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REVIEW

Pathology reporting of hepatoblastoma resections: recommendations from the international collaboration on cancer reporting

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Pathology reporting of hepatoblastoma resections: recommendations from the international collaboration on cancer reporting

Aims: Hepatoblastoma is the most common primary malignant tumour of the liver diagnosed in children and its incidence is increasing worldwide. Ongoing international clinical trials and scientific collaborative efforts are attempting to standardize the diagnosis, risk stratification and management of young patients diagnosed with this rare cancer, which includes surgical resection of the tumour. Here we report the

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Abbreviations: AFP, alpha-fetoprotein; CAP, College of American Pathologists; CHIC, Children's Hepatic tumors International Collaboration; CK19, cytokeratin 19; CK7, cytokeratin 7; COG, Children's Oncology Group; DAC, Data Authoring Committee; DSC, Dataset Steering Committee; EMH, extramedullary hematopoiesis; GPC3, Glypican 3; GS, gluthamine synthetase; HCC, hepatocellular carcinoma; HCN-NOS, Hepatocellular Neoplasm not otherwise specified; ICCR, International Collaboration on Cancer Reporting; ICD, International Classification of Diseases; IHC, Immunohistochemistry; IPPA, International Paediatric Pathology Association; NHMRC, National Health and Medical Research Council; PHITT, Paediatric Hepatic International Tumour Trial; POSTEXT, extent of tumor after therapy; PPS, Paediatric Pathology Society; PRETEXT, pretreatment extent of tumor; SCU, small cell undifferentiated; SIOPEL, International Society of Paediatric Oncology Liver Tumour Group; SPP, Society for Pediatric Pathology; WHO, World Health Organization.

international consensus-based dataset for the pathology reporting of hepatoblastoma resection specimens. The dataset was developed under the auspices of the International Collaboration on Cancer Reporting (ICCR), a global alliance of international pathology and cancer organizations.

Methods and results: According to the ICCR's guidelines for dataset development, an international expert panel including paediatric pathologists and a paediatric oncologist specialized in liver tumours developed a set of core and non-core data items for hepatoblastoma resection specimens based on critical review and discussion of current evidence available. Members of the panel were specialists working in tertiary paediatric hospitals, central reviewers for international paediatric liver tumours consortia and/or involved in paediatric liver tumour trials expert committees. Commentaries were provided to support each data item, explaining the rationale for selecting them as a 'core' or 'non-core' elements, their clinical relevance and highlighting potential areas of lack of evidence, including clinical, macroscopic, microscopic and ancillary testing considerations. The hepatoblastoma dataset was finalized and ratified following international public consultation and is published on the ICCR website for wide implementation.

Conclusion: This is the first international dataset developed by an international expert panel for reporting hepatoblastoma resection specimens aimed to promote high-quality, standardized pathology reporting of these rare paediatric liver tumours. The adoption and implementation of this hepatoblastoma data set, freely available worldwide on the ICCR website (www.iccr-cancer.org/data-sets), will facilitate accurate reporting and enhance the consistency of data collection, support retrospective and inform prospective research and ultimately help to improve clinical outcomes of children with hepatoblastoma.

Keywords: checklist, dataset, hepatoblastoma, ICCR guidelines, liver tumours, paediatrics, protocol, structured report, synoptic report

Introduction

Hepatoblastoma is the most common primary malignant tumour of the liver in children, frequently diagnosed during the first 2 years of life. Complete surgical resection is curative but only achievable in a proportion of patients. Most children are treated by surgical resection in combination with chemotherapy, which has significantly improved survival. International, collaborative, multidisciplinary initiatives have developed standardized staging and diagnostic criteria, including imaging and histological guidelines, now incorporated into a multi-institutional cooperative international trial called the Paediatric Hepatic International Tumour Trial (PHITT).[1] Given the rarity of hepatoblastoma, continued international cooperation is essential to establish better clinical standards, improve outcomes and further characterize the biology of these tumours. These efforts require a systematic approach to pathology reporting of hepatoblastoma resection specimens worldwide in order to assure comprehensive collection of data and to allow the comparison of clinical data sets worldwide.

The International Collaboration on Cancer Reporting (ICCR) initiated the development of datasets for the structured reporting of pathology data for paediatric tumours following the publication of the 5th Edition of the World Health Organization (WHO) Classification of Paediatric Tumours in 2022.[2] The ICCR aims to develop internationally standardized and evidence-based datasets for the global pathology reporting of cancer. This report provides a summary of the ICCR recommendations for the pathology reporting of hepatoblastoma resection specimens.

