Intrahepatic Cholangiocarcinoma, Perihilar Cholangiocarcinoma and Hepatocellular Carcinoma Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

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

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

SPECIMEN(S) SUBMITTED (select all that apply) (Note 1)

- ◯ Not specified
- ◯ Indeterminate
- ☐ Liver
  - ☐ Total hepatectomy
  - ☐ Segmental resection, *specify segment(s) or type of segmentectomy*
  - ☐ Wedge resection, *specify site/segment*
- ☐ Extrahepatic bile duct
- ☐ Gallbladder
- ☐ Diaphragm
- ☐ Lymph nodes, *specify site(s), distinguishing between portal and extra-portal nodes*
- ☐ Other, *specify*

SPECIMEN DIMENSIONS

(Indicate greatest measurement for each parameter in an irregularly shaped specimen)

mm x mm x mm

Length of extrahepatic bile duct *(Applicable to perihilar cholangiocarcinoma only)* mm

SPECIMEN WEIGHT

g

SATELLITOSIS (Note 2)

(Applicable to hepatocellular carcinoma only)

◯ Cannot be assessed ◯ Not identified ◯ Present

MACROSCOPIC TUMOUR RUPTURE (Note 3)

(Applicable to hepatocellular carcinoma and perihilar cholangiocarcinoma only)

◯ Fragmented specimen ◯ Ruptured ◯ Intact

TUMOUR SITE AND NUMBER (Note 4)

◯ No macroscopic residual tumour

Tumour ID	Specify	No./site, *if possible*

MAXIMUM TUMOUR DIMENSION (Note 5)

◯ Cannot be assessed

Tumour ID	Maximum dimension
	mm
	mm
	mm
	mm
	mm

For a large number of tumours include a range mm to mm

Linear extent of tumour along the bile duct *(Applicable to perihilar cholangiocarcinoma only, where possible)* mm

HISTOLOGICAL TUMOUR TYPE (Note 6)

(Value list from the World Health Organization Classification of Tumours of the Gastrointestinal Tract (2019))

- ◯ Hepatocellular carcinoma
- ◯ Intrahepatic cholangiocarcinoma
  - ◯ Large duct ◯ Small duct ◯ Other
- ◯ Perihilar cholangiocarcinoma
- ◯ Combined hepatocellular – cholangiocarcinoma
- ◯ Intraductal papillary neoplasm with an associated invasive carcinoma
- ◯ Mucinous cystic neoplasm with an associated invasive carcinoma
- ◯ Undifferentiated carcinoma
- ◯ Carcinoma, type cannot be determined

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HEPATOCELLULAR CARCINOMA SUBTYPE

- ◯ Steatohepatitic
- ◯ Clear cell
- ◯ Macrotrabecular massive
- ◯ Scirrhous
- ◯ No special type
- ◯ Chromophobe
- ◯ Fibrolamellar
- ◯ Neutrophil-rich
- ◯ Lymphocyte-rich

TUMOUR GROWTH PATTERN (Note 7)

Hepatocellular carcinoma

- ◯ Cannot be determined
- ◯ Early hepatocellular carcinoma
- ◯ Single distinct nodule
- ◯ Large dominant nodule with multiple small satellite nodules
- ◯ Cirrhotomimetic
- ◯ Multiple distinct nodules

Intrahepatic and perihilar cholangiocarcinoma

- ◯ Cannot be determined
- ◯ Mass-forming
- ◯ Intraductal-growth
- ◯ Periductal infiltrating
- ◯ Mixed mass-forming and periductal infiltrating

HISTOLOGICAL TUMOUR GRADE (Note 8)

- ◯ Not applicable
- ◯ Cannot be assessed
- ◯ Grade 1: Well differentiated
- ◯ Grade 2: Moderately differentiated
- ◯ Grade 3: Poorly differentiated

EXTENT OF INVASION (Note 9)

- ◯ Cannot be assessed
- ◯ No evidence of primary tumour
- ◯ Macroscopic invasion
  - ◯ Tumour confined to liver
  - ◯ Tumour confined to the extrahepatic bile ducts (carcinoma in situ/high grade dysplasia) *(Applicable to perihilar cholangiocarcinoma only)*
  - ◯ Tumour involves visceral peritoneum
  - ◯ Tumour directly invades gallbladder
  - ◯ Invasion of periductal tissue - either adipose or hepatic tissue *(Applicable to perihilar cholangiocarcinoma only)*
  - ◯ Tumour directly invades other adjacent organs, *specify*
- ◯ Microscopic invasion
  - ◯ Tumour confined to liver
  - ◯ Tumour confined to the bile duct mucosa histologically (carcinoma in situ/high grade dysplasia) *(Applicable to perihilar cholangiocarcinoma only)*
  - ◯ Tumour involves visceral peritoneum
  - ◯ Tumour directly invades gallbladder
  - ◯ Invasion of periductal tissue - either adipose or hepatic tissue *(Applicable to perihilar cholangiocarcinoma only)*
  - ◯ Tumour directly invades other adjacent organs, *specify*

PERINEURAL INVASION (Note 10)

(Applicable to intrahepatic and perihilar cholangiocarcinoma)

◯ Not identified ◯ Indeterminate ◯ Present

VASCULAR INVASION (Note 11)

- ◯ Not identified
- ◯ Indeterminate
- ◯ Present macroscopically (large portal or hepatic veins)
- ◯ Present microscopically (small portal or hepatic veins or microvessels)

COEXISTENT PATHOLOGY (Note 12)

Other histopathological features (select all that apply)

- ◯ None identified
- ☐ Steatosis
- ☐ Steatohepatitis
- ☐ Iron overload
- ☐ Biliary disease, *specify if known*
- ☐ Chronic hepatitis, *specify type if known*
- ☐ Other, *specify*

Fibrosis

◯ Not identified ◯ Indeterminate ◯ Present

ISHAK stage	/6
OR	
KLEINER stage	/4
OR	
METAVIR stage	/4
OR	
BATTS-LUDWIG stage	/4
OR	
SAF system	/4

Dysplastic/pre-malignant lesions

◯ None identified

BILIARY INTRA-EPITHELIAL NEOPLASIA (BilIN)

