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REVIEW

2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT)

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Abstract

Imaging is crucial in the assessment of children with a primary hepatic malignancy. Since its inception in 1992, the PRETEXT (PRE-Treatment EXTent of tumor) system has become the primary method of risk stratification for hepatoblastoma and pediatric hepatocellular carcinoma in numerous cooperative group trials across the world. The PRETEXT system is made of two components: the PRETEXT group and the annotation factors. The PRETEXT group describes the extent of tumor within the liver while the annotation factors help to describe associated features such as vascular involvement (either portal vein or hepatic vein/inferior vena cava), extrahepatic disease, multifocality, tumor rupture and metastatic disease (to both the lungs and lymph nodes). This manuscript is written by members of the Children's Oncology Group (COG) in North America, the International Childhood Liver Tumors Strategy Group (SIOPEL) in Europe, and the Japanese Study Group for Pediatric Liver Tumor (JPLT; now part of the Japan Children's Cancer Group) and represents an international consensus update to the 2005 PRETEXT definitions. These definitions will be used in the forthcoming Trial to Pediatric Hepatic International Tumor Trial (PHITT).

Keywords Children · Computed tomography · Hepatoblastoma · Hepatocellular carcinoma · Liver tumors · Magnetic resonance imaging · Staging

Introduction

The PRE-Treatment EXTent of tumor (PRETEXT) system was first described by members of the Société Internationale d'Oncologie Pédiatrique — Epithelial Liver Tumor Study Group (SIOPEL) in 1992 as a method to standardize the imaging evaluation and risk stratification for children afflicted with hepatoblastoma prior to administration of neoadjuvant

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chemotherapy [1]. Since that time, the PRETEXT groups and annotation factors have served as some component of the risk stratification scheme in several cooperative group trials focused on hepatoblastoma and pediatric hepatocellular carcinoma across the world. These trials have shown that PRETEXT groups are reproducible and provide prognostic information related to overall survival [2–6]. The most recent published revision of PRETEXT was made in 2005 and was published in 2007 [7]. In that revision, several of the original SIOPEL definitions were refined and new criteria were added. However, since that revision the Children's Oncology Group (COG) has modified several definitions for use in their AHEP-0731 trial [8].

In the last decade, SIOPEL, COG and the Japanese Study Group for Pediatric Liver Tumor (JPLT) have launched trials evaluating children with hepatoblastoma. Although all trials used the same PRETEXT groups (I, II, III and IV), there were some differences in how each cooperative group defined the annotation factors, which define vascular involvement, multifocality, rupture, extrahepatic extent of tumor, and metastases. The differences primarily related to philosophies of treatment and study aims. Namely, SIOPEL institutions have treated all children with neoadjuvant chemotherapy whereas the COG AHEP-0731 study used the PRETEXT group and annotation factors to define surgical guidelines that identified subsets of children who should be resected at diagnosis versus those who should be treated with neoadjuvant chemotherapy, and in some cases have an early referral to a liver center with liver transplant capability.

Since 2011, SIOPEL, COG and JPLT have worked toward creating a common international study of pediatric hepatoblastoma and hepatocellular carcinoma. Preparation for this global study required a common risk stratification scheme across all study groups. Development of this common scheme was the primary aim of the Children's Hepatic tumors International Collaboration (CHIC) [9, 10]. The CHIC group retrospectively reviewed data from each of the cooperative group studies [5, 6, 11–17] in order to standardize data across trials [9]. This analysis identified several clinical and imaging risk factors that portend a worse prognosis [10]. The CHIC risk stratification scheme uses PRETEXT groups and PRETEXT annotation factors, as well as age and alpha-fetoprotein (AFP) levels, to determine treatment cohorts on the new Trial to Pediatric Hepatic International Tumor Trial (PHITT). The purpose of this manuscript is to describe the PRETEXT system, highlight the different methods by which SIOPEL and COG have assessed children in prior trials, and provide a new, common set of definitions to be used in future trials including PHITT.

