



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

☐ indicates multi-select values ☐ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

(Applicable to primary resections only)

☐ Information not provided

☐ Information provided

▼ **Age (years)**

☐ 0-<1 ☐ ≥1-<8 ☐ ≥8

Serum alpha fetoprotein (AFP) level at diagnosis (ng/mL)

☐ Information not provided

☐ <100

☐ 100-1.2 million

☐ >1.2 million

Preoperative chemotherapy

☐ Information not provided

☐ No known preoperative chemotherapy given

☐ Preoperative chemotherapy given, *specify*

History of prematurity

☐ No

☐ Yes

Associated genetic syndromes, malformations or other conditions, *specify*

PRETEXT clinical staging, *specify*

Low birth weight (<1,500 grams)

☐ No

☐ Yes

Other clinical information, *specify*

OPERATIVE PROCEDURE (Note 2)

☐ Not specified

☐ Right lobectomy

☐ Extended right lobectomy

☐ Medial segmentectomy

☐ Left lateral segmentectomy

☐ Total left lobectomy

☐ Orthotopic liver transplant

☐ Non-anatomic/wedge resection

☐ Other, *specify*

▼

TUMOUR SITE (Note 3)

☐ Not specified

☐ Left lobe

☐ Right lobe

☐ Other, *specify*

▼

TUMOUR FOCALITY (Note 4)

☐ Unifocal

☐ Multifocal

▼ Specify number of tumours in specimen

☐ Cannot be assessed, *specify*

▼

TUMOUR DIMENSIONS^a (Note 5)

Nodule 1

Greatest dimension mm

Additional dimensions mm x mm

Nodule 2

Greatest dimension mm

Additional dimensions mm x mm

Nodule 3

Greatest dimension mm

Additional dimensions mm x mm

☐ Cannot be assessed, *specify*

▼

^a Specify for each nodule.

BLOCK IDENTIFICATION KEY (Note 6)

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

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 7)

(Value list based on the World Health Organization Classification of Paediatric Tumours, 5th edition (2023))

- ☐ Hepatoblastoma, epithelial type, fetal pattern (mitotically inactive/well differentiated, well-differentiated fetal)
- ☐ Hepatoblastoma, epithelial type, fetal pattern (mitotically active/crowded)
- ☐ Hepatoblastoma, epithelial type, embryonal pattern
- ☐ Hepatoblastoma, epithelial type, pleomorphic pattern (poorly differentiated)
- ☐ Hepatoblastoma, epithelial type, macrotrabecular pattern
- ☐ Hepatoblastoma, epithelial type, small cell undifferentiated pattern
- ☐ Hepatoblastoma, epithelial and mesenchymal type, without teratoid features
- ☐ Hepatoblastoma, epithelial and mesenchymal type, with teratoid features
- ☐ Hepatocellular neoplasm, not otherwise specified (NOS)
- ☐ Hepatoblastoma, other (i.e., blastemal, cholangioblastic), specify

TREATMENT EFFECT (Note 8)

- ☐ Not identified
- ☐ Present

Percentage of tumour necrosis

	%
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MARGIN STATUS (Note 9)

- ☐ Cannot be assessed
- ☐ No viable tumour at the margin

Distance of tumour from closest margin

	mm
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Specify closest margin(s), if possible

- ☐ Viable tumour present at the margin

Specify margin(s), if possible

LYMPHOVASCULAR INVASION (Note 10)

- ☐ Indeterminate
- ☐ Not identified
- ☐ Present

LYMPH NODE STATUS (Note 11)

- ☐ No nodes submitted or found

Number of lymph nodes examined

--

- ☐ Not involved
- ☐ Involved

Number of involved lymph nodes

--

Location of involved lymph nodes, specify

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COEXISTENT PATHOLOGY (Note 12)

- ☐ None identified
- ☐ Present, specify

ANCILLARY STUDIES (Note 13)

- ☐ Not performed
- ☐ Performed (select all that apply)

- ☐ Beta-catenin immunohistochemistry
- ☐ Glypican 3
- ☐ INI1
- ☐ Other immunohistochemical stains, specify test(s) and result(s)

- ☐ Other, record test(s), methodology and results

Representative blocks for ancillary studies, specify those blocks best representing tumour and/or normal tissue for further study

HISTOLOGICALLY CONFIRMED DISTANT METASTASES

(Note 14)

- ☐ Not applicable
- ☐ Not identified
- ☐ Present (select all that apply)