Methods

This dataset was created for the reporting of hepatoblastoma resection surgical specimens. A separate dataset for the reporting of hepatoblastoma biopsy specimens will be drafted in the future. The process of dataset development by the ICCR was overseen by a Dataset Steering Committee (DSC). The DSC appointed a 'Series Champion' (MRM) to coordinate the development of all datasets for paediatric tumours, and a Chair (DLT) to oversee the production of the hepatoblastoma resection dataset. An international expert panel was established, including 12 paediatric pathologists (all authors on this paper), one paediatric oncologist and a Project Manager (FW), forming the Dataset Authoring Committee (DAC). The final document includes a set of elements and value lists

(responses), followed by an explanatory commentary section.

The expert panel categorized each element as core or non-core, following literature review and available evidence. Core elements were those considered to be essential in the pathology report and essential for diagnosis, risk stratification and patient management. In general, core elements had evidentiary support at Level III-2 or above, based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence document.[3] Elements that did not meet these criteria were deemed non-core and considered to be clinically important and appropriate for good practice, but not yet validated or used regularly for patient management at the time of dataset development.

The working draft was first developed by the Project Manager after reviewing all published datasets pertaining to hepatoblastoma resection specimens. This draft was edited by the Chair and circulated to the DAC for discussion during a series of teleconferences. After additional review by the Chair, the draft was recirculated to the DAC for further review and approval. The draft was uploaded to the ICCR website for a period of 2 months for public comment.

The ICCR notified all members and relevant stakeholders via email, including global pathology and cancer organizations. The draft dataset was also publicized on the ICCR website. The documents were reviewed after compilation of all feedback; approved by the DAC; and finally ratified by the DSC. The reporting guide is freely available at https://www.iccr-cancer.org/datasets/published-datasets/paediatrics/hepatoblastoma/.

Results

SCOPE

The dataset was developed for the pathological reporting of resection specimens of 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.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world, these types of testing are limited by the available resources. To encourage the global adoption of ancillary tests for patient benefit, 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. A summary of the core elements is outlined in Table 1, and each is described below:

CLINICAL INFORMATION

Many features relating to clinical information are core; although there are some considered non-core features (Table 1). Clinical information can be provided by the clinician, included in the pathology request form, pathology report or patient medical record.

Age

Hepatoblastoma occurs most often in infants and young children between 6 months and 4 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.[4] When diagnosed in older children, hepatoblastoma is associated with a worse prognosis,[5] and more frequently shows features seen in the HCN-NOS diagnostic group.[6]

Serum alpha-fetoprotein level at diagnosis

Alpha-fetoprotein (AFP) is elevated in more than 90% of patients with hepatoblastoma and is a useful diagnostic biomarker 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 2 years of age.[7] An AFP level less than 100 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 categorized as SCU prior to their molecular characterization, 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.[8]

Preoperative chemotherapy

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

Table 1. Core and non-core elements for the pathology reporting of the hepatoblastoma dataset

Core	Non-core
Clinical information • Age • Serum alpha-fetoprotein (AFP) level at diagnosis • Preoperative chemotherapy	Clinical information • History of prematurity • Associated genetic syndromes, malformations or other conditions • PRETEXT clinical staging • Low birth weight (<1500 g) • Other clinical information
Operative procedure	
Tumour site	
Tumour focality • Unifocal • Multifocal	Tumour focality • Specify number of tumours
Tumour dimensions Nodule 1 • Greatest dimension Nodule 2 • Greatest dimension Nodule 3 • Greatest dimension	Tumour dimensions Nodule 1 • Additional dimensions Nodule 2 • Additional dimensions Nodule 3 • Additional dimensions
Histological tumour type	Block identification key
Margin status	Treatment effect
Lymphovascular invasion	Coexistent pathology
Lymph node status	
Ancillary studies • Beta-catenin immunohistochemistry • Glypican 3 • INI 1	Ancillary studies • Other immunohistochemical stains • Other • Representative blocks for ancillary studies
Histologically confirmed distant metastases	Pathological staging (Children's Oncology Group staging)

OPERATIVE PROCEDURE

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.

TUMOUR SITE

Hepatoblastoma usually presents as a single mass, involving the right lobe (55%–60%), the left lobe (15%) or both lobes of the liver.[10] It is important to know the location of the tumour to determine surgical resectability.