Imaging recommendation

Ultrasound remains the imaging modality of choice for primary assessment of pediatric abdominal masses. Ultrasound, because of its lack of ionizing radiation, its utility in performing a real-time examination without the need for sedation or anesthesia, and its utility in assessing the vasculature, is preferred as the initial imaging assessment tool. The most important purpose of ultrasound is to identify the organ of origin of the mass. At times it can be difficult to determine whether a lesion arises from the liver. In these instances, two clues can be used. First, extrahepatic masses do not move in concert with the liver. Instead, the liver slips over retroperitoneal tumors. Second, large liver tumors are often associated with large regional intrahepatic vessels, both hepatic arteries and hepatic veins.

Determining the organ of origin of an abdominal mass allows the radiologist to appropriately protocol the subsequent cross-sectional imaging study. Once a mass is confirmed to arise from the liver, careful attention should be paid to the identification and assessment of the portal vein (and its primary branches), the hepatic veins and the inferior vena cava. Ultrasound might be useful in identifying subtle vascular invasion that is not visible on other modalities and can be used for problem-solving or to provide a second look following more complex cross-sectional imaging.

Contrast-enhanced ultrasound is an emerging modality. As such, it has not been studied in the setting of hepatoblastoma or pediatric hepatocellular carcinoma. At this time, it should not be used as the primary modality for diagnosis or response assessment. However this modality might have use in identifying satellite lesions or in assessing a tumor's effect on the hepatic vasculature, particularly in children who cannot undergo MRI.

MRI has quickly become the cross-sectional modality of choice for the evaluation of pediatric liver masses. This is a result of several factors including its lack of ionizing radiation and superior soft-tissue contrast resolution. In addition, the advent of hepatocyte-specific MRI contrast agents has improved radiologists' ability to identify and diagnose liver tumors [18–21]. Currently, there are two hepatocyte-specific contrast agents on the market: gadoxetate disodium (Gd-EOB-DTPA, Eovist/Primovist; Bayer, Leverkusen, Germany) and gadopentetate dimeglumine (Gd-BOPTA, MultiHance; Bracco, Milan, Italy). Each agent has advantages and disadvantages. These issues are discussed in more detail in other publications [20, 21]. It should be noted that these agents do not have official pediatric age group marketing approval in several countries. The use of such contrast agents is thus based on local practice and local law. While there is some discussion regarding the adequacy of using hepatocyte-specific contrast agents to image the hepatic vasculature in adults, this concern has not been described or shown to be an issue in children. Thus no additional abdominal imaging is needed if a hepatocyte-specific contrast agent is used.

Over the last decade, fast MRI sequences have made multiphase vascular imaging possible. Today MRI excels in the detection of vascular invasion by tumor. The major limitations of MRI include the need for anesthesia in young children, limited

access to scanners in some locales, and the propensity for artifacts based on patient motion. One recent study demonstrated that the additional hepatocyte phase of imaging was able to detect more lesions than all of the other pre- and post-contrast imaging sequences [18]. Because multifocal disease is an important determinant for risk stratification [9, 22], surgical therapy, and overall prognosis, imaging with a hepatocyte-specific contrast agent is recommended at every time point, if possible. A protocol for MR imaging with a hepatocyte-specific contrast agent has recently been published (Table 1) [20, 21].

CT has fallen from favor over the last decade because of its reliance on ionizing radiation. However this modality still plays a role in the imaging assessment of pediatric liver tumors [23–25]. Because the lungs are the most common site of metastasis in children with hepatoblastoma, a chest CT is required at diagnosis. Because of its scan speed, spatial resolution, and multiple reconstruction algorithms, clinicians at many sites choose to image the child entirely with CT to minimize the length of anesthesia/sedation and avoid multiple contrast administrations. In children with suspected or known hepatoblastoma, imaging in the portal venous phase might be the only phase required [25]. In children with risk factors for or with suspected hepatocellular carcinoma, additional imaging of the abdomen in the arterial phase is recommended because small tumors might only be identified in this phase [26, 27]. Additional portal venous phase and delayed portal venous phase imaging is also recommended to identify washout and to better assess the vasculature. In the setting of either known or suspected hepatoblastoma or hepatocellular carcinoma, reformatted images should be created in the coronal plane (and possibly in the sagittal plane) to allow for better assessment of the tumor and affected structures.