- ☐ Lung
- ☐ Brain
- ☐ Bone
- ☐ Other, specify site(s)

PATHOLOGICAL STAGING (Note 15)**Children's Oncology Group (COG) staging^b**

- ☐ Stage I Tumour completely resected, margins grossly and microscopically negative for tumour
- ☐ Stage II Tumour grossly resected with evidence of microscopic residual tumour
- ☐ Microscopic residual tumour present at hepatic resection margin
- ☐ Microscopic residual tumour present at extrahepatic resection margin
- ☐ Intraoperative tumour spill
- ☐ Stage III Unresectable tumour^c
- ☐ Tumour within explant
- ☐ Macroscopic tumour visible at resection margin(s)
- ☐ Regional lymph node metastasis present

^b Czauderna P, Lopez-Terrada D, Hiyama E, Häberle B, Malogolowkin MH, Meyers RL. Hepatoblastoma state of the art: pathology, genetics, risk stratification, and chemotherapy. *Curr Opin Pediatr.* 2014 Feb;26(1): 19-28.

^c Tumours that are considered by the attending surgeon not to be resectable without undue risk to the patient, tumours within explanted livers, partially resected tumours with macroscopic tumour left at margin, or tumours with regional lymph node metastasis (regional lymph nodes include hilar, hepatoduodenal ligament, or caval lymph nodes).

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 (NHMRC) levels of evidence¹). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC).

Non-morphological testing e.g., molecular or immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

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 DAC.

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Scope

The dataset has been developed for the pathological reporting of resection specimens of paediatric hepatoblastoma, including tumours in the hepatocellular neoplasm not otherwise specified (HCN-NOS) category. It is not applicable to hepatocellular carcinomas (HCC) nor to other primary or metastatic paediatric neoplasms of the liver.

The authors of this dataset can be accessed [here](#).

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Note 1 – Clinical information (Core and Non-core)

Clinical information can be provided by the clinician, included in the pathology request form, pathology report, or patient medical record.

Hepatoblastoma is an aggressive embryonal tumour with a historically high mortality of approximately 76% reported in the early 1980s.^{2,3} However, recent advances in chemotherapy and the development of new surgical techniques have dramatically improved the prognosis of these children to up to 90% five year survival in some regions.⁴ Tumour-specific adverse prognostic factors include high stage using the COG surgical or PRETEXT staging systems, certain histologic subtypes, older age, vascular invasion and multifocality.^{3,5-7}

Age (Core)

Hepatoblastoma occurs most often in infants and young children between six months and four years of age, with a median age of onset of 18 months. Occasionally, cases are diagnosed in neonates, and in less than 10% of cases, hepatoblastomas are diagnosed prenatally.⁸ When diagnosed in older children, hepatoblastoma is associated with a worse prognosis,⁹ and more frequently shows features seen in the HCN-NOS diagnostic group.¹⁰

Serum alpha fetoprotein (AFP) level at diagnosis (Core)

Alpha-fetoprotein (AFP) is elevated in more than 90% of patients with hepatoblastoma and is a useful diagnostic biomarker also used to monitor response to therapy and disease progression; however, elevated serum AFP can be detected in other tumours. Given physiologic high AFP levels at birth and during the first months of life, correct reference values should be used in infants up to two years of age.¹¹ An AFP level less than 100 nanograms per millilitre (ng/mL) was previously considered an adverse prognostic factor and associated with small cell undifferentiated (SCU) histology. However, a recent Children's Oncology Group (COG) study suggests that once malignant rhabdoid tumours are excluded, which were previously categorised as SCU prior to their molecular characterisation, SCU histology occurring within a hepatoblastoma with otherwise typical morphology is not a poor prognostic variable, and AFP levels less than 100 ng/mL in patients with SCU histology are rare.¹²

Preoperative chemotherapy (Core)

It is important to know if the patient has received prior chemotherapy in order to correctly evaluate histological findings in hepatoblastoma specimens.

History of prematurity (Non-core)

There is extensive evidence supporting the association of hepatoblastoma and extreme prematurity,^{13,14} with a risk increase by 15- to 40-fold in children with very low birth weight (less than 1,500 grams).¹⁵

Associated genetic syndromes, malformations or other conditions (Non-core)

Several congenital abnormalities, constitutional genetic syndromes, malformations, and other clinical conditions have been associated with hepatoblastoma.¹⁶ Increased incidence warranting surveillance is seen in patients with Beckwith-Wiedemann syndrome, hemihypertrophy syndromes, Trisomy 18 and other rare syndromes.^{13,17} However, the majority of hepatoblastomas appears to be sporadic.