TUMOUR FOCALITY

Tumour focality is a core element; although the number of tumours is a non-core feature (Table 1).

Hepatoblastoma is an aggressive embryonal tumour with a historically high mortality of approximately 76% reported in the early 1980s.[11,12] However, recent advances in chemotherapy and the development of new surgical techniques have dramatically improved the prognosis of these children to up to 90% 5-year survival in some regions.[13] 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.[12,14-16]

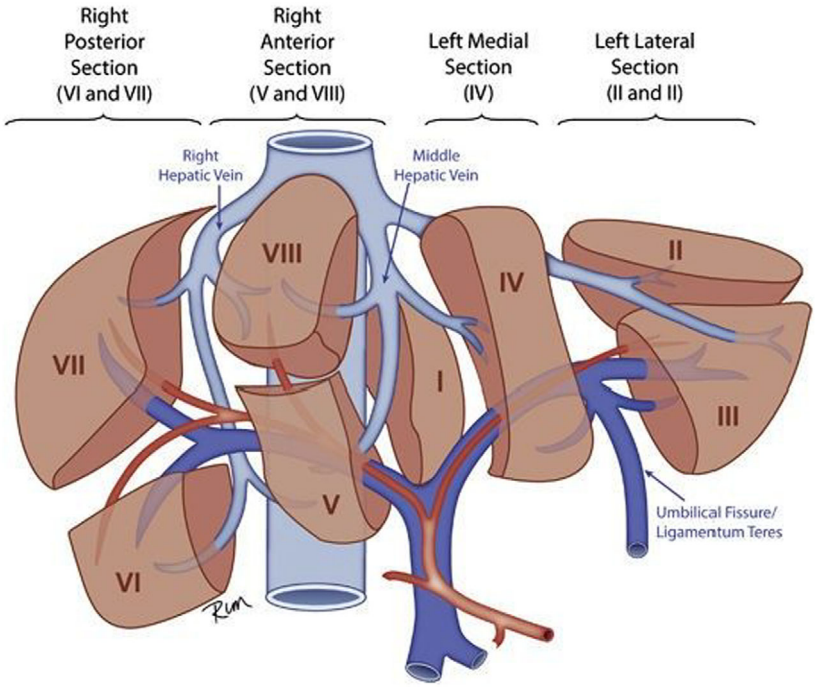

Figure 1. PRETEXT is distinct from Couinaud 8-segment (I–VIII) anatomic division of the liver. PRETEXT defines 4 'Sections'. Boundaries of each section are defined by the right and middle hepatic veins and umbilical fissure. This figure was published in Modern Pathology (2014), 27, Dolores López-Terrada *et al.*, Towards an International Paediatric Liver Tumour Consensus Classification: Proceedings of the Los Angeles COG Liver Tumours Symposium, pp. 472–491, Copyright Elsevier.[9]

Multifocal disease has been shown to be an independent factor associated with worse event-free survival and overall survival.[14] For these reasons, it has been recommended that the presence of tumour multifocality be a component of prognostic stratification.[14,16]

TUMOUR DIMENSIONS

The greatest dimension of each nodule is a core feature of Tumour dimensions (Table 1). Hepatoblastoma often presents as a single, large expansive mass compressing the surrounding liver, which is generally architecturally and functionally normal. Occasionally, intrahepatic dissemination via portal veins leads to multiple discrete nodules, but most cases have only contiguous extension. Evaluation of the extent of hepatic involvement and metastases is of most importance in the management of children with hepatoblastoma. The PRETEXT system,[17] developed by the SIOPEL, is currently the primary mode for determining stage and assigning risk categorization, given its strong prognostic value, as documented by the Children's Hepatic Tumours International Collaboration (CHIC) Group in 2017.[18]

HISTOLOGICAL TUMOUR TYPE

Histologic diagnosis of paediatric hepatoblastoma is based on the 2023 WHO Classification of Paediatric Tumours, 5th edition (Table 2).[2]

Hepatoblastoma

Hepatoblastomas are embryonal tumours that are classified by the presence of epithelial, mesenchymal and/or primitive components (Table 2). 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 characterized 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

Table 2. World Health Organization classification of paediatric liver tumours[2]

Descriptor	ICD-O codes[a]
Hepatoblastoma	8970/3
Fibrolamellar variant of 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, third Edition, second revision (ICD-O-3.2). 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.

and dark' pattern (Figure 2). Extramedullary haematopoiesis (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 characterized by cells displaying a fetal pattern with only a few mitoses. It is important that the diagnosis of PFH, a relatively rare histological type of hepatoblastoma associated with a very favourable prognosis, only applies to entirely upfront, resected tumours consisting of 100% of this pattern.

