

# Intrahepatic Cholangiocarcinoma, Perihilar Cholangiocarcinoma and Hepatocellular Carcinoma Histopathology Reporting Guide



Family/Last name  Date of birth

Given name(s)

Patient identifiers  Date of request  Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED. [SCOPE OF REPORTING GUIDE](#)

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

- Not specified       Indeterminate
- Liver
  - Total hepatectomy
  - Segmental resection (List segments or type of segmentectomy)
  - Wedge resection (Describe site/segment)
- Extrahepatic bile duct
- Gallbladder
- Diaphragm
- Lymph nodes (Specify site/s)
- 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

Specify site	No./site (if possible)
<input type="text"/>	<input type="text"/>

## MAXIMUM TUMOUR DIMENSION (Note 5)

Cannot be assessed

Tumour identification	Max dimension
<input type="text"/>	<input type="text" value=""/> mm
<input type="text"/>	<input type="text" value=""/> mm
<input type="text"/>	<input type="text" value=""/> mm
<input type="text"/>	<input type="text" value=""/> mm
<input type="text"/>	<input type="text" value=""/> mm

For a large number of tumours include a range

mm to  mm

## BLOCK IDENTIFICATION KEY (Note 6)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

## HISTOLOGICAL TUMOUR TYPE (Note 7)

- Hepatocellular carcinoma
- Hepatocellular carcinoma, fibrolamellar variant
- 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

**TUMOUR GROWTH PATTERN** (Note 8)

**Hepatocellular carcinoma:**

- Cannot be determined
- Small nodular type with indistinct margin
- Margin distinct
  - Simple nodular type
  - Simple nodular type with extranodular growth
  - Confluent multinodular type
- Margin irregular (infiltrative type)

**Intrahepatic, and perihilar cholangiocarcinoma:**

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

**HISTOLOGICAL GRADE** (Note 9)

- Not applicable  Well differentiated/G1
- Cannot be assessed  Moderately differentiated/G2
- Poorly differentiated/G3

**EXTENT OF INVASION** (Note 10)

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

**VASCULAR INVASION** (Note 11)

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

**PERINEURAL INVASION** (Note 12)

- (*Applicable to intrahepatic and perihilar cholangiocarcinoma*)
- Not identified  Indeterminate  Present

**RESPONSE TO NEOADJUVANT THERAPY** (Note 13)

- Complete necrosis (no viable tumour)
  - Incomplete necrosis (viable tumour present)
- ↓
- Percentage necrosis  %
- No necrosis
  - No prior treatment
  - Response cannot be assessed (Explain reasons)

**MARGIN STATUS** (Note 14)

- Cannot be assessed
- Not involved by invasive carcinoma
  - Distance of tumour to closest margin  mm
  - OR
  - Clearance is  $\geq 10$  mm
- Involved by invasive carcinoma
  - Specify margin/s, if possible
- Involved by high-grade dysplasia/carcinoma in situ (*Applicable to cholangiocarcinoma only*)
  - Specify margin/s, if possible

**LYMPH NODE STATUS** (Note 15)

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

**COEXISTENT PATHOLOGY** (Note 16)

**Other histopathological features**

- Steatosis  None identified
- 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

### Dysplastic/pre-malignant lesions

None identified

#### BILIARY INTRA-EPITHELIAL NEOPLASIA (BiIN)

Absent  Present



- BiIN-1  
 BiIN-2  
 BiIN-3

#### LOW-GRADE HEPATOCELLULAR DYSPLASTIC NODULE

Absent  Present

#### HIGH-GRADE HEPATOCELLULAR DYSPLASTIC NODULE

Absent  Present

Other


### ANCILLARY STUDIES (Note 17)

Not performed OR describe


### PATHOLOGICAL STAGING (TNM 8th edition)##

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

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

#### Primary tumour (pT)

##### HEPATOCELLULAR CARCINOMA (Liver excluding intrahepatic and perihilar bile ducts)

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

##### INTRAHEPATIC CHOLANGIOCARCINOMA\*\* (Intrahepatic bile ducts)

- TX Primary tumour cannot be assessed  
 T0 No evidence of primary tumour  
 Tis Carcinoma in situ (intraductal tumour)  
 T1a Solitary tumour 5cm or less in greatest dimension without vascular invasion  
 T1b Solitary tumour more than 5cm 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 structures by direct hepatic invasion