PRETEXT clinical staging (Non-core)

The TNM staging system is not used for hepatoblastoma. In North America, the COG staging system, based on postoperative evaluation, was historically used. Stage I pure fetal hepatoblastoma with complete surgical

resection can be cured with excellent long-term survival with surgery alone and without the need for adjuvant chemotherapy.¹⁸ The PRETEXT (PRE-Treatment EXTent of disease) clinical staging system is based on radiological analysis of tumour location, described by involvement of surgical liver segments, and extrahepatic extent, and it was designed by the International Childhood Liver Tumour Strategy Group (SIOPEL).¹⁹ Based on multiparameter analysis, including PRETEXT, four risk groups have currently been adopted in the ongoing prospective international clinical trial for the risk stratification of children with hepatoblastoma.²⁰

Other clinical information, including low birth weight (Non-core)

Additional clinical findings, such as low birth weight, also add to the clinical context.

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Note 2 – Operative procedure (Core)

Information regarding the nature of the operative procedure should be provided, with any additional annotation that may be necessary (Figure 1). The various surgical procedures listed include those that attempt primary resection or resection post chemotherapy, and the judicious use of transplant where necessary for conventionally unresectable cases. Should the operative specimen not be one typically obtained for hepatoblastoma resection or transplantation, this needs to be clearly indicated.

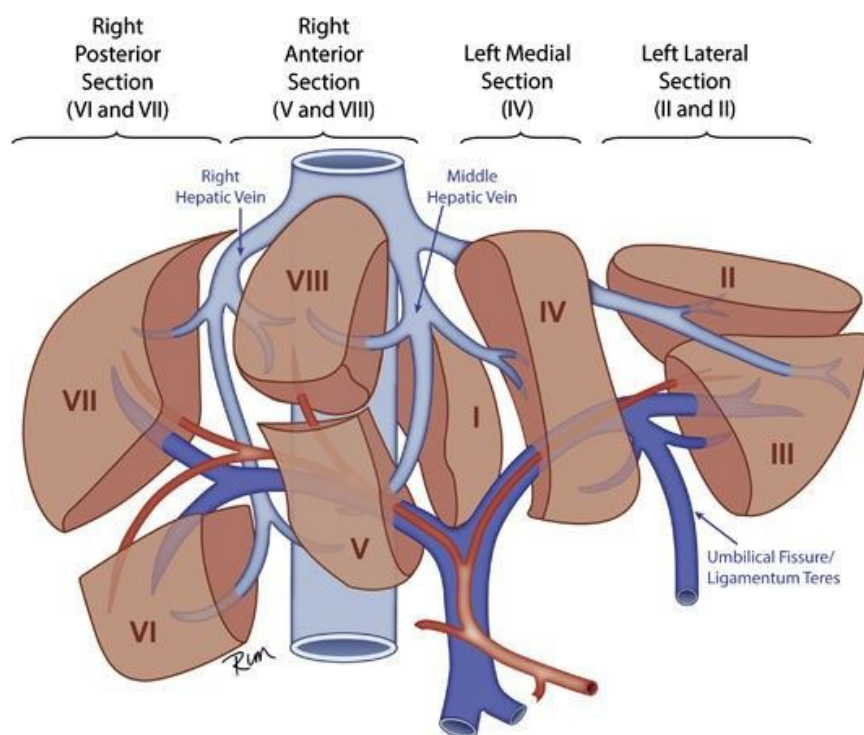


Figure 1: PRETEXT is distinct from Couinaud 8-segment (I–VIII) anatomic division of the liver. PRETEXT defines 4 ‘Sections’. Boundaries of each section defined by the right and middle hepatic veins, and umbilical fissure. This figure was published in *Modern Pathology* (2014), 27, Dolores López-Terrada et al, Towards an international pediatric liver tumor consensus classification: proceedings of the Los Angeles COG liver tumors symposium, pages 472-491, Copyright Elsevier.²¹

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Note 3 – Tumour site (Core)

Hepatoblastoma usually presents as a single mass, involving the right lobe (55-60%), the left lobe (15%) or both lobes of the liver.²² It is important to know the location of the tumour to determine surgical resectability.