Differentiating this pattern from the uninvolved adjacent liver may be challenging and require 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 characterized 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.

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 a high nuclear to cytoplasmic ratio, large, angulated nuclei organized in trabeculae and sometimes forming rosettes, tubular or glandular structures (Figure 3).

Mitoses are frequent. Embryonal pattern is often encountered adjacent to or admixed with fetal pattern, sometimes organized in nests or tumour

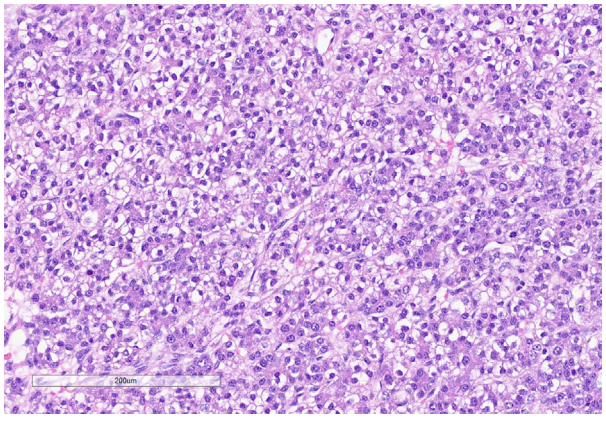

Figure 2. Epithelial hepatoblastoma, fetal pattern, uniform, polygonal cells with pink and clear cytoplasm, rich in glycogen.

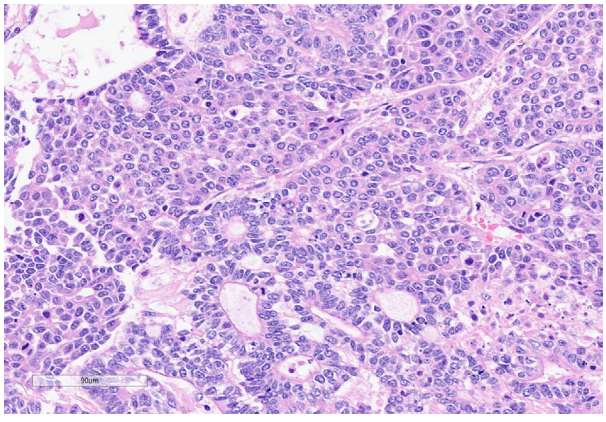

Figure 3. Epithelial hepatoblastoma, fetal cells (upper left) with central nuclei and pink cytoplasm, adjacent to the embryonal component containing cells with a higher nuclear/cytoplasmic ratio, angulated nuclei and scant cytoplasm forming glandular, tubular structures.

nodules. Tumour cells are diffusely nuclear beta-catenin positive, GPC3 and SALL4 strongly positive, and variably GS positive.[2]

Epithelial patterns: Pleomorphic

This pattern is characterized 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.[2] 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 characterized 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.[6]

Epithelial patterns: SCU

Primitive small blue, round to ovoid cells with scant cytoplasm and stippled chromatin, either organized 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, characterized by *SMARCB1* alterations, by either INI1 immunohistochemistry or molecular testing.[8]

The presence of SCU was historically believed to be associated with unfavourable outcomes. However, molecular characterization of rhabdoid tumours of the liver and recent follow-up COG and CHIC studies,[19] 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 (Figure 4), 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 this primitive hepatoblastoma component is not totally understood.[2]

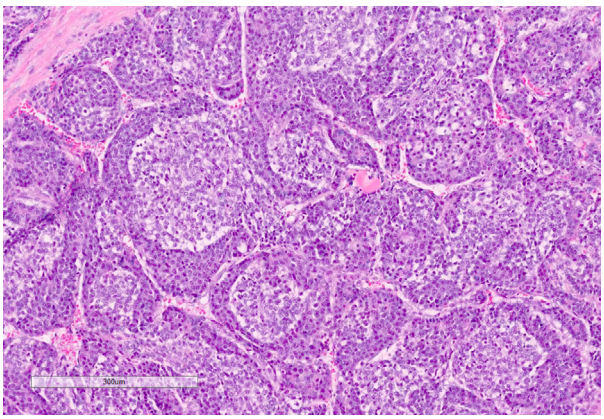

Figure 4. Epithelial hepatoblastoma, fetal and small cell component (centre, INI1 retained).

