Cancer Imaging (2009) **9,** S98–S103
DOI: 10.1102/1470-7330.2009.9041

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PAEDIATRIC TUMOURS

Saturday 3 October 2009, 09:00–10:30

Assessment of malignant liver tumors in children

Derek J. Roebuck

Department of Radiology, Great Ormond Street Hospital, London, WC1N 3JH, UK

Corresponding address: Derek J. Roebuck, Department of Radiology, Great Ormond Street Hospital, London, WC1N 3JH, UK.
Email: roebud@gosh.nhs.uk

Abstract

Imaging plays a crucial role in the management of a child with a suspected liver tumor. There are various important differences between pediatric and adult practice, and in particular several liver tumor types that are almost never seen in adults are not uncommon in children. The radiologist makes important contributions to the diagnosis through non-invasive imaging and often biopsy. This paper describes imaging tips for the radiologist, including a discussion of the PRETEXT system for staging primary malignant tumors.

Keywords: *Imaging; hepatoblastoma; hepatocellular carcinoma; PRETEXT.*

Introduction

The radiologist faced with a child with a suspected liver tumor has several roles[1]. First, the organ of origin of the mass must be confirmed. It is then necessary to depict both the extent of the mass within the liver and any extrahepatic disease. Next, a differential diagnosis must be constructed. Finally, the best approach for further management (observation, medical management, percutaneous biopsy or immediate resection) must be decided.

The most useful imaging techniques are ultrasound (US) and magnetic resonance imaging (MRI), but in suspected malignant tumors, where lung computed tomography (CT) is mandatory, coverage is often extended to include the liver as well. There is no single best modality, and it is not unreasonable to perform all three of these investigations in certain patients. Other imaging, such as radionuclide bone scanning or positron emission tomography, can be considered after malignancy is confirmed by a tissue diagnosis.

Although malignant hepatic tumors are unusual in children, they are more common than benign solid masses after the first few months of life. Hepatoblastoma and hepatocellular carcinoma together account for the overwhelming majority of cases. A combination of clinical, laboratory and imaging findings can usually, but not always, distinguish between benign and malignant entities[2].

Imaging techniques

Ultrasound

US is currently the best first imaging technique for any child with a suspected abdominal mass[1,3]. A relatively low-frequency (<7 MHz) sector transducer is ideal for confirming the organ of origin of the mass. In cases of doubt, real-time assessment of the motion of the mass relative to normal structures may be helpful[1]. US allows excellent evaluation of vascular anatomy, an important part of staging because the hepatic segments are bounded by planes determined by vascular structures, and because venous involvement is common. Second look US after CT or MRI examination is often helpful to complete the evaluation of the hepatic and portal veins. High-frequency (>7 MHz) linear array transducers and color Doppler imaging and pulsed wave Doppler examination are often useful for this purpose[1].

Computed tomography

Much of the impetus for the use of CT for pediatric liver tumors has come from surgeons, possibly related to their

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enthusiasm for 3-dimensional imaging[4,5]. The standard approach is to avoid non-contrast and multiphase images, and to use relatively low-dose techniques compared to adult practice[3]. Portal venous phase images are the most useful for evaluation of primary liver tumors in children[6].

Performance and interpretation of lung CT in small children may be challenging. Both sedation and general anesthesia tend to cause atelectasis in the posterior parts of the lungs, which may mimic or obscure metastatic disease. This may be mitigated to some extent by careful anesthetic technique[7].

In children with hepatoblastoma it is not unusual to see one or more small lung nodules, in which case interpretation is difficult, as benign lesions are also common. Although large size and multiplicity have been regarded as evidence of metastatic disease, for example in the SIOPEL 4 protocol, this is not proven.

Magnetic resonance imaging

Although this is a rapidly changing field, and numerous different approaches to MRI have been suggested[3,7 8], there is general agreement on certain key points. In pediatric liver imaging it is important to use the smallest suitable coil, which in small children and infants is usually a head coil[7,8]. In older children a flexible phased-array body coil is used[7,8]. A breath-holding technique is preferred, but respiratory gating may be used when this is not possible.