##### 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 perihilar 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 metastases (pM)

- Not applicable  
 M1 Distant metastasis

\*\* Combined Hepatocellular-Cholangiocarcinomas are staged as per Intrahepatic Cholangiocarcinoma

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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 carcinomas, hepatoblastoma, carcinomas of the extrahepatic bile ducts, gall bladder and benign lesions such as adenomas, nor does it apply to non-epithelial malignancies.

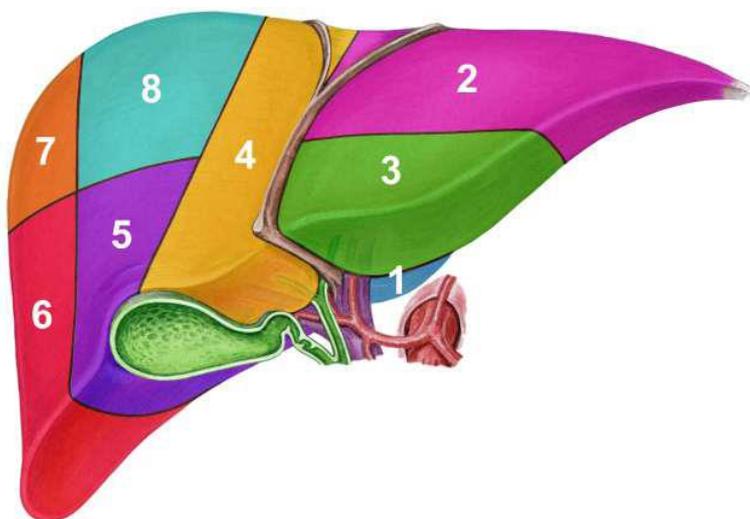
## Note 1 – Specimen(s) submitted (Required)

### Reason/Evidentiary Support

In assessing macroscopic specimens which contain malignant epithelial tumours of the liver it is important to establish the nature of the surgical resection.<sup>1</sup> Liver tumours are resected either by segmental resection<sup>2</sup> 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 specimens<sup>3</sup>**

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

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. Note that this reporting guide does not apply to more distal bile duct carcinomas resected without hepatectomy. 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).<sup>4</sup> Regional lymph nodes are those in the hepaticoduodenal ligament: hilar, cystic duct, pericholedochal, hepatic artery, portal vein for perihilar CC. More distant 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 TNM8 for cases with four or more metastases.<sup>4,5</sup>

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## Note 2- Satellitosis (Recommended)

### Reason/Evidentiary Support

#### Hepatocellular carcinoma

In hepatocellular carcinoma (HCC) several studies have found that the presence of satellite tumours is related to recurrence but there is no consensus on the definition of satellitosis.<sup>6-13</sup> Roayaie et al<sup>11</sup> used a definition of tumours less than or equal to 2 cm and located of less than or equal to 2 cm from the main tumour. The Liver Cancer Study Group of Japan included in their definition that the satellite nodules should be histologically similar or less differentiated than the main tumour.<sup>7</sup> Reviewing the additional literature we suggest a definition of “*when a satellite nodule is separated from the main tumour by a distance greater than that of the satellite diameter*”. It is acknowledged however that accurate distinction between satellitosis and intrahepatic metastasis can be difficult.

#### Cholangiocarcinoma

No data are available on intrahepatic or perihilar cholangiocarcinoma.