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Note 4 – Tumour focality (Core and Non-core)

It has been shown that multifocal disease is an independent factor associated with worse event free and overall survival.⁵ For these reasons, it has been recommended that the presence of multifocality should be a component of prognostic stratification.^{5,7} Reporting of tumour focality is a core reporting item, while recording the number of tumours in any multifocal specimen is a non-core reporting item.

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Note 5 – Tumour dimensions (Core and Non-core)

Hepatoblastoma often presents as a single, large expansive mass compressing the surrounding liver, which usually is architecturally and functionally normal. Occasionally, intrahepatic dissemination via portal veins leads to multiple discrete nodules, but most cases have only contiguous extension. Evaluating the extent of hepatic involvement and metastases is of utmost importance in the management of children with hepatoblastoma. The PRETEXT system,²³ developed by the SIOPEL, is currently the primary mode for determining stage and assigning risk categorisation, given its strong prognostic value, as documented by the Children's Hepatic Tumours International Collaboration (CHIC) Group in 2017.²⁰ Reporting of greatest dimension is a core reporting item, whereas reporting additional dimensions is a non-core reporting item.

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Note 6 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and 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. It may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

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

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Note 7 – Histological tumour type (Core)

Histologic diagnosis of paediatric hepatoblastoma is based on the 2023 World Health Organization (WHO) Classification of Paediatric Tumours, 5th edition (Table 1).²⁴

Table 1: 5th edition World Health Organization classification of paediatric liver tumours.²⁴

Descriptor	ICD-O codes ^a
Hepatoblastoma	8970/3
Fibrolamellar hepatocellular carcinoma	8171/3
Paediatric hepatocellular carcinoma	8170/3
Mesenchymal hamartoma	
Calcifying nested stromal-epithelial tumour	8975/1
Embryonal sarcoma of the liver	8991/3
Hepatic congenital haemangioma	9120/0
Hepatic infantile haemangioma	9131/0
Hepatic angiosarcoma	9120/3

^a These morphology codes are from the International Classification of Diseases for Oncology, fourth edition (ICD-O-4).²⁵ Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site.

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Hepatoblastoma

Hepatoblastomas are embryonal tumours that are classified by the presence of epithelial, mesenchymal and, or primitive components. The majority of hepatoblastomas are epithelial, demonstrating a combination of patterns that may recapitulate stages of liver development.

Epithelial pattern: Fetal

The fetal pattern is characterised by uniform epithelial, round to polygonal cells with central, small nuclei, typically without nucleoli, showing granular, eosinophilic, or clear cytoplasm. Cells are generally arranged in thin trabeculae and may display a distinctive ‘light and dark’ pattern. Extramedullary hematopoiesis (EMH) is often present.

Epithelial patterns: Fetal, mitotically inactive/well-differentiated (Pure fetal)

The Pure Fetal histology (PFH, also known as ‘well differentiated’ or mitotically inactive fetal’) is characterised by cells displaying fetal pattern with only a few mitoses. It is important that the diagnosis of PFH, a relatively rare histological type of hepatoblastoma associated with very favourable prognosis, only applies to entirely upfront resected tumours consisting 100% of this pattern.

Differentiating this pattern from the uninvolved adjacent liver may be challenging and requires immunohistochemistry (IHC), particularly in very young patients. Beta-catenin, glypican 3 (GPC3) and glutamine synthetase (GS), usually positive in the tumour cells, may be helpful in these instances.

Epithelial patterns: Fetal, mitotically active/crowded

The fetal, mitotically active hepatoblastoma pattern is a common epithelial pattern characterised by cells similar to those in the PFH, but mitotically active. Tumour cells, sometimes larger than those in PFH, generally show granular, eosinophilic cytoplasm, nuclear beta-catenin and GPC3 diffuse cytoplasmic staining.

Extramedullary hematopoiesis (EMH) is frequently encountered. Mitotically active/crowded and pleomorphic fetal subtypes are not associated with favourable prognosis.

Epithelial patterns: Embryonal

The embryonal pattern is one of the most common epithelial hepatoblastoma types and typically replicates the histology of the developing liver in the embryo. It is composed of medium-sized cells with high nuclear to cytoplasmic ratio, large, angulated nuclei, organised in trabeculae and sometimes forming rosettes, tubular or glandular structures.

