic vascular invasion	yes <input type="checkbox"/>	no <input type="checkbox"/>

Evidence of response to pre-operative treatment yes no

Background liver:

Fibrosis:	none present <input type="checkbox"/>	Aetiology:	not known <input type="checkbox"/>	Other
	not bridging <input type="checkbox"/>		hepatitis B <input type="checkbox"/>	
	bridging <input type="checkbox"/>		hepatitis C <input type="checkbox"/>	
	bridging with nodules <input type="checkbox"/>		autoimmune hepatitis <input type="checkbox"/>	
	complete cirrhosis <input type="checkbox"/>		haemochromatosis <input type="checkbox"/>	
			alcohol <input type="checkbox"/>	
			NAFLD <input type="checkbox"/>	

Number of lymph nodes examined: Number with metastases:

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 ≤50mm	pN1 lymph node metastases
pT3 Multiple ≥50mm or invades major vein	
pT4 Invades adjacent organs/perforates peritoneum	

Histological evidence of response to prior treatment yes no

Signature of pathologist..... **Date**/..../..... **SNOMED codes T**/M

DATASET FOR LIVER RESECTION: Cholangiocarcinoma histopathology report

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

Gross description and core macroscopic items

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

Site of tumour: intrahepatic hilar both

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 adjacent tissue yes no if yes, which organ?.....

Lymph nodes(s) received yes no

Histology: core microscopic items

Tumour grade (adenocarcinoma): Well differentiated Other histological type (specify).....
Moderately differentiated Poorly differentiated

Tumour cells present at hepatic margin yes no

Tumour cells present at extrahepatic duct resection margin yes no N/A

Tumour cells present at circumferential margin yes no N/A

If no: margin >10mm or minimum distance to marginmm

Microscopic vascular invasion yes no

Perineural invasion yes no

Background liver disease: none primary sclerosing cholangitis chronic viral hepatitis B C
Other

Number of lymph nodes examined: Number with metastases:

Pathological staging: intrahepatic cholangiocarcinoma

pT..... pN.....

PT0 No tumour identified

pT1 Solitary without vascular invasion

pN0 no lymph node metastases

pT2 Solitary with vascular invasion or multiple ≤50mm

pN1 lymph node metastases

pT3 Multiple ≥50mm or invades major vein

pT4 Invades adjacent organs/perforates peritoneum

Pathological staging: hilar cholangiocarcinoma

pT..... pN.....

PTis Carcinoma *in situ*

pN0 no lymph node metastases

pT1a Tumour invades subepithelial connective tissue

pN1 lymph node metastases

pT1b Tumour invades fibromuscular layer

pT2 Tumour invades perifibromuscular connective tissue

pT3 Tumour invades adjacent structures

Signature of pathologist..... Date/..../..... SNOMED codes T/M

APPENDIX D IMMUNOHISTOCHEMISTRY FOR THE DIFFERENTIAL DIAGNOSIS OF LIVER TUMOUR BIOPSIES

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 & 18 in HCC
Care with: PGP – 87% HCC+ve; synaptophysin 9%+ve, CD56 14% TTF1 – 63% HCC cytoplasmic +ve, 0% nuclear +ve		

Tumours that resemble HCC: support metastasis

Antibody	% in HCC	Comments
mCEA	3	Positive in adenocarcinoma including cholangiocarcinoma
S100	0	Differential v. melanoma
Vimentin,	7	Differential v. renal cell carcinomas
RCC	0	Differential v. renal cell carcinoma
CK7, CK20	15, 9	Useful in conjunction with CAM5.2

Investigation of origin of adenocarcinoma³³

Adenocarcinoma – % positivity for each marker										
Primary site	PSA	TTF1	GCDFP15	CDX2	CK20	CK7	ER	Mesothelin	CA 125	Lysozyme
Breast	0	0	49	0	0	87	79	4	13	11
Colon	0	0	6	86	76	3	1	7	1	43
Lung	0	90	3	1	1	90	6	36	38	35
Ovary serous	0	0	4	0	0	93	81	96	93	7
Ovary mucinous	7	0	14	14	14	57	50	36	36	29
Pancreas	0	4	1	1	2	94	0	49	50	51
Stomach	2	2	0	0	21	50	0	19	8	81
Prostate	100	8	4	4	0	0	8	0	0	4
HCC		0	0	0	9	15	12	0	10	
Cholangiocarcinoma		0	0	22	49	95	0	44	56	

The data for metastatic adenocarcinoma in this table is based on tissue micro-array technology in one centre.³³

The same authors have also published a collation of immunohistochemistry results in metastatic adenocarcinoma drawn from 19 publications; this table also includes data for Ca19-9 and CEA.³⁴

APPENDIX E 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. alpha-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.