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## Note 3 - Macroscopic tumour rupture (Recommended)

### Reason/Evidentiary Support

#### Hepatocellular carcinoma

There are several studies describing spontaneous rupture of hepatocellular carcinoma. This is most commonly seen in the East, associated with large tumours and with a worse prognosis than non-ruptured HCC. This is largely a clinical diagnosis, typically presenting with abdominal pain and haemorrhage and confirmed radiologically/surgically. A review in 2006<sup>14</sup> summarises a number of small series of patients who either underwent immediate resection at the time of rupture, or staged resection. The largest of these described series was in 60 patients.<sup>14</sup> 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 (Required)

### Reason/Evidentiary Support

#### Hepatocellular carcinoma

Tumour site, size and number are important prognostic factors in hepatocellular carcinoma. Based on survival data, the 8th edition of the TNM system<sup>4</sup> has subdivided the T category by tumour size and number. For TNM staging, multiple tumours include satellitosis, multifocal tumours and intrahepatic metastases. Treatment guidelines for HCC based on the Barcelona Clinic Liver Cancer staging system (also proposed in Europe and the United States) recommend liver resection only for patients with a single HCC (without portal hypertension).<sup>15,16</sup> The number of tumours is one of the most significant predictors of recurrence and overall survival<sup>17-21</sup> and it is correlated with the presence of microvascular invasion.<sup>22</sup> 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.<sup>23</sup> In this setting, the apparent satellite may represent an irregular leading edge of the tumour.

#### Intrahepatic cholangiocarcinoma

The number of tumours and tumour size (refer to **Note 5 MAXIMUM TUMOUR DIMENSION**) have also been recognized as important prognostic factors in intrahepatic cholangiocarcinoma.<sup>24-28</sup> Multifocality has been incorporated into the TNM staging system (8<sup>th</sup> edition).<sup>4</sup> In the study by Nuzzo et al<sup>29</sup> 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. The presence of satellite lesions has been demonstrated to negatively impact on overall survival on both univariate and multivariate analyses.<sup>30</sup> Roayaie et al<sup>31</sup> 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. Representative sections should be obtained from each nodule.

#### Perihilar cholangiocarcinoma

Perihilar cholangiocarcinoma is defined as a cholangiocarcinoma 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 (Required)

### Reason/Evidentiary Support

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,<sup>32</sup> 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.<sup>33,34</sup> TNM8 also uses a dimension of 2cm to divide stage pT1 into pT1a solitary HCC <2 cm irrespective of microvascular invasion and pT1b for patients with solitary HCC >2 cm without microvascular invasion. Tumour size is associated with the pathological grade of HCC, the probability of vascular invasion, and with the prognosis of HCC patients, after potentially curative treatments such as surgical resection and medical ablation.<sup>35-38</sup> However, data on tumour size are controversial. In a recent paper by Goh et al<sup>39</sup> the number of nodules (>3) but not the size has been found an independent negative predictors of overall survival (OS). The study by Kluger et al<sup>40</sup> also demonstrated that size alone is a limited prognostic factor.

#### Intrahepatic cholangiocarcinoma

Using a large multi-institutional data set, it has been noted that the prognostic importance of tumour size in intrahepatic cholangiocarcinoma has a nonlinear threshold effect on prognosis.<sup>25</sup> 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.<sup>41</sup>

#### 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. 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 - Block identification key<sup>42</sup> (Recommended)**

### **Reason/Evidentiary Support**

The origin/designation of all tissue blocks should be recorded and it is preferable to document this information in the final pathology report. This is 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. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. Photography of macroscopic specimens is used with resection specimens in many laboratories and considered best practice. Annotation of captured images can facilitate an understanding of the origin of specimens in such circumstances and aids with review of the case at a later date. Furthermore it can provide useful information in the context of multidisciplinary meetings.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks, for example for further immunohistochemical 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. Occasionally different colours can be used to identify specific surgical margins. This information should also be recorded in the block key.