Unenhanced T1- and T2-weighted fast spin echo images are usually obtained, often supplemented with unenhanced 3-dimensional gradient echo sequences. Diffusion-weighted imaging is optional[9].

Dynamic 3-dimensional gradient echo images are repeated after the administration of a conventional extracellular gadolinium-based contrast agent[7,8,10]. Although superparamagnetic iron oxide contrast agents are not widely used in children, they may be helpful for evaluation of suspected focal nodular hyperplasia[11].

Benign liver masses

Liver hemangiomas

In my opinion, the understanding of these lesions has been hindered by ambiguous terminology and poor appreciation of the complexity of the topic. Christison-Lagay *et al*. have addressed this issue in an important review article[12]. The term *infantile hemangioma* (IH) refers to a benign endothelial neoplasm. This lesion is completely distinct from the adult type of liver hemangioma, which is felt by many to be a vascular malformation rather than a neoplasm. IHs are typically multifocal or diffuse, and have a distinctive clinical course and histological appearance, equivalent to the skin lesions sometimes known as strawberry hemangiomas. They express the glucose transporter 1 (*GLUT1*) gene, strongly in their proliferative phase and progressively less as they stabilize and involute, and identification of the gene product by immunohistochemistry may be a useful diagnostic test.

The term 'hemangioendothelioma' should not be used interchangeably with hemangioma, but should instead be reserved for other lesions including epithelioid hemangioendothelioma (see below), and kaposiform hemangioendothelioma, another complicated entity of infancy that is the usual cause of the Kasabach–Merritt phenomenon. Rapidly involuting congenital hemangioma (RICH) was first recognized in the skin, but lesions with exactly the same clinical course occur in the liver, usually as solitary masses. Although congenital hemangiomas that neither involute nor grow have been identified in the liver, it is not known whether these are equivalent to the non-involuting congenital hemangioma (NICH) of the skin. It is also unclear which lesions are at risk for malignant transformation to angiosarcoma, and whether anything can be done to prevent this rare but fatal complication. Finally, the relationship, if any, between IH and focal nodular hyperplasia (FNH) is not well understood[13]. Regrettably, many papers confuse rather than illuminate the classification of hemangiomas and vascular malformations of the liver[2,8,10].

(Congenital) mesenchymal hamartoma

Although most mesenchymal hamartomas have a characteristic multiseptated cystic appearance, which is rarely seen in other liver neoplasms, many are mixed solid and cystic or completely solid[14,15]. Although most of these lesions grow slowly and require resection, some remain stable in size or even involute[16], and a trial of conservative management may be appropriate in some cases. There are a few reports of apparent malignant transformation to undifferentiated (embryonal) sarcoma, but it is not clear if resection is justified on these grounds alone.

Focal nodular hyperplasia

FNH and related lesions are uncommon, especially in young children. Conservative management is possible, but resection is required if the child is symptomatic or if there is clear evidence of growth of the lesion[11].

Malignant primary liver tumors

The management of most malignant primary liver tumors follows a standard path: imaging, biopsy, preoperative chemotherapy, surgery, and post-operative chemotherapy. Until recently the Children's Oncology Group (COG) recommended an attempt at resection at diagnosis, but this approach has been largely discarded as improvements in diagnostic imaging have permitted accurate preoperative prediction of unresectability. Future COG protocols will include up-front resection only for PRETEXT I and easy PRETEXT II tumors. This appears to be an ideal compromise with the approach of the

International Children's Liver Tumor Strategy Group (SIOPEL), who currently still prefer biopsy of easily resectable lesions, unless hepatocellular carcinoma is suspected.