◯ Absent ◯ Present
- ◯ High grade BilIN
- ◯ Low grade BilIN

INTRADUCTAL PAPILLARY NEOPLASM OF THE BILE DUCTS (IPNB)

◯ Absent ◯ Present
- ◯ High grade IPNB
- ◯ Low grade IPNB

LOW GRADE HEPATOCELLULAR DYSPLASTIC NODULE

◯ Absent ◯ Present

HIGH GRADE HEPATOCELLULAR DYSPLASTIC NODULE

◯ Absent ◯ Present

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RESPONSE TO NEOADJUVANT THERAPY (Note 13)

- ◯ No neoadjuvant treatment
- ◯ Complete response – no viable cancer cells
- ◯ Partial response – residual cancer with some tumour regression
  - Percentage necrosis ____ %
- ◯ No response – extensive residual cancer with no evident tumour regression
- ◯ Cannot be assessed, *specify*

MARGIN STATUS (Note 14)

- ◯ Cannot be assessed
- ◯ Not involved by invasive carcinoma
  - Distance of tumour to closest margin ____ mm
  - OR
  - ◯ Clearance is ≥10 mm
- ◯ Involved by invasive carcinoma
  - Specify margin(s), if possible
- ◯ Involved by BilIN *(Applicable to cholangiocarcinoma only)*
  - Specify margin(s), if possible

LYMPH NODE STATUS (Note 15)

- ◯ Cannot be assessed
- ◯ No nodes submitted or found
  - Number of lymph nodes examined
  - ◯ Not involved
  - ◯ Involved
    - Number of involved lymph nodes
    - ◯ Number cannot be determined

ANCILLARY STUDIES (Note 16)

- ◯ Not performed
- ◯ Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[a]

Primary tumour (pT)

INTRAHEPATIC CHOLANGIOCARCINOMA[b]
(Intrahepatic bile ducts)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ (intraductal tumour)
  - ◯ T1a Solitary tumour 5 cm or less in greatest dimension without vascular invasion
  - ◯ T1b Solitary tumour more than 5 cm in greatest dimension without vascular invasion
- ◯ T2 Solitary tumour with intrahepatic vascular invasion or multiple tumours, with or without vascular invasion
- ◯ T3 Tumour perforating the visceral peritoneum
- ◯ T4 Tumour involving local extrahepatic strcutures by direct hepatic invasion

HEPATOCELLULAR CARCINOMA
(Liver excluding intrahepatic and perihilar bile ducts)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
  - ◯ T1a Solitary tumour 2 cm or less in greatest dimension with or without vascular invasion
  - ◯ T1b Solitary tumour more than 2 cm in greatest dimension without vascular invasion
- ◯ T2 Solitary tumour more than 2 cm dimension with vascular invasion or multiple tumours none more than 5 cm in greatest dimension
- ◯ T3 Multiple tumours any more then 5 cm in greatest dimension
- ◯ T4 Tumour(s) involving a major branch of the portal or hepatic vein or with direct invasion of adjacent organs (including the diaphragm), other than the gallbladder or with perforation of visceral peritoneum

PERIHILAR CHOLANGIOCARCINOMA
(Perihilar bile ducts)

- ◯ TX Primary tumour cannot be assessed
- ◯ T0 No evidence of primary tumour
- ◯ Tis Carcinoma in situ
- ◯ T1 Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
  - ◯ T2a Tumour invades beyond the wall of the bile duct to surrounding adipose tissue
  - ◯ T2b Tumour invades adjacent hepatic parenchyma
- ◯ T3 Tumour invades unilateral branches of the portal vein or hepatic artery
- ◯ T4 Tumour invades main portal vein or its branches bilaterally; or the common hepatic artery; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (pN)

- ◯ No nodes submitted or found

HEPATOCELLULAR CARCINOMA & INTRAHEPATIC CHOLANGIOCARCINOMA
(Liver including intrahepatic bile ducts and excluding perhilar bile ducts)

- ◯ NX Regional lymph nodes cannot be assessed
- ◯ N0 No regional lymph node metastasis
- ◯ N1 Regional lymph node metastasis

PERIHILAR CHOLANGIOCARCINOMA
(Perihilar bile ducts)

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

Distant metastasis (pM)

- ◯ Not applicable
- ◯ M1 Distant metastasis

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

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

[a] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley-Blackwell.*

[b] *Combined Hepatocellular-Cholangiocarcinomas are staged as per Intrahepatic Cholangiocarcinoma.*

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Definitions

CORE elements

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

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

NON-CORE elements

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

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

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Scope

This dataset has been developed for resection specimens of the liver with intrahepatic, and perihilar cholangiocarcinoma and hepatocellular carcinoma. It does not apply to neuroendocrine neoplasms, hepatoblastoma, carcinomas of the extrahepatic bile ducts and gall bladder as well as benign lesions, such as adenomas, nor does it apply to non-epithelial malignancies.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Tumours, Digestive System Tumours, 5th edition, 2019.[2]

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Note 1 – Specimen(s) submitted (Core)

In assessing macroscopic specimens which contain malignant epithelial tumours of the liver it is important to establish the nature of the surgical resection.[3] Liver tumours are resected either by segmental resection[4] 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.

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.

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.

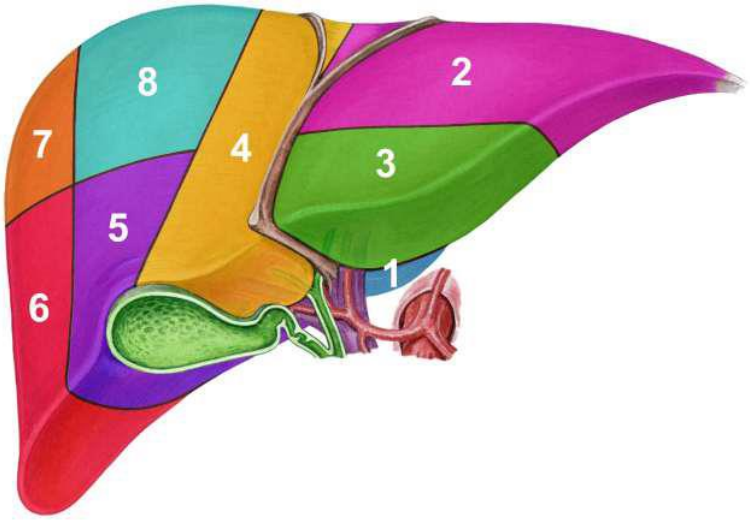

Figure 1: Segmentectomy and hepatectomy specimens. Reproduced with permission from The Royal College of Pathologists (2012). *Dataset for histopathology reporting of liver resection specimens (including gall bladder) and liver biopsies for primary and metastatic carcinoma, 2nd edition.* The Royal College of Pathologists.[5]
Right hepatectomy segments 5–8
Right trisectionectomy (extended right hepatectomy) segments 4–8
Left lateral sectionectomy segments 2–3
Left hepatectomy segments 2–4
Left trisectionectomy (extended left hepatectomy) segments 1–5 and 8
Total hepatectomy segments 1–8