The precise blocks will vary according to specimen and tumour type.<sup>43-46</sup> The number of blocks is influenced by tumour type. For HCC, it is recommended that a minimum of three tumour blocks be examined and all macroscopically distinctive areas should be sampled. 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).

- 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 vascular or bile duct invasion.
- Background liver (taken as far away as possible from the tumour).

A block of representative background liver should be taken, 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 7 - Histological tumour type (Required)**

### **Reason/Evidentiary Support**

#### Hepatocellular carcinoma

With the exception of the fibrolamellar variant of HCC, which is regarded in the current World Health Organisation (WHO) classification as a distinct tumour from HCC, the architectural and cytological variants of HCC (such as trabecular, compact, pseudoacinar, scirrhous, sarcomatoid, clear cell, steatohepatic etc) are all considered as HCC.

Early HCC is a low grade and early stage HCC measuring 2 cm diameter and with a vaguely nodular appearance that merges imperceptibly into the adjacent parenchyma.<sup>47</sup> It has a different blood supply and imaging profile compared with conventional (progressed) HCC, and can co-exist with progressed HCC giving a nodule-in-nodule appearance. It is not separately classified from HCC in the current WHO schema.

Fibrolamellar 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.<sup>48,49</sup>

#### Cholangiocarcinoma

Cholangiocarcinoma is further classified by site into intrahepatic, perihilar and distal types.<sup>50</sup> 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 is defined as containing unequivocal, intimately mixed elements of both hepatocellular carcinoma and cholangiocarcinoma.<sup>51</sup> Collision tumours are not considered as combined neoplasms. The classical type shows areas of typical HCC and cholangiocarcinoma, which can be confirmed with histochemical (mucin) and immunohistochemical stains.<sup>52</sup> Some tumours exhibit putative stem cell or progenitor cell features, now recognised as a specific subtype in the 2010 WHO classification.<sup>51</sup> A variety of immunohistochemical markers can be used to support the diagnosis, but these tumours remain incompletely understood. Although the demographics and clinical features of combined HCC-ICCs including age, gender, association with HBV, HCV and cirrhosis resemble those of HCC in both TNM 8<sup>th</sup> edition and 7<sup>th</sup> edition of WHO classification such combined tumours are staged as for IH-CC and for reporting purposes we recommend that the data set is used as for typical IH-CCs.

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.<sup>53</sup>

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

There are other liver tumours such as hepatoblastoma, neuroendocrine tumours, rhabdoid tumour, carcinosarcoma etc, which have an epithelial component, however, it is not envisaged that this dataset would be used for such resections.

## WHO classification of tumours of the liver and intrahepatic bile ducts<sup>a</sup>

Descriptor	ICD-O codes
<b>Epithelial tumours: hepatocellular</b>	
<i>Malignant</i>	
Hepatocellular carcinoma	8170/3
Hepatocellular carcinoma, fibrolamellar variant	8171/3
Undifferentiated carcinoma	8020/3
<b>Epithelial tumours: biliary</b>	
<i>Malignant</i>	
Intrahepatic cholangiocarcinoma	8160/3
Intraductal papillary neoplasm with an associated invasive carcinoma	8503/3*
Mucinous cystic neoplasm with an associated invasive carcinoma	8470/3
<i>Malignancies of mixed or uncertain origin</i>	
Combined hepatocellular-cholangiocarcinoma	8180/3

<sup>a</sup> 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.

\* These new codes were approved by the IARC/WHO Committee for ICD-O at its meeting in March 2010.

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## Note 8 - Tumour growth pattern (Recommended)

### Reason/Evidentiary Support

#### Hepatocellular carcinoma

There are two principal forms of nomenclature about HCC growth pattern. In the WHO blue book 4th edition<sup>51</sup>; nodular, massive, and diffuse macroscopic types are described for progressed HCC. Early hepatocellular carcinoma is a separate entity, which is a low-grade, early-stage tumour. Grossly, early HCC usually is a poorly defined nodular lesion 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).