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 staining, no nuclear staining) beta-catenin.

Mesenchymal hepatoblastoma

The 2014 International Paediatric Liver Tumour Consensus Classification noted this component as part of a mixed epithelial-mesenchymal hepatoblastoma with or without teratoid elements.[9] Mixed hepatoblastomas are characterized by the presence of any epithelial elements admixed with mesenchymal components, including spindle cells, osteoid, cartilage, rhabdomyoblastic differentiation and fat.[20] 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

Hepatocellular neoplasm not otherwise specified (HCN-NOS) is a 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

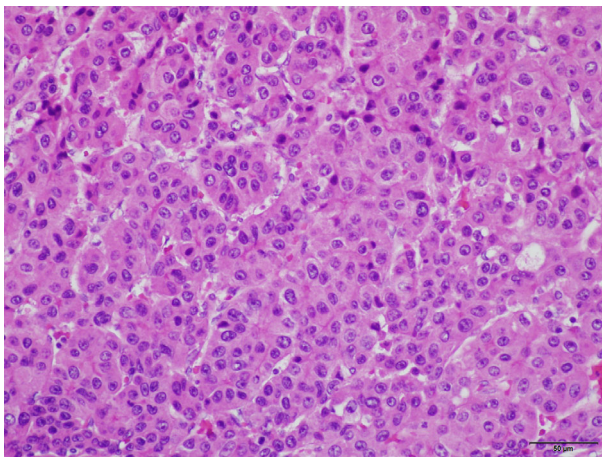

Figure 5. Hepatocellular Neoplasm, not otherwise specified (HCN-NOS) carrying a TERT promoter mutation, diagnosed in an 8-year-old boy. Tumour cells are large, pleomorphic, with round nuclei, nucleoli and abundant cytoplasm.

described as highly aggressive tumours with overlapping features of epithelial hepatoblastoma and HCC,[9] and are currently not classifiable as reported by SIOPEL and COG studies (Figure 5). 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, emphasizing the importance of molecular testing and early therapeutic intervention in patients with HCN-NOS tumours.[6] However, it is acknowledged that molecular testing may not be available in some parts of the world.

Patients with hepatocellular neoplasms not otherwise specified (HCN-NOS) are currently treated as hepatoblastoma and not as HCC patients in the PHITT.[1]

MARGIN STATUS

Due to the overall rarity of hepatoblastoma, there are only a few published studies describing 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.[21-23] 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.[24] Grossly positive margins should be confirmed microscopically and documented, with the margin specified, if possible. If the margins are grossly 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,[25,26] particularly for those nodules that may not have been radiographically apparent on preoperative imaging.

LYMPHOVASCULAR INVASION

Macroscopic portal and hepatic venous involvement may have prognostic significance and therefore should be reported as detected by preoperative imaging.[16,18] 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 3-year overall survival.[27] 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.[28] Other studies support the association between lymphovascular invasion and survival.[29-31] 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.

LYMPH NODE STATUS

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.[17]

ANCILLARY STUDIES

Most features relating to Ancillary studies are core; although there are some non-core features (Table 1).

Beta-catenin IHC for the demonstration of nuclear or nuclear and cytoplasmic expression in the various components, especially the embryonal type, is important diagnostically and can be useful for its differential diagnosis (Figure 6). Glypican-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 post-chemotherapy resection specimen differs from the biopsy to highlight viable tumour areas and to distinguish different tumour components.

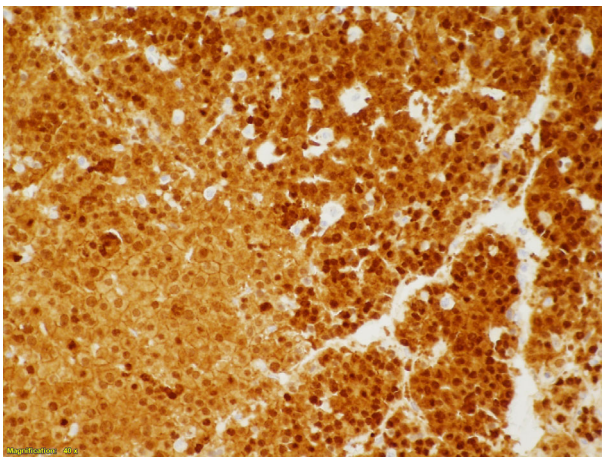

Figure 6. Epithelial hepatoblastoma prominent nuclear and cytoplasmic beta-catenin expression by immunohistochemistry.