Surgical intervention for cholangiocarcinomas arising at the hilum (i.e., proximal to the junction of the cystic and common hepatic duct) will generally include a length of extrahepatic duct in continuity with segments or lobes of liver. There is considerable 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 information provided on the request form. Specimens may include lymph nodes, either dissected separately by the surgeon or found at the liver hilum in the resected specimen. A regional lymphadenectomy specimen will ordinarily include six or more lymph nodes for primary intrahepatic and gallbladder cancers, and 15 lymph nodes for perihilar cholangiocarcinomas (CC).[6] Regional lymph nodes (portal nodes) are those in the hepaticoduodenal ligament: hilar, cystic duct, pericholedochal, hepatic artery, portal vein for perihilar CC. More distant nodes (extra-portal nodes) are occasionally resected and involvement of such nodes is classified as distant metastasis (M1). There is

no pN2 category for intrahepatic cholangiocarcinoma, but because the number of positive lymph nodes correlates with survival, pN2 has been added in the 8th edition of the TNM classification for cases of perihilar CC with four or more nodal metastases.[6,7]

Block identification key

The origin/designation of all tissue blocks is essential information and particularly important should the need for internal or external review arise. The reviewer needs to be clear about the origin of each block in order to provide an informed specialist opinion. Imaging documentation of macroscopic specimens, ideally with annotation, is recommended for resection specimens and can aid microscopic-macroscopic correlation. It may facilitate an understanding of the origin of specimens and aids with review of the case at a later date, as well as providing useful information for multidisciplinary meetings.

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

Because of the importance of resection margin status, it is recommended that all surgical surfaces (hepatic transection plane and hilar tissues for perihilar cholangiocarcinoma) are painted prior to specimen dissection and recorded in the block key.

The precise blocks will vary according to specimen and tumour type.[8-11] The number of blocks is influenced by tumour type. For hepatocellular carcinoma (HCC), it is recommended that a minimum of three tumour blocks be examined and all macroscopically distinctive areas should be sampled. When previous therapy has been administered microscopic examination of the entire tumour should be done when feasible. For selective sampling, sampling an entire cross section has been recommended if the tumour is $\leq$2 centimetres (cm) with an additional section for each 1 cm for larger tumours.[12] Additional sampling of areas that appear grossly viable is often necessary.

The following guidelines are provided for intrahepatic tumours:

- 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 (MiVI)).
- Liver capsule if there is a possibility of capsular invasion, i.e., where there is subjacent tumour and overlying adherent tissue or macroscopic capsular invasion. Where the capsule appears intact over subcapsular tumour, with a smooth shiny surface, histology is not required to confirm capsular integrity.
- Gallbladder bed and wall where there is adjacent intrahepatic tumour.
- Any site macroscopically suggestive of macrovascular or bile duct invasion.
- Background liver (taken as far away as possible from the tumour).

A block of representative background liver should be taken at a distance from the tumour, whether or not it looks abnormal macroscopically.

For perihilar cholangiocarcinoma, careful dissection and block taking from the biliary tree is necessary to delineate the extent and margin status. 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.

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Note 2 – Satellitosis (Core)

Hepatocellular carcinoma

In hepatocellular carcinoma (HCC) several studies have found that the presence of satellite tumours is related to recurrence but there has hitherto been little consensus on the definition of satellitosis.[13-20] The International Collaboration on Cancer Reporting (ICCR) supports the definition within the most recent WHO Classification[2] which notes that with respect to satellitosis "they may occur in close proximity to a single large dominant nodule, are often multiple and usually within 2 cm of the main tumour". They are considered to represent local spread generally within portal venules. This is to distinguish this pattern from multiple distinct (progressed HCC) and indistinct (early HCC) nodules that may represent independent primaries (refer to Figure 2). Care must be taken to distinguish genuine separate foci from apparent separation when there is actually continuous spread with an irregular leading edge.

Cholangiocarcinoma

No data are available on intrahepatic or perihilar cholangiocarcinoma.