In the schema of the Liver Cancer Study Group of Japan<sup>54</sup> macroscopic types of HCC include margin indistinct (small nodular type with indistinct margin), margin distinct (simple nodular type, simple nodular type with extranodular growth, confluent multinodular type), and margin irregular (infiltrative type). In this classification the small nodular type with indistinct margin (vaguely nodular appearance) corresponds to early HCC histologically.<sup>47,55,56</sup> Early HCC is well differentiated, and has a longer time to recurrence and a higher 5-year survival rate compared with progressed HCC.<sup>57</sup>

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”.<sup>57,58</sup>

**Figure 2: Schematic diagram of the macroscopic types of hepatocellular carcinoma**

Small nodular type with indistinct margin	
Simple nodular type with distinct margin	
Simple nodular type with extranodular growth	
Confluent multinodular type	
Margin irregular (infiltrative 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.<sup>51</sup> 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.<sup>59</sup> 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.<sup>27,60</sup>

### Perihilar cholangiocarcinoma

The periductal infiltrating growth pattern is the characteristic pattern for periductal cholangiocarcinoma, with or without an associated mass lesion. 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 be distinguished by naked eye. There may be associated bile duct scarring or peritumoral fibrosis, while isolated tumour cells may be present in fatty tissue beyond the apparent tumour margin. Extensive sampling of hilar cholangiocarcinoma is necessary to identify the extent, dimension and margin status of these tumours. When there is direct invasion of the adjacent liver (pT2b) there is usually a more cellular, expansile growth pattern.

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## **Note 9 - Histological grade (Required)**

### **Reason/Evidentiary Support**

#### Hepatocellular carcinoma

Tumour grade is also related to prognosis in HCC.<sup>43,46,61-63</sup> Grading has conventionally been divided into four categories based on architectural and nuclear features according to the 1954 classification of Edmondson and Steiner.<sup>64</sup> This classification is also quoted in standard reference texts.<sup>65</sup> 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.<sup>63</sup> 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.

In a systematic review of studies investigating outcomes following liver transplantation or surgical resection for HCC, fifteen specifically mentioned the prognostic role of grading: in 8 studies grading was statistically related to prognosis both by univariate as well as at multivariate analysis. In 4 studies it was statistically related to prognosis at univariate but not at multivariate analysis, whilst in the remaining 3 studies grading was not statistically related to prognosis.

However most studies only refer to grading being assessed according to Edmondson and Steiner criteria but several mention G1 G2 G3 whereas others mention G1 G2 G3 G4. Almost all of them condense G1 and G2 as “Low Grade” and G3 and G4 as “High Grade” (studies where only G1 G2 G3 are mentioned always considered G3 as “High Grade”). A single study addressed inter-observer variation and the performance of pathologists was poor when applying G1 G2 G3 G4 and better when comparing only Low versus High Grade. We recommend use of the three point scale (G1, G2, G3).

#### Cholangiocarcinoma

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

- Grade cannot be assessed

- Well differentiated (more than 95% of tumour composed of glands)
- Moderately differentiated (50% to 95% of tumour composed of glands)
- Poorly differentiated (5% 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.

**↑ Back**

## **Note 10 - Extent of invasion (Required)**

### **Reason/Evidentiary Support**

#### 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.<sup>4</sup>

The presence of histological tumour invasion of adjacent organs indicates poor prognosis.<sup>66-68</sup> 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 HCC extending to the adjacent organs was suspected during surgery had histological confirmation of tumour invasion.<sup>69-72</sup> In a more recent study,<sup>67</sup> preoperative diagnosis by radiological investigation was confirmed in only 12 (28.5%) cases following surgical resection.

#### Cholangiocarcinoma

Intrahepatic cholangiocarcinoma extending to extra-hepatic structures is classified as stage pT4 by the TNM system. According to international guidelines,<sup>73</sup> stage pT4 ICC are considered unresectable tumours.