HISTOLOGICALLY CONFIRMED DISTANT METASTASES

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 or cytopathology 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'.

Non-core elements

Non-core elements are those unanimously agreed to be included in the dataset but are not supported by NHMRC level III-2 evidence.[3] 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.

A summary of the non-core elements is outlined in Table 1 and each is described below:

CLINICAL INFORMATION

There are a number of non-core features relating to Clinical information (Table 1).

History of prematurity

There is extensive evidence supporting the association of hepatoblastoma and extreme prematurity,[32,33] with a risk increase of 15- to 40-fold in children with very low birth weight (less than 1,500 grams).[34]

Associated genetic syndromes, malformations or other conditions

Several congenital abnormalities, constitutional genetic syndromes, malformations and other clinical conditions have been associated with hepatoblastoma.[35] Increased incidence warranting surveillance is seen in patients with Beckwith-Wiedemann syndrome, hemihypertrophy syndromes, Trisomy 18 and other rare syndromes.[32,36]

However, the majority of hepatoblastomas appear to be sporadic.

PRETEXT clinical staging

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.[37] 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).[38] 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.[18]

Other clinical information

Additionally, other non-core items such as low birth weight or other clinical findings also enhance the completeness of specimen context.

TUMOUR FOCALITY

The number of tumours is a non-core feature of Tumour focality (Table 1).

TUMOUR DIMENSIONS

Additional dimensions of each nodule are a non-core feature of Tumour dimensions (Table 1).

BLOCK IDENTIFICATION KEY

The origin/designation of all tissue blocks should be recorded and ideally documented in the final pathology report and is particularly important should the need for internal or external review arise. 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.

TREATMENT EFFECT

The extent of tumour necrosis following neoadjuvant chemotherapy has been suggested as an independent prognostic factor in newly diagnosed hepatoblastoma.[39] However, it has not been confirmed in large clinical studies; therefore, 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 represent 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 characterized by rounded pools of blood within epithelial tumour sinusoids surrounded by tumour cells.[15]
- 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 glypican-3 is valuable.

COEXISTENT PATHOLOGY

Hepatoblastoma usually arises in 'healthy' livers; therefore, the presence of coexistent pathology could be helpful to differentiate hepatoblastoma from HCC, which can occur in about 20% of paediatric cases, including patients 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 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 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.

ANCILLARY STUDIES

Some features relating to ancillary studies are non-core (Table 1). 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 panels, and 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.[40]

PATHOLOGICAL STAGING

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.[41] COG pathologic staging has been clinically replaced by the PRETEXT/POSTTEXT staging system in current trials, which is strictly based on imaging data.[1]

PRETEXT/POSTEXT 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.[17,1] 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.

Discussion

Here we report the development and content of a dataset for the pathology reporting of hepatoblastoma resection specimens. The dataset was created based on curated, current evidence, including relevant hepatoblastoma peer-reviewed literature and existing clinical practice guidelines, such as the College of American Pathologists (CAP) protocol.[42] This hepatoblastoma dataset represents an international consensus statement from a multidisciplinary group of paediatric liver tumour experts, including central reviewers of international clinical trials and members of paediatric subspecialty committees. This ICCR dataset aims to provide a guide for adequate tumour reporting independently of the degree of development in a given geographical location, specifically considering the setting of low and middle-income countries.

The use of standardized reporting templates and structured pathology reporting will ensure a more consistent, comprehensive reporting and accurate diagnosis of hepatoblastoma patients and will promote better informed treatment decisions and outcomes. In addition, structured reporting will facilitate systematic data collection and extraction by consortia and cancer registries, enabling clinical and scientific studies of these rare neoplasms. Utilization of standardized reporting is compatible with laboratory and clinical information systems and will facilitate communication between members of multidisciplinary teams.

In summary, we present the first international dataset for standardized reporting of hepatoblastoma resection specimens. International adoption of this dataset will improve clinical data collection and extraction and will further strengthen international collaborations and our approach to future international prospective trials. Most importantly, it will optimize diagnosis, prognostication, treatment and outcome of young patients with hepatoblastoma globally.

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Author contributions

DLT and FW wrote the initial draft manuscript with final review and revision by RA, JB, SC, RDeK, TI, AO, APA, SR, JS, YT, MC and MRM.

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Conflict of interest

The authors report no relevant conflicts of interest.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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