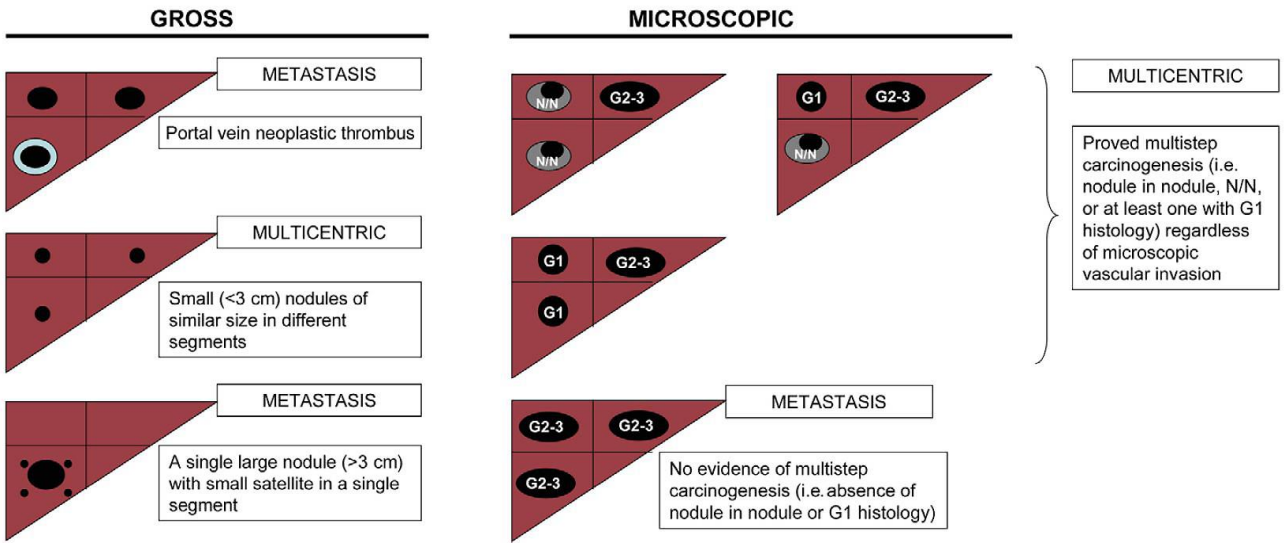

Figure 2: Multinodular HCC: main features of aid in the distinction between multicentric versus metastatic disease. Reproduced with permission from Roncalli M, Park YN and Di Tommaso L (2010). Histopathological classification of hepatocellular carcinoma. *Dig Liver Dis* 42 Suppl 3:S228-234.[21]
Legend: Multicentric versus metastatic disease can be reasonably addressed by gross (radiological) features only in the conditions depicted on the left side of the figure. In all the other conditions (right side of the figure) only a microscopic examination can address the issue by proving the multistep carcinogenesis. The possibility of a multicentric disease, followed by a metastatic one, is not illustrated in the figure. The accuracy of this evaluation is not absolute and tumour allelotyping should be performed.

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Note 3 – Macroscopic tumour rupture (Non-core)

Hepatocellular carcinoma

There are several studies analysing the role of spontaneous rupture of hepatocellular carcinoma. This is most commonly seen in Eastern Asian countries, where it is commonly associated with large tumours and often considered to carry a worse prognosis than non-ruptured HCC. This is largely a clinical diagnosis, with a typical presentation of abdominal pain and haemorrhage and confirmed radiologically/surgically. A review in 2006 by Lai et al,[22] summarised a number of small clinical studies (the largest being 60 patients) who either underwent immediate resection at the time of rupture, or staged resection. Interestingly, pathological stage and grade were not statistically different compared to non-ruptured series. Time to recurrence was shorter, but not survival. This study only described cases with hepatocellular carcinoma and rupture needs to be distinguished from peri-operative fragmentation of the capsule, which occasionally occurs with a large, bulging, soft/friable tumour.

Cholangiocarcinoma

No data are available on intrahepatic or perihilar cholangiocarcinoma.

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Note 4 – Tumour site and number (Core)

Hepatocellular carcinoma

Tumour size and number are important prognostic factors in hepatocellular carcinoma while the site may determine resectability. Based on survival data, the 8th edition of the TNM system[6,7] has subdivided the T category by tumour size, number and invasion of vessels and/or adjacent structures. For TNM staging, multiple tumours include satellitosis, multifocal nodules and intrahepatic metastases. Several clinical algorithms are used in practice to guide treatment decisions including rationale for transplantation. Guidelines for HCC based on the Barcelona Clinic Liver Cancer Classification (BCLC) (the most widely used algorithm) recommend liver resection only for patients with a single HCC (without portal hypertension).[23,24] The number of tumours is one of the most significant predictors of recurrence and overall survival[25-29] and it is correlated with the presence of microvascular invasion.[30] A tumour with an apparent surrounding satellite nodule(s) should be regarded as a single tumour when the co-nodule(s) is attached to the main tumour.[31] In this setting, the apparent satellite may represent an irregular leading edge of the tumour.

Intrahepatic cholangiocarcinoma

The number of tumours is also recognized as an important prognostic factor in intrahepatic cholangiocarcinoma.[32-36] Multifocality has been incorporated into the TNM staging system (8th edition).[6,7] In the 2010 study by Nuzzo et al,[37] patients with greater than four lesions showed significantly lower disease free and overall survival. Additionally, having greater than four lesions was found to be an important prognostic factor for recurrence. For TNM staging, multiple tumours include satellites and intrahepatic metastases.[6,7] The presence of satellite lesions has been demonstrated to negatively impact on overall survival on both univariate and multivariate analyses.[38] Roayaie et al (1998)[39] demonstrated the presence of satellite lesions to be associated with shorter disease-free survival. However, a clear definition of satellites in the setting of intrahepatic cholangiocarcinoma does not currently exist.

Location of all tumours (HCC and intrahepatic cholangiocarcinoma) should be reported since this is important for correlation with imaging when this is available.

Perihilar cholangiocarcinoma

Perihilar cholangiocarcinoma is defined as a primary carcinoma arising above the junction of the common hepatic duct and the cystic duct, and up to the second order divisions of the left and right hepatic duct – corresponding to the ducts that have peribiliary glands. The site of the perihilar CC should be described according to the ducts involved macroscopically (right, left, common hepatic duct).

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Note 5 – Maximum tumour dimension (Core)

Size of the tumour is an important determinant of stage and should be recorded in all cases of both HCC and CC. The maximum diameter, measured to the nearest millimeter, can be assessed both on the unfixed or fixed specimen (unfixed specimen avoids underestimation resulting from formalin fixation-induced shrinkage). For cases with multiple tumours, it has been recommended that size of at least 5 largest tumour nodules should be provided,[40] while a range can be expressed for additional tumour nodules.

Hepatocellular carcinoma

Large size (>5 cm) and multiple tumour nodules are unfavorable prognostic factors for patients with HCC after hepatic resection.[41,42] The TNM classification (8th edition)[6,7] also uses a dimension of 2 cm to divide stage pT1 into pT1a (solitary HCC <2 cm irrespective of vascular invasion (VI)) and pT1b (solitary HCC >2 cm without microvascular invasion). Tumour size is associated with the pathological grade of HCC, the probability of VI, and with the prognosis of HCC patients, after potentially curative treatments such as surgical resection and ablative treatments.[43-46] However, data on tumour size are controversial. In the 2014 paper by Goh et al[47] the number of nodules (>3) but not the size has been found an independent negative predictors of overall survival. The 2015 study by Kluger et al[48] also demonstrated that size alone is a limited prognostic factor.