**↑ Back**

## **Note 11 - Vascular invasion (Required)**

### **Reason/Evidentiary Support**

#### Hepatocellular carcinoma

Vascular invasion (VI) is an independent prognostic factor in HCC after resection<sup>46,61,74-79</sup> as well as after transplantation.<sup>80-85</sup> VI affects survival also in early HCC.<sup>86</sup> For the TNM staging system, vascular invasion is a component of the pT stage.<sup>4</sup>

VI is classified as macroscopic or microscopic (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 staging systems, such as Barcelona Clinic Liver Cancer classification (BCLC).

For the pathological classification in the 8<sup>th</sup> edition of TNM,<sup>4</sup> involvement of major branch of portal vein or hepatic vein is classified as pT4. This refers to the main right or left branch of the vein, as distinct from macroscopic vascular invasion 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.

MiVI is usually defined as tumour within a vascular space lined by endothelium, visible only on 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.<sup>87</sup> Inter-observer and intra-observer variability in the evaluation of MiVI in HCC has been reported.<sup>11</sup>

MiVI can be assessed in Haematoxylin-Eosin 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 for larger blood vessels). In challenging cases, the use of immunohistochemical staining specific for smooth muscle (such as h-caldesmon) may be helpful to confirm the vascular nature of the suspicious lesions. Special stains for elastic fibres (e.g. Victoria blue, Orcein, E-VG) also can be useful.<sup>87</sup> When appearances are suspicious for vascular invasion, but the criteria above are not met, this 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 channels involved and/or number of cancer cells identified within the vessel, which are able to demonstrate prognostic significance for survival.<sup>59,88, 89, 90</sup> However, these studies have not been validated by prospective studies and/or independent groups, and therefore sub classification of MiVI is not a required item at this stage.

### Cholangiocarcinoma

Vascular invasion is an important prognostic factor for ICC.<sup>91-95</sup> Macroscopic vascular invasion is a strong predictor of survival: 5-year survival has been reported to be 0% for patients with macroscopic vascular invasion.<sup>91,92</sup>

For TNM staging system, vascular invasion is a component of the pT stage.

**↑ Back**

## **Note 12 - Perineural invasion (Recommended)**

### **Reason/Evidentiary Support**

The significance of perineural invasion is greater for intrahepatic cholangiocarcinoma than for hepatocellular carcinoma. Mavros et al<sup>95</sup> undertook a systematic review of 57 studies incorporating 4756 patients with ICC. 29% of patients had evidence of perineural invasion. In 7 of 12 studies in which data was available this was seen to be a significant prognostic indicator on univariate analysis but did not have independent prognostic value on multivariate analysis.

Perineural invasion is particularly common in perihilar CC and is a significant prognostic indicator for recurrence.<sup>96</sup> Recognition of perineural invasion, considered 'indeterminate' on H&E stains can be aided by S100 immunohistochemistry.

**↑ Back**

## Note 13 - Response to neoadjuvant therapy (Recommended)

### Reason/Evidentiary Support

#### 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.<sup>97-99</sup> The response to therapy is assessed by imaging and/or decrease in AFP level.

Down-staging or total necrosis of the tumour following therapy has been associated with improved outcome after liver resection and transplantation.<sup>100-103</sup> There are limited data to determine the significance of pathologic quantification of tumour necrosis after locoregional therapy. Although figures such as 50%<sup>104</sup> and 90%<sup>105</sup> 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 down-staging observed on imaging.<sup>100,102</sup>

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. 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  $\leq 2$  cm with an additional section for each 1 cm for larger tumours.<sup>63</sup> Additional sampling of areas that appear grossly viable is often necessary. The overall extent of necrosis should be estimated based on a combination of gross and microscopic findings. The extent of necrosis should be reported in up to 5 of the largest tumour nodules.<sup>63</sup>