Hepatoblastoma

Hepatoblastoma is the most common primary malignant liver tumor of childhood. Predisposing features include Beckwith–Wiedemann syndrome, familial adenomatous polyposis and extremely low birth weight. The median age at presentation is about 18 months. The improvement in survival following combined treatment with chemotherapy and surgery is one of the great successes of pediatric oncology. Five-year overall survival has improved from 30% to over 70%, and is now approximately 90% for the majority of children who present with standard-risk disease. Children tend to present with an abdominal mass. Serum alpha-fetoprotein is almost always elevated, often to extreme levels ($>10^5$ ng/mL), and thrombocytosis is common. Metastases occur almost exclusively in the lungs. COG and SIOPEL have adopted risk-stratified therapy for hepatoblastoma, albeit using different definitions.

Hepatocellular carcinoma (HCC)

HCC tends to occur in older children than hepatoblastoma. Although worldwide its incidence in childhood is falling, due to widespread immunization against hepatitis B, it remains a difficult problem as chemotherapy has made little or no impact on survival and most tumors are unresectable. Predisposing factors include tyrosinemia and progressive familial intrahepatic cholestasis. Serum alpha-fetoprotein is often elevated, but usually not to extreme levels.

Fibrolamellar carcinoma

Fibrolamellar carcinoma is a distinctive neoplasm, which is usually seen in older children and young adults. It has a similar prognosis to HCC, but is not associated with hepatitis.

Undifferentiated (embryonal) sarcoma

This tumor tends to occur in children in the second half of the first decade of life. It may be suspected in many cases by its strikingly low attenuation at CT[17].

Epithelioid hemangioendothelioma

This tumor of intermediate malignancy occurs in older children and adults. It is typically multifocal and therefore often requires transplantation for cure. Alomari's lollipop sign may be a clue to the diagnosis[18].

Staging

There are two major systems for staging pediatric liver tumors. The COG system (Table 1) has the advantage that it is well established, but it includes a treatment variable, extent of resection, which makes comparison between different trials difficult. For this reason, all of the major international study groups now additionally use the PRETEXT system[19].

In addition to staging the extent of tumor within the liver (Table 2, Fig. 1), PRETEXT also requires assessment of various additional factors, involving both detailed abdominal imaging and chest CT.

Table 1 Children's Oncology Group staging of liver cancer

Stage I	Tumor completely resected
Stage II	Tumor grossly resected with microscopic residual disease
Stage III	Tumor unresectable, or resected with gross residual disease
	Nodal involvement
	Tumor spill
	Gross residual intrahepatic disease
Stage IV	Distant metastases

Table 2 PRETEXT staging of hepatic tumors (see also Fig. 1).

PRETEXT I	One section is involved and three adjoining sections are free
PRETEXT II	One or two sections are involved, but two adjoining sections are free
PRETEXT III	Two or three sections are involved, and no two adjoining sections are free
PRETEXT IV	All four sections are involved

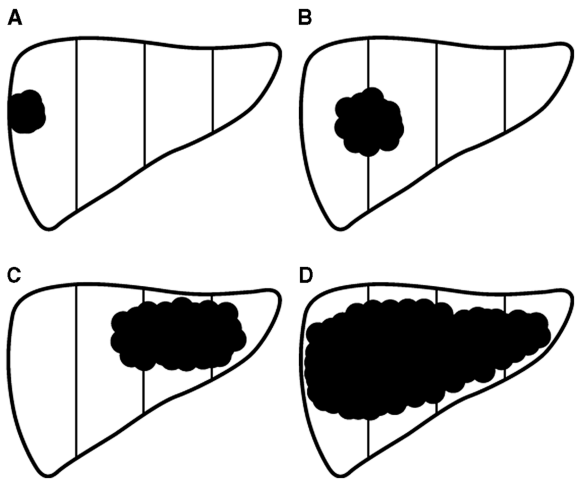

Figure 1 **The PRETEXT system classifies malignant primary liver tumors of childhood according to the potential amount of unaffected liver that would remain after a typical surgical resection. Various other configurations are possible for each stage[19]. (A) PRETEXT I; (B) PRETEXT II; (C) PRETEXT III; (D) PRETEXT IV.**