Intrahepatic cholangiocarcinoma

Using a large multi-institutional dataset, it has been noted that the prognostic importance of tumour size in intrahepatic cholangiocarcinoma has a nonlinear threshold effect on prognosis.[33] In another study, unifocal intrahepatic cholangiocarcinoma <2 cm diameter was shown to have a superior prognosis after liver transplantation compared with larger or multifocal tumours.[49]

Perihilar cholangiocarcinoma

The maximum tumour dimension is more difficult to measure for perihilar cholangiocarcinoma, since the extent of the tumour requires histological confirmation for accurate assessment. Where possible both the linear extent of the tumour along the bile duct, and the maximum diameter of any mass lesion should be included, for correlation with pre-operative imaging.

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Note 6 – Histological tumour type (Core)

Hepatocellular carcinoma

The current WHO Classification[2] has defined specific histological/cytological subtypes of HCC (steatohepatitic hepatocellular carcinoma; clear cell hepatocellular carcinoma; macrotrabecular massive hepatocellular carcinoma; scirrhous hepatocellular carcinoma; chromophobe hepatocellular carcinoma; fibrolamellar carcinoma; neutrophil-rich hepatocellular carcinoma; lymphocyte-rich hepatocellular carcinoma) that amount together 20-30% of all HCCs and are to be distinguished from conventional/Not Otherwise Specified (NOS) HCC.

In general, the predominant subtype is used to inform the diagnosis but minimum criteria exist for clear cell, at >80%[2] and steatohepatitic HCC, at 50%.[50]

There is increasing interest in the correlation of subtypes with gene mutations.[2,51-53] As outlined in the most recent WHO Classification,[2] the diagnosis of HCC is usually straightforward with current tools of imaging and histology and molecular confirmation is not required. However, molecular analysis can help in the diagnosis of difficult cases and in the identification of specific subtypes. Several purely molecular HCC classifications have been proposed as well but none of them has yet been incorporated into routine clinical care. Integrated morphological-molecular classifications of HCC are the most likely to be robust and clinically useful but have not yet been fully validated.

The fibrolamellar subtype of HCC has a better prognosis when compared to conventional HCC as a whole, but the outcome is similar when compared to conventional HCC arising in non-cirrhotic liver.[54,55]

Cholangiocarcinoma

Cholangiocarcinoma is further classified by site into intrahepatic, perihilar and distal types.[56] Intrahepatic cholangiocarcinoma is defined as being located upstream of the second degree bile ducts. Perihilar cholangiocarcinoma is localised to the area between second degree bile ducts and the insertion of the cystic duct into the common bile duct.

Combined hepatocellular – cholangiocarcinoma (cHCC-CCA) is defined as containing unequivocal, intimately mixed elements of both hepatocellular carcinoma and cholangiocarcinoma.[2] In the WHO 5th edition,[2] these have been considered within the category of malignant biliary tumours. Collision tumours are not considered as combined neoplasms. A minimum cut off amount of each component for the diagnosis of cHCC-CCA has not been established and the diagnosis should be made regardless of the percentage of each component. The diagnosis of cHCC-CCA is based on routine histo-morphologic features and may be supported by IHC stains.[2] Some primary liver carcinomas are composed entirely of cells with histological features that are intermediate between those of hepatocytes and cholangiocytes. Such tumours also typically express IHC markers of both hepatocytic and cholangiocytic differentiation and are currently referred to as intermediate cell carcinoma.[57]

Intraductal papillary neoplasm (IPN) with an invasive component should specify the type of invasive carcinoma. IPN with pancreatobiliary differentiation of the lining epithelium usually give rise to tubular adenocarcinoma, whilst those with intestinal-type lining may be associated with a mucinous (colloid) type of invasive carcinoma, which has a better prognosis.[58]

According to the current WHO Classification 5th edition[2] (Table 1), the two main histological subtypes of intrahepatic CC are the large duct type, arising in the intrahepatic large ducts and composed of mucin secreting tumour cells and the small duct type (non-mucin secreting and mainly occurring in the hepatic periphery). Cholangiolocarcinoma (CLC) and intrahepatic cholangiocarcinoma with ductal plate malformation pattern are subtypes of small duct intrahepatic CC.

Distinction from metastatic adenocarcinoma is based on the presence of a single or dominant intrahepatic mass and absence of a known extra-hepatic primary tumour.

Rare subtypes listed in the WHO Classification[2] include adenosquamous, squamous, mucinous, signet ring, clear cell, mucoepidermoid, lymphoepithelioma-like (Epstein-Barr Virus (EBV) associated) and sarcomatous intrahepatic CCs. These are predominantly seen in large duct/perihilar tumours.

Table 1: World Health Organization classification of tumours of liver and intrahepatic bile ducts.[2]

Descriptor	ICD-O codes[a]
Malignant hepatocellular tumours and precursors	
Hepatocellular carcinoma, NOS	8170/3
Hepatocellular carcinoma, Fibrolamellar	8171/3
Hepatocellular carcinoma, Scirrhous	8172/3
Hepatocellular carcinoma, Clear cell type	8174/3
Hepatocellular carcinoma, Steatohepatitic	
Hepatocellular carcinoma, Macrotrabecular massive	
Hepatocellular carcinoma, Chromophobe	
Hepatocellular carcinoma, Neutrophil-rich	
Hepatocellular carcinoma, Lymphocyte-rich	
Malignant biliary tumours	
Cholangiocarcinoma	8160/3
Large duct intrahepatic cholangiocarcinoma	
Small duct intrahepatic cholangiocarcinoma	
Carcinoma, undifferentiated, NOS	8020/3
Combined hepatocellular carcinoma and cholangiocarcinoma[b]	8180/3

[a] The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

[b] This entity is included in the WHO Classification under Malignant biliary tumours - it is recognised that they contain two component parts.