Mitoses are frequent. Embryonal pattern is often encountered adjacent or admixed with fetal pattern, sometimes organised in nests or tumour nodules. Tumour cells are diffusely nuclear beta-catenin positive, GPC3 and SALL4 strongly positive, and variably GS positive.²⁴

Epithelial patterns: Pleomorphic

This pattern is characterised by pleomorphic tumour cells with variation in nuclear size and shape that may or may not meet criteria for anaplasia as defined for Wilms tumours.²⁴ Tumour cells may demonstrate giant cell transformation. GPC3 and beta-catenin (nuclear) staining are usually positive in these areas.

Epithelial patterns: Macrotrabecular

The macrotrabecular pattern is characterised by the presence of trabeculae five or more cells thick, characteristic of paediatric HCCs. When this pattern is seen in hepatoblastoma, consideration should be given to the diagnosis of HCN-NOS for tumours positive for nuclear beta-catenin, or HCC, particularly for older children and when underlying liver disease is present.¹⁰

Epithelial patterns: Small cell undifferentiated (SCU)

Primitive small blue, round to ovoid cells with scant cytoplasm and stippled chromatin, either organised in nests or admixed with other components, are often seen in hepatoblastoma. Primitive SCU cells generally show nuclear expression of beta-catenin, as well as co-expression of cytokeratins and vimentin. Tumours exhibiting diffuse SCU pattern must be differentiated from rhabdoid tumours, characterised by *SMARCB1* alterations, by either INI1 IHC or molecular testing.¹²

The presence of SCU was historically believed to be associated with unfavorable outcomes. However, immunohistochemical and/or molecular characterisation of rhabdoid tumours of the liver and recent follow up COG and CHIC studies,²⁶ have demonstrated that, while rhabdoid tumours are associated with poor outcomes, the presence of SCU 'component' retaining INI1 expression is not associated with adverse prognosis, as previously proposed.

The term 'blastemal component' is sometimes used to designate nests of primitive cells with SCU morphology at the periphery of tumour nodules, occasionally associated with crowded fetal cells. These two patterns (SCU and blastemal), sometimes used interchangeably, are believed to represent primitive, multipotent cells capable of multidirectional differentiation, although the true significance of these primitive hepatoblastoma component is not totally understood.²⁴

Other epithelial patterns

Other epithelial patterns of hepatoblastoma include squamoid, glandular and biliary differentiation. In the cholangioblastic hepatoblastoma type the biliary proliferation is neoplastic and exhibits nuclear beta-catenin staining, in contrast to reactive ductules, often seen admixed with other patterns in the periphery of the tumour nodules. These reactive duct proliferations, often seen in treated tumours, display CK19, less often CK7, and characteristically negative (membranous-only with no nuclear staining) beta-catenin.

Mesenchymal hepatoblastoma

The 2014 International Pediatric Liver Tumour Consensus Classification noted this component as part of a mixed epithelial-mesenchymal hepatoblastoma with or without teratoid elements.²¹ Mixed hepatoblastomas are characterised by the presence of any epithelial elements admixed with mesenchymal components, including spindle cells, osteoid, cartilage, rhabdomyoblastic differentiation, and fat.²⁷ Hepatoblastomas are classified as mixed with teratoid elements when containing neuroectodermal derivatives such as neuroepithelium, melanin, or glial cells. Glandular elements including epithelium resembling yolk sac tumour, may sometimes be present. Mesenchymal components generally express nuclear beta-catenin but are GPC3 and SALL4 negative.

Hepatocellular neoplasm not otherwise specified (HCN-NOS)

The provisional term HCN-NOS is used for malignant paediatric hepatocellular tumour difficult to classify. The usual differential diagnosis is hepatoblastoma versus HCC. Nuclear beta-catenin immunoreactivity is present, at least focally. This provisional entity was created to include lesions previously described as often aggressive tumours with overlapping features of epithelial hepatoblastoma and HCC,²¹ and are currently not classifiable as reported by SIOPEL and COG studies. HCN-NOS occur most frequently in older children presenting with very high AFP levels, and no predisposing hepatic disease. The 'NOS' nomenclature reflects the necessity to highlight the provisional nature of this category until molecular studies better define its biology.

Hepatoblastoma or well-differentiated HCC type cells in a macrotrabecular or nested pattern, as well as pleomorphic or multinucleated cells may be present in HCN-NOS tumours. Beta-catenin nuclear expression further supports the biologic relationship of these tumours with hepatoblastoma. Furthermore, recent molecular profiling of a series of HCN-NOS revealed biological features common to both hepatoblastoma and HCC and showed that tumours exhibiting these features had poor outcomes irrespective of patient age, emphasising the importance of molecular testing and early therapeutic intervention in patients with HCN-NOS tumours.¹⁰ However, it is acknowledged that molecular testing may not be available in some parts of the world.