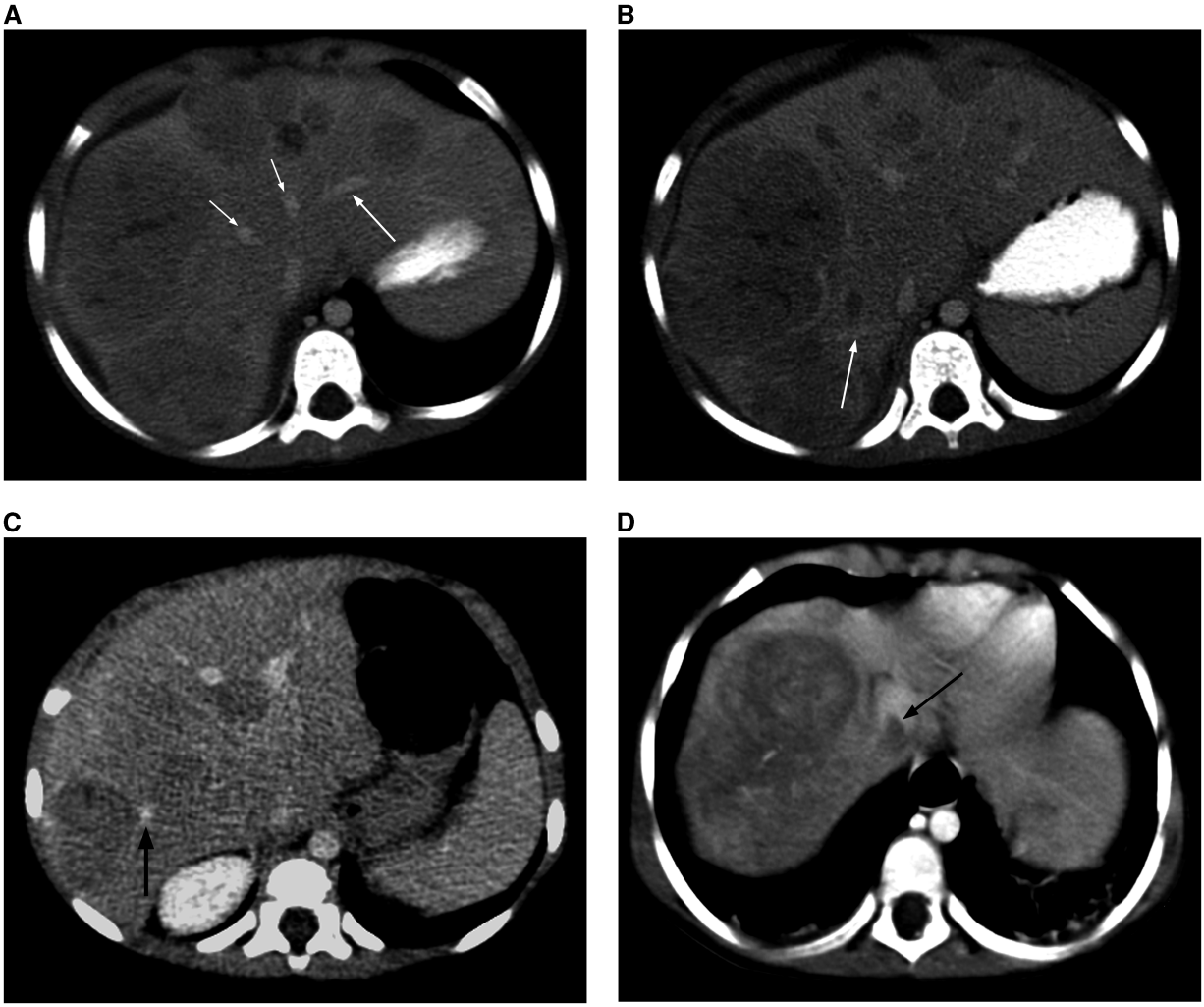

Figure 2 **Venous involvement in the PRETEXT system as shown in three patients with hepatoblastoma. Involvement is defined as obliteration (A,B) or encasement (C) of the vein, or the presence of intravascular tumor (D). (A) The left hepatic vein (long arrow) and two middle hepatic veins (short arrows) are seen, but no vessel is identified in the expected position of the right hepatic vein. (B) A large accessory right hepatic vein (arrow) is identified on a more caudal image. It can be inferred that the right hepatic vein is completely obliterated. (C) The right hepatic vein is completely surrounded by tumor (arrow). (D) There is intravascular tumor in the right atrium (arrow).**

Bone scintigraphy is appropriate in children with HCC, because although bone metastases are fairly uncommon their detection will significantly affect management[20].

Additional PRETEXT criteria

Eight additional criteria are defined in the revised PRETEXT system[19]. Three of these are relatively straightforward. Patients are classified as C1 if there is involvement of the caudate lobe, F1 is there is more than one liver tumor, and H1 if there is clinical and radiological evidence of tumor rupture (and C0, F0 and H0 respectively if these findings are not present).

Involvement of the systemic or portal venous systems is defined as encasement, obliteration or intravascular tumor extension (Fig. 2). The scoring of these criteria is more complicated (Table 3).

Intraabdominal extrahepatic disease is scored as E1 if there is direct extension of tumor into adjacent organs, including the diaphragm, and E2 if there is transperitoneal spread with nodules.

Metastatic disease is coded as M1 for presumed hematogenous spread and N1 (abdominal) or N2 (distant) for nodal metastases. Lymph node involvement must be proved by biopsy in patients with hepatoblastoma[19].

Biopsy

In most parts of the world it is considered mandatory to obtain a tissue diagnosis before starting chemotherapy.

Table 3 PRETEXT staging of venous involvement (see also Fig. 2)

Portal vein involvement	
P0	no involvement of the (main) portal vein or its left or right branches
P1	involvement of either the left or right branch of the portal vein