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Note 7 – Tumour growth pattern (Non-core)

Hepatocellular carcinoma

In the WHO 5th edition[2] four growth patterns of HCC are listed: i) single distinct nodule; ii) large dominant nodule with multiple small satellite nodules; iii) cirrhotomimetic; and iv) multiple distinct nodules. Early hepatocellular carcinoma is a non encapsulated tumour with poorly defined margins measuring <2 cm in diameter (hence the terms “vaguely nodular small HCC” and “small HCC with indistinct margins” that have been used for this tumour).[59-61,62]

Early HCC is well differentiated, and has a longer time to recurrence and a higher 5-year survival rate compared with progressed HCC.

Progressed HCC shows a distinct margin (simple nodular type, simple nodular type with extranodular growth, and confluent multinodular type) or irregular margin (infiltrative type), and is mostly moderately to poorly differentiated, often with evidence of microvascular invasion. For progressed HCC of distinct nodular macroscopic type, the “simple nodular type” has a better prognosis than “simple nodular type with extranodular growth” or “confluent multinodular type”.

Intrahepatic cholangiocarcinoma

Four tumour growth patterns of intrahepatic cholangiocarcinoma are described: the mass-forming type, the periductal infiltrating type, the intraductal growth type and the mixed type.[2] Mass-forming intrahepatic cholangiocarcinoma (65% of cases) forms a well-demarcated nodule growing in a radial pattern and invading the adjacent liver parenchyma. The periductal-infiltrating type of cholangiocarcinoma (6% of cases) spreads in a diffuse longitudinal growth pattern along the bile duct, and the intra-ductal growth type (4% of cases) shows a polypoid or papillary tumour within the dilated bile duct lumen. The remaining 25% of cases of intrahepatic cholangiocarcinoma grow in a mixed mass-forming/periductal-infiltrating pattern.[62] Limited analyses suggest that the diffuse periductal-infiltrating type may be associated with a poor prognosis but the prognostic significance of growth pattern is controversial.[35,63]

Perihilar cholangiocarcinoma

The periductal infiltrating growth pattern with or without an associated mass lesion is the characteristic pattern for perihilar cholangiocarcinoma. When present, mass lesions within the perihilar tissues are frequently sparsely cellular with abundant desmoplastic stroma. Unlike most intrahepatic tumours, in which the tumour margins are clearly evident macroscopically, the extent of perihilar cholangiocarcinoma cannot always be distinguished by naked eye. There may be associated bile duct scarring or peritumoural fibrosis leading to overestimation of the tumour size macroscopically. Alternatively, isolated tumour cells without desmoplastic stroma may be present in fatty tissue beyond the apparent tumour margin. When there is direct invasion of the adjacent liver (pT2b) there is usually a more cellular, expansile growth pattern.

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Note 8 – Histological tumour grade (Core)

Hepatocellular carcinoma

Tumour grade is also related to prognosis in HCC.[8,11,12,64,65] Grading has conventionally been divided into four categories based on architectural and nuclear features according to the 1954 grading scheme of Edmondson and Steiner.[66] This classification is also quoted in standard reference texts.[67] A recent consensus document advocated a three-point grading system (well, moderately or poorly differentiated), also recommended by the WHO Classification of tumours 5th edition,[2] with the worst grade determining the overall grade. This is supported by the prognostic significance being in the separation of well- and poorly differentiated neoplasms.[12] 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), whereas poorly differentiated HCC are those where the hepatocellular nature of the tumour is not evident from the morphology. Moderately differentiated HCCs show some degree of hepatocytic differentiation.

Cholangiocarcinoma

Definitive criteria for histological grading of cholangiocarcinomas have not been established; however, the following semiquantitative grading system based on the proportion of gland formation within the tumour is commonly used for intrahepatic cholangiocarcinomas:

- Well differentiated (more than 95% of tumour composed of glands)
- Moderately differentiated (50% to 95% of tumour composed of glands)
- Poorly differentiated (up to 49% of tumour composed of glands).

It is recognized however that there are biological differences between perihilar and intrahepatic cholangiocarcinomas and it is recommended that perihilar CC should be considered as per pancreatic/large bile

duct adenocarcinomas with respect to classifying differentiation where grading is governed by the least well differentiated component rather than by assessment of the proportion of tumour composed of glandular elements. Corresponding to grading of pancreatic cancer it should be divided into 3 grades and is based on the degree of glandular differentiation, mucin production, mitotic activity and nuclear features. If heterogeneity is present then the worst grade is reported.

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Note 9 – Extent of invasion (Core)

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) can directly invade adjacent organs. Perforation of visceral peritoneum or extension to adjacent organ (other than gallbladder) is classified as pT4 with the TNM staging system.[6,7]

The presence of histological tumour invasion of adjacent organs (other than the gallbladder) indicates poor prognosis.[68-70] The most frequent location of HCC extension in other organs is the diaphragm, followed by the right adrenal gland, abdominal wall, colon, stomach and pancreas.

Tumour extension to adjacent organs should be confirmed histologically, since discrepancy may occur between macro- and microscopic examination. Published studies have demonstrated that 7%-43% of cases where invasion of HCC into an adjacent organs was suspected during surgery had histological confirmation of tumour invasion.[71-74] In a study by Zhou et al (2012),[69] preoperative diagnosis by radiological investigation was confirmed in only 12 (28.5%) cases following surgical resection.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma extending to extra-hepatic structures is classified as stage pT4 by the TNM system.[6,7] According to international guidelines,[75] stage pT4 intrahepatic cholangiocarcinoma are considered unresectable tumours.

Perihilar Cholangiocarcinoma

Accurate determination of the extent of invasion is necessary for staging, and is determined by combined macroscopic and histologic assessment of the resection specimen. Extension beyond the wall of the bile duct to surrounding adipose tissue or into adjacent hepatic parenchyma are the criteria for pT2a and pT2b tumours respectively. Stage pT3 depends on identifying invasion of the unilateral portal vein or hepatic artery, and stage pT4 on invasion of the main portal vein or hepatic artery or second order biliary radicals and contralateral portal vein or hepatic artery involvement. In practice, these are difficult to identify unless marked by the surgeon; the extent of invasion of pT4 tumours means these are rarely considered resectable.