Patients with HCN-NOS are currently treated as hepatoblastoma and not as HCC patients in the Paediatric Hepatic International Tumour Trial (PHITT).²⁸

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Note 8 – Treatment effect (Non-core)

The extent of tumour necrosis following neoadjuvant chemotherapy has been reported as an independent prognostic factor in newly diagnosed hepatoblastoma.²⁹ However, it has not been confirmed in large clinical studies and so this element is considered non-core. Macroscopically these are well-demarcated areas of congestion/haemorrhage, calcifications and fibrosis. However, it is difficult to predict whether these areas present necrosis or viable hepatoblastoma components; therefore, adequate sampling with a photographic tumour block diagram is useful.

Histological features include coagulative-type necrosis, cystic degenerative changes, a fibrohistiocytic response with haemosiderin-laden and/or foamy macrophages.

Also noted are:

- So-called peliosis-like round foci surrounded by a thick fibrous wall showing no endothelial lining and containing densely packed erythrocytes in various stages of degeneration.
- Peliotic foci characterised by rounded pools of blood within epithelial tumour sinusoids surrounded by tumour cells.⁶
- Bands of fibrosis adjacent to viable tumour/necrosis often containing ductular proliferations.
- Increased osteoid formation and/or squamous/keratin formations often eliciting a foreign body-type granulomatous response in mixed hepatoblastoma.

Chemotherapy effect on viable hepatoblastoma cells includes either differentiation into fetal epithelial hepatoblastoma or into pleomorphic/HCC-like features. For all components, immunostaining for beta catenin and GPC3 is valuable.

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Note 9 – Margin status (Core)

Due to the overall rarity of hepatoblastoma, there are only few published studies regarding the predictive value of positive tumour margins or the distance of tumour to various margins in disease recurrence or prognosis, and their conclusions have not been uniform.³⁰⁻³² However, it is the consensus opinion of the DAC that tumour involvement of the margin or distance from the margins be considered a core element. It is recommended that the surgeon be consulted to determine critical foci within margins for microscopic evaluation.³³ Macroscopically positive margins should be confirmed microscopically and documented, with the margin specified, if possible. If the margins are macroscopically free of tumour, sampling of the margin in the region closest to the nearest identified tumour nodule should be performed, and the tumour distance to the margin should be documented, with the margin specified if possible. In cases with multiple nodules, documentation of the location of the tumour nodule(s) and margin status may be important in correlating with imaging findings,^{34,35} particularly for those nodules that may not have been radiographically apparent on preoperative imaging.

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Note 10 – Lymphovascular invasion (Core)

Macroscopic portal and hepatic venous involvement may have prognostic significance, and therefore should be reported, typically by preoperative imaging.^{7,20} Pathologic vascular invasion has been investigated in a limited number of studies. A retrospective study found that patients with invasion identified by microscopic examination were more likely to be older, present with metastatic disease, and have a worse three year overall survival.³⁶ Another retrospective study reported the presence of either macroscopic or microscopic lymphovascular invasion resulted in a significantly decreased disease-free survival period, when compared to those that did not demonstrate lymphovascular invasion.³⁷ Other studies support the association between lymphovascular invasion and survival.³⁸⁻⁴⁰ Given the preliminary evidence in the literature that vascular invasion as a whole may be prognostic in hepatoblastoma, the consensus opinion of the DAC is that macroscopic lymphovascular invasion be reported when identified, and that microscopic intratumoral and

extratumoral vascular invasion be recorded at the discretion of the pathologist, but not required to be reported, until further evidence is available.

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Note 11 – Lymph node status (Core)

Lymph node metastases are not common in hepatoblastoma. Regional lymph nodes of the hepatic region include the hilar, hepatoduodenal ligament, and caval lymph nodes, which are likely to be sampled at the time of surgical resection or transplant. Nodal involvement of the inferior phrenic lymph nodes or other lymph nodes distal to the hilar, hepatoduodenal ligament, and caval lymph nodes is considered distant metastasis.²³

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Note 12 – Coexistent pathology (Non-core)

Hepatoblastoma usually arises in ‘healthy’ livers, therefore, the presence of coexistent pathology could be helpful to differentiate hepatoblastoma from HCC, which has an incidence of about 20% in paediatric patients, including children with chronic viral hepatitis, congenital metabolic/cholestatic diseases, and other miscellaneous disorders. Tumour mass effect should not be confused with underlying liver disease in hepatoblastoma. Some hepatoblastoma cases may be rarely associated with underlying liver diseases (such as cancer predisposition syndromes). However, the clinical impact of these associations has not been well evaluated.