P2	involvement of the (main) portal vein and/or both branches
Involvement of the hepatic veins and/or inferior vena cava (IVC)	
V0	no involvement of the hepatic veins or IVC
V1	involvement of one hepatic vein (but not the IVC)
V2	involvement of two hepatic veins (but not the IVC)
V3	involvement of all three hepatic veins and/or the IVC

In each case the suffix 'a' is added if there is evidence of intravascular tumor.

The risks of biopsy are not trivial, however, and as our German colleagues have shown, the diagnosis of hepatoblastoma is almost certain in a child aged between 6 months and 3 years with compatible imaging and significantly elevated serum alpha-fetoprotein[21]. Despite this, it seems that future major trials will insist on biopsy. Although a laparoscopic or open surgical biopsy is considered by some to be the standard technique, SIOPEL currently recommend image-guided coaxial plugged needle biopsy (obtaining numerous cores). Although fine needle aspiration cytology is possible, it is not favored in most centers because of problems distinguishing hepatoblastoma from HCC[22], the inability to store tissue for research and the lack of evidence that it is safer than core needle biopsy.

Interventional techniques

Various interventional radiology techniques have been adapted from adult practice for use in children with liver tumors. The dual blood supply of the liver from the hepatic arteries and branches of the portal vein makes hepatic artery chemoembolization (HACE) feasible. Various potential indications have been suggested. Malogolowkin *et al*. obtained encouraging results using HACE in an attempt to convert both hepatoblastoma and HCC from unresectable to resectable[23]. HACE has also been used as a bridge to transplantation[24], for recurrent tumors and for palliation.

Radioembolization with yttrium-90 microspheres, sometimes known as selective internal radiation, has also been used in a few children. Another potential approach is radiofrequency ablation, which has been used in children with recurrent hepatoblastoma[25,26].

Conclusion

The various roles of the radiologist in diagnosis, staging and treatment are a crucial part of the management of children with known or suspected liver tumors.

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