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Note 10 – Perineural invasion (Non-core)

The significance of perineural invasion is greater for intrahepatic cholangiocarcinoma than for hepatocellular carcinoma and is particularly relevant for large duct/perihilar tumours. Mavros et al (2014)[76] undertook a systematic review of 57 studies incorporating 4756 patients with intrahepatic cholangiocarcinoma; 29% of patients had evidence of perineural invasion. In 7 of 12 studies in which data was available perineural invasion was seen to be a significant prognostic indicator on univariate analysis but did not have independent prognostic value on multivariate analysis.

Perineural invasion is a significant prognostic indicator for recurrence.[77] Recognition of perineural invasion, considered 'indeterminate' on haematoxylin-eosin (H&E) stains can be aided by IHC, e.g., for S100.

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Note 11 – Vascular invasion (Core)

Hepatocellular carcinoma

Vascular invasion (VI) is an independent prognostic factor in HCC after resection[11,64,78-83] as well as after transplantation.[84-89] VI affects survival also in early HCC.[90] For the 8th edition TNM staging system,[6,7] VI is a component of the pT stage for tumours >2 cm diameter.[6] However, tumours <2 cm diameter are staged as pT1a whether or not VI is present.

Vascular invasion (VI) is classified as MiVI. Macroscopic VI is defined as invasion of tumour into a major vessel that can be identified during macroscopic examination or radiological imaging and is part of established clinical algorithms, such as the BCLC and contributes to TNM assessment.

In the 8th edition of TNM,[6,7] involvement of a major branch of portal vein or hepatic vein is classified as (p)T4. This refers to the main right or left branch of the vein, as distinct from macroscopic VI which relates to macroscopically visible involvement of any vessel – the width of the vessel is not helpful as intravascular tumour may distend the calibre of the vein.

Microscopic vascular invasion (MiVI) is usually defined as tumour within a vascular space lined by endothelium, visible only by microscopy, identified in the liver tissue surrounding the tumour and venous vessels in the tumour capsule and/or non-capsular fibrous septa. However, there is a lack of consensus for the definition of MiVI.[91] Inter-observer and intra-observer variability in the evaluation of MiVI in HCC has been reported.[18]

Microscopic vascular invasion (MiVI) can be assessed in H&E stained sections, following strict criteria to avoid misinterpretation (i.e., presence of tumour cells in a space lined by endothelial cells, attachment of tumour cells to the vascular wall, or identification of muscular wall or elastic lamina of larger blood vessels). In challenging cases, the use of an IHC staining specific for smooth muscle or special stains for elastic fibres (e.g., Victoria blue, Orcein, E-VG) may be helpful to confirm the vascular nature of the affected structure.[91] Tumour structures suspicious for VI, but for which the criteria above are not met, can be recorded as 'indeterminate'; this would not be regarded as MiVI for staging purposes.

There are several studies that sub-classify MiVI according to distance of vessels from the HCC, number of vascular structures involved and/or number of cancer cells identified within the vessel, which were able to demonstrate prognostic significance for survival.[62,92,93,94] Recently, microscopic portal vein invasion was reported to be associated with poorer survival compared to microvessel invasion only, which was defined as newly developed microvascular structure in the tumour capsule or compressed and fibrotic peritumoral non-neoplastic liver.[95] However, these findings have not been validated by prospective studies and/or independent groups, and therefore subclassification of MiVI is not a required item at this stage.

Cholangiocarcinoma

Vascular invasion (VI) is an important prognostic factor for intrahepatic cholangiocarcinoma.[76,96-99] Macroscopic VI is a strong predictor of survival: 5-year survival has been reported to be 0% for patients with macroscopic VI.[96,97]

In the TNM classification staging system,[6,7] VI is a component of the pT stage; intrahepatic VI is important for stage pT2 in intrahepatic cholangiocarcinoma while involvement of main portal veins and hepatic arteries are staging criteria for pT3 and pT4 in perihilar CC.

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Note 12 – Coexistent pathology (Core)

Hepatocellular carcinoma

The prognosis following resection of HCC is strongly dependent on the presence and severity of underlying chronic liver disease as assessed, for example, by clinical scoring systems. Background liver disease may affect postoperative management of patients with HCC or intrahepatic cholangiocarcinoma. The severity of underlying chronic liver disease is more important that its aetiology, which may not be known to the pathologist although there may be histological pointers such as iron overload, evidence of HBV infection (ground glass hepatocytes) or a1AT accumulation. It is important to assess this as far away from the main tumour mass as possible to avoid the confounding factor of peritumoral effects. The grade of activity of steatohepatitis or chronic hepatitis for example may affect outcome and the stage of disease (i.e., degree of fibrosis) has prognostic implications in those undergoing resections as opposed to liver transplantation.[8,100] We recommend that the type of disease and degree of fibrosis are recorded separately; for the latter any one of the three main systems in widespread use for semi-quantitative assessment is suitable although it is recognised that the Kleiner and SAF systems were developed for non-alcoholic fatty liver disease while the METAVIR, Ishak and Batts-Ludwig systems were designed for those with chronic (viral) hepatitis.

The presence of dysplastic or other pre-malignant lesions in liver resections for hepatocellular carcinoma may be of value in assessing risk of second primary liver tumours in the remaining liver. Dysplastic nodules are generally divided into low and high grade.[101] Application of immunohistochemistry for glypican-3, heat shock protein 70 (HSP70) and glutamine synthetase can be helpful in the detection of early hepatocellular carcinoma in this setting.[102]

Cholangiocarcinoma

Intrahepatic CC (small duct type) has an association with cirrhosis of various causes including chronic viral hepatitis,[103] and this is emerging as an important feature in intrahepatic CC. For dysplasia involving large bile duct radicles we recommend the use of the BilIN and Intraductal papillary neoplasm of the bile ducts (IPNB) classifications described in the WHO 5th edition guidelines,[2] both of which distinguish low grade from high grade change.

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Note 13 – Response to neoadjuvant therapy (Non-core)

Hepatocellular carcinoma

Patients with HCC in cirrhosis increasingly undergo locoregional therapy using a wide variety of modalities such as radiofrequency ablation and transarterial chemo-embolization. In some instances, tumours that are beyond acceptable criteria for transplantation are successfully down-staged.[104,105-107] The response to therapy is assessed by imaging and/or decrease in α-fetoprotein (AFP) level.