Although coexistent pathology is considered as a non-core element, the following findings are recommended to be reported, if present:

- Fibrosis: portal/periportal/bridging/cirrhosis
- Inflammation: portal/lobular/interface, mild/moderate/severe
- Steatosis: proportion/type/distribution
- Cholestasis: canalicular/hepatocellular
- Other factors: vascular abnormalities, parenchymal abnormalities such as nodular regenerative hyperplasia, etc.

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Note 13 – Ancillary studies (Core and Non-core)

Beta-catenin IHC for the demonstration of nuclear or nuclear and cytoplasmic expression in the various tumour components, especially the embryonal type, is important diagnostically and can be useful for its differential diagnosis. GPC 3 IHC is also useful for the diagnosis of hepatoblastoma and to confirm hepatocellular differentiation. Finally, INI1 serves to exclude the diagnosis of malignant rhabdoid tumour in hepatoblastomas with SCU areas. For these reasons, the three above-mentioned markers may be critical for the diagnosis of hepatoblastoma and are regarded as core elements. However, beta-catenin, Glypican-3 and INI1 IHC may not be required in all cases.

Resection specimens of hepatoblastoma patients do not usually cause major differential diagnostic problems. However, IHC may be required for diagnosis in several instances, including when the tumour histology of the resection specimen differs from the biopsy post chemotherapy, to highlight viable tumour areas, and to distinguish different tumour components.

Other IHC markers may be considered as optional, such as cytokeratin 19 for highlighting cholangioblastic differentiation, and co-expression of cytokeratin and vimentin for SCU or blastemal areas. Molecular studies are currently not considered core elements in the reporting of hepatoblastoma resection specimens as the evidence is still emerging. However, single gene tests, targeted next generation sequencing studies, or other genomic or profiling studies such as SNP arrays, may provide a comprehensive molecular profile, or be diagnostically or prognostically useful for these tumours that are known for their low mutational burden, and for the diagnosis of HCN-NOS or HCC.⁴¹

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Note 14 – Histologically confirmed distant metastases (Core)

Documentation of known metastatic disease is an important part of the pathology report. Such information, if available, should be recorded with as much detail as is available, including the site, whether the specimen is a histopathology or cytopathology specimen and with reference to any relevant prior surgical pathology specimens.

If distant sites are sampled and histologically shown to be negative, metastatic disease is 'not identified', whereas if sampling is not performed, this section is 'not applicable'.

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Note 15 – Pathological staging (Non-core)

Currently, no pathologic staging system is clinically applicable in hepatoblastoma. Historically, COG staging was used in the United States, which combines data from imaging and pathologic data from surgical resections and is still useful to pathologists reviewing the specimens.⁴² COG pathologic staging has been clinically replaced by the PRETEXT/POSTTEXT staging system in current trials, which is strictly based on imaging data.²⁸

PRETEXT/POSTTEXT staging uses computed tomography and magnetic resonance imaging exclusively to determine the location and extent of hepatic involvement of hepatoblastoma pre-treatment (PRETEXT) based on the Couinaud's system of segmentation of the liver.^{23,28} PRETEXT is based on cross-sectional imaging assessment of the extent of tumour involvement of the four main sections of the liver: right posterior section (Couinaud 6 and 7); right anterior section (Couinaud 5 and 8); left medial section (Couinaud 4a and 4b); and left lateral section (Couinaud 2 and 3). PRETEXT assignment to groups I-IV (PRETEXT I, II, III, or IV) is determined by the number of contiguous uninvolved sections of the liver. Annotation factors are additionally evaluated to indicate vascular involvement, nodal involvement, caudate involvement, tumour multifocality, rupture, and metastases.

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References

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- 4 Kahla JA, Siegel DA, Dai S, Lupo PJ, Foster JH, Scheurer ME and Heczey AA (2022). Incidence and 5-year survival of children and adolescents with hepatoblastoma in the United States. *Pediatr Blood Cancer* 69(10):e29763.
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