#### 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.<sup>106,107</sup> 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<sup>108</sup> (Required)

### Reason/Evidentiary Support

#### Hepatocellular carcinoma

A meta-analysis of 5 trials of treatment in hepatocellular carcinoma found no difference in recurrence or survival for  $<10$  mm compared with  $>10$  mm margin.<sup>109</sup> A review of 14 retrospective case series (4197 patients with 10 year survival data) found a margin  $>10$  mm was a significant positive prognostic factor.<sup>110</sup> More recently margins  $<$  or  $>1$  mm are reported in several series as significant on multivariate analysis, including for large HCC  $>10$  cm,<sup>111</sup> and predictive of margin recurrence.<sup>112</sup> The actual distance in mm up to 10 mm is a component of the Singapore nomogram predicting freedom from relapse.<sup>113</sup>

#### Intrahepatic cholangiocarcinoma

For cholangiocarcinoma there are a few publications citing margin status as a prognostic factor on multivariate analysis<sup>114-116</sup> A systematic review of intrahepatic CC did not include margin status among significant prognostic factors.<sup>95</sup> There are no systematic reviews or meta-analysis specifically addressing perihilar cholangiocarcinoma.

### Perihilar cholangiocarcinoma

The question of microscopic margin involvement is considered in detail in the Royal College of Pathologists (RCPATH) dataset<sup>117</sup> for pancreatic, ampulla of Vater and common bile duct cancers (2010). The distinction between transection margin, dissection (circumferential) margin and peritoneal surface is well described. The recommendation is that involvement of dissection or transection margins of <1 mm should be regarded as R1 positive margin, whereas peritoneal surface involvement requires carcinoma cells to be seen on the surface. There is evidence cited of the prognostic relevance of this approach in pancreatic and distal bile duct cancer. Given the absence of published evidence for perihilar cholangiocarcinoma, and the similarities between biliary and pancreatic duct cancer, the same approach to the definition of R1 resection - i.e. cancer cells <1 mm from the transection or dissection margin - is appropriate. Using this approach, there is an association of positive margin with prognosis.<sup>118</sup>

Therefore margin status is considered to be a required item for all three tumour types in the dataset, with the clearance in mm if under 10 mm. 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 hilar/porta hepatis, hepatic vein, and radial margins. 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. Tumours with a margin <1 mm are generally regarded as R1 resection, in line with other sites, although there is not currently a specific evidence base for this approach in HCC or CC.

**↑ Back**

## **Note 15 - Lymph node status (Required)**

### **Reason/Evidentiary Support**

#### 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 variant 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 liver the regional nodes include the hilar, periduodenal and peripancreatic chains. For left sided tumours 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.<sup>27,95</sup> As noted, a pN2 category has been introduced in TNM8 for perihilar CC with four or more lymph node metastases.

**↑ Back**

## Note 16 - Coexistent pathology (Required)

### Reason/Evidentiary Support

#### 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 ICC. The severity of underlying chronic liver disease is more important than its aetiology, which may not be known to the pathologist. 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 explant.<sup>43,119</sup> 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 system was developed for steatotic conditions 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.<sup>120</sup> 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.<sup>121</sup>

#### Cholangiocarcinoma

Intrahepatic CC has an association with cirrhosis of various causes including chronic viral hepatitis,<sup>122</sup> and this is emerging as an important feature in intrahepatic CC. For dysplasia involving bile duct radicles we recommend the use of the BillIN classification described in the WHO 4<sup>th</sup> Edition guidelines where BillIN 3 is equivalent to high grade dysplasia.

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## Note 17 - Ancillary findings (Recommended)

### Reason/Evidentiary Support

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. There is some evidence that immunoreactivity markers of “stemness” (e.g. K19, Epcam, etc) in hepatocellular carcinoma in >5% of cells may endow a poorer prognosis<sup>123</sup> but this is not yet widely applied in practice.<sup>124-126</sup>

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