Down-staging or total necrosis of the tumour following therapy has been associated with improved outcome after liver resection and transplantation.[108-111] There are limited data to determine the significance of pathologic quantification of tumour necrosis after locoregional therapy. Although figures such as 50%[112] and 90%[113]

necrosis have been used in some studies, there is insufficient evidence to make definite recommendations about cut off values for necrosis that correlate with outcome. Although not required, an estimate of extent of necrosis can provide valuable feedback to the clinical team to correlate it with the therapy response as assessed by imaging.[108,110]

There are no definite guidelines on how to assess the extent of necrosis and the pathological analysis in most studies has not been performed in a systematic manner. The overall extent of necrosis and any accompanying fibrosis should be estimated based on a combination of gross and microscopic findings. The extent of necrosis should be reported in up to five of the largest tumour nodules.[12]

Cholangiocarcinoma

Neoadjuvant chemoradiotherapy has been used in patients with cholangiocarcinoma. The presence of complete tumour necrosis is associated with a favourable prognosis in patients subsequently undergoing liver transplantation for perihilar cholangiocarcinoma.[114,115] However, at the present time there are no definite guidelines on how to assess the extent of necrosis or other features that may be indicative of tumour regression in cholangiocarcinoma.

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Note 14 – Margin status[116] (Core)

The status of residual tumour following treatment is classified in TNM8[6,7] as follows: R0 – no residual tumour; R1 – microscopic residual tumour; and R2 – macroscopic residual tumour. Wittekind et al (2009)[117] further refined this in rectal carcinoma where R1 refers to tumours with a clearance of <1 mm. This approach has subsequently been variably adopted by pathologists with respect to oesophageal, stomach and pancreatic carcinomas. It is worthy of note however that many other ICCR tumour datasets include resection margin status but do not use this form of R classification, and the TNM Cancer Staging Manuals[6,7] do not comment on R status for liver cancers. Given the lack of an international consensus or clear evidence base in malignant liver tumours it may be most appropriate to document clearance and distance to margins (including liver parenchyma, bile ducts, vessels and porta hepatis connective tissue) with such malignancies rather than apply the refined R0, 1, 2 approach taken in gastrointestinal tumours.

Hepatocellular carcinoma

A meta-analysis of 5 trials of treatment in hepatocellular carcinoma found no difference in recurrence or survival for <10 millimetres (mm) compared with ≥10 mm minimal distance of the tumour to the resection margin.[118] However, a review of 14 retrospective case series (4197 patients with 10 year survival data) found that a distance of the tumour >10 mm from the resection margin was a significant positive prognostic factor.[119]

More recently margins <1 mm or >1 mm are reported in several series as significant on multivariate analysis, including large HCCs >10 cm,[120] and may be predictive of local recurrence.[121]

Intrahepatic cholangiocarcinoma

For intrahepatic cholangiocarcinoma there are a few publications citing margin status as a prognostic factor on multivariate analysis.[122-124] A systematic review of intrahepatic CC did not include margin status among significant prognostic factors.[76]

Perihilar cholangiocarcinoma

In the absence of published evidence for perihilar cholangiocarcinoma, and the similarities between biliary and pancreatic duct cancer, some have argued that the same approach to the definition of R1 resection - i.e., cancer cells <1 mm from the transection or dissection margin - is appropriate[125] but evidence for the prognostic significance of this is limited.[126] The presence of BilIN at the bile duct transection margin should be recorded although again the clinical significance of this is uncertain in perihilar tumours.

In summary, margin status is considered to be a required item for all three tumour types in the dataset. In line with other sites, margins should be assessed macroscopically, and blocks taken to confirm microscopically, noting that in addition to the parenchymal margin there are bile duct and vascular transection margins and porta hepatis and bile duct radial margin (for perihilar cholangiocarcinoma[125]) representing the dissection plane. For this reason, painting the surface of the specimen prior to dissection is important, so that the margins can be identified from the block key and assessed microscopically.

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Note 15 – Lymph node status (Core)

Hepatocellular carcinoma

It should be noted that lymph nodes may not always be present in specimens resected for hepatocellular carcinoma. There is no strong evidence of prognostic significance of local nodal metastases in hepatocellular carcinoma. Lymph node involvement is common in fibrolamellar subtype of HCC.

Cholangiocarcinoma

The pattern of metastatic spread of intrahepatic cholangiocarcinoma to lymph nodes is in part determined by the location of the tumour. For those involving the right lobe of the liver the regional nodes include the hilar, periduodenal and peripancreatic chains. For tumours in the left lobe the regional lymph nodes include hilar and gastrohepatic nodes. Spread to coeliac and/or periaortic and caval nodes is regarded as distant metastases.

Lymph node metastases in intrahepatic and perihilar cholangiocarcinoma have been identified as an important predictor of prognosis.[35,76] As noted, a pN2 category has been introduced in TNM8[6,7] for perihilar CC with four or more lymph node metastases.

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Note 16 – Ancillary studies (Non-core)

The recording of additional studies performed on tissue from resections with cholangiocarcinoma or hepatocellular carcinoma is regarded as good practice. This includes molecular analysis and immunohistochemistry. Immunohistochemical markers that may be used to demonstrate hepatocellular differentiation in poorly differentiated tumours include arginase-1, Hep Par 1, pCEA, CD10, BSEP, AFP and glypican-3.[127,128] There is some evidence that immunoreactivity for markers (e.g., K19) in hepatocellular carcinoma in >5% of cells may endow a poorer prognosis[129] but this is not yet widely applied in practice.[130-132] Studies involving high-throughput sequencing and gene expression profiling have identified distinct molecular subtypes of HCC, with some clinico-pathological correlates. Although these approaches are not currently used in routine practice it is anticipated that an improved understanding of HCC biology may eventually translate into developing novel targeted therapies.[51-53,133] Recent successes in immunotherapies against liver tumours, including immune checkpoint inhibitors, have further raised interests in the immune microenvironment. This involves interactions between tumour cells, immune cells, and non-immune stromal cells including fibroblasts

and endothelial cells. Understanding the comprehensive histopathological picture of the tumour immune microenvironment, in addition to molecular and genetic approaches, may further potentiate the effort for precision medicine in the era of tumour-targeting immunotherapy in liver malignancies.[134]

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