There is no defined role for positron emission tomography (PET)/CT, brain MRI or bone scan in the primary assessment of pediatric liver tumors. This recommendation is made based on hepatoblastoma's propensity to metastasize primarily to the lungs. These imaging modalities should be reserved for symptomatic children or, in the case of PET/CT, for the assessment of treated patients with a rising AFP level and an unidentified source of tumor, to guide further imaging.

PRETEXT groups (I, II, III, IV)

Multiple trials have confirmed that the PRETEXT groups are a powerful predictor of overall survival in children with hepatoblastoma and hepatocellular carcinoma [2–5, 10, 28–31]. The PRETEXT group (I, II, III or IV) is based on determining the number of contiguous tumor-free liver sections. The PRETEXT group can be determined calculating the number of contiguous sections that would have to be resected to completely remove the tumor (Figs. 1, 2, 3 and 4). For example, central tumors affecting both the left medial and right anterior sections are considered PRETEXT III, even though only two sections are involved. This type of tumor is considered to be a PRETEXT III because there is only one "contiguous" tumor-free section, either the left lateral or right posterior section. Similarly, with multifocal tumors, nodules might be present in only the left lateral and right anterior sections; however such a tumor would be PRETEXT III because, even though two sections are free of tumor, there is only one "contiguous" section of tumor-free liver, the right posterior section. In this scenario, the left medial section would be resected as part of an extended right hepatectomy in order to completely remove the tumor.

The hepatic veins and portal veins divide the liver into its four sections: left lateral (Couinaud segments 2 and 3), left medial (segments 4a and 4b), right anterior (segments 5 and 8) and right posterior (segments 6 and 7). The hepatic sections are delineated in the following manner:

- Left lateral/left medial section. The left hepatic sections are delineated by the plane that extends along the hepatic fissure and the umbilical portion of the left portal vein. It should be noted that the left hepatic vein *is not* used in determining involved sections. Instead, the left hepatic vein separates Couinaud segments 2 and 3 [7, 32–34].
- Left medial/right anterior section. The right and left lobes are separated by the plane drawn between the middle hepatic vein and the middle of the gall bladder fossa (also referred to as Cantlie's line).
- Right anterior/right posterior section. The right hepatic sections are separated by the course of the right hepatic vein.

There are several challenges in assigning a PRETEXT group that should be addressed prior to a more detailed description of each of the groups.

Hepatic venous anomalies

Variations in hepatic venous anatomy are common. The most common anomalies include the presence of four or more major hepatic veins (accessory veins) or confluence of two major hepatic veins prior to junction with the inferior vena cava. The presence of venous anomalies can make determination of the PRETEXT group difficult. The common venous anomalies should be handled in the following manner.

- Duplicated right hepatic vein. If more than one major right hepatic vein is present, the vessel closest to the middle hepatic vein's insertion on the inferior vena cava should be considered the right hepatic vein.
- Duplicated middle hepatic vein. This is a particularly difficult scenario. Typically, the vessel that best aligns with the middle of the gall bladder fossa should be selected as

Table 1 Sample MRI protocol using a hepatocyte-specific contrast agent [21]

MRI sequence	Rationale
Axial T2-weighted fast-spin echo with fat suppression	Detection of fluid/edema; many tumors are hyperintense to normal liver
Axial T1-weighted fast spin echo	Detection of macroscopic fat and blood products
	Visible vascular flow voids help with PRETEXT staging
Axial T1-weighted in-/opposed-phase	Signal loss on opposed-phase images indicates presence of fat
Axial T1 pre 3-D SPGR	Allows for comparison with post-contrast images
Axial T1-weighted post dynamic 3-D SPGR (arterial, portal venous, and late portal venous phases)	Assessment of enhancement characteristics
Axial 2-D time-of-flight	Assessment of vasculature; can be used to problem-solve if other sequences are degraded by motion
Axial diffusion-weighted imaging	Detection of highly cellular masses
Coronal 3-D T2-weighted FSE	Isotropic 3-D sequences allow for reconstruction in multiple imaging planes. Assessment of biliary tree
Axial T1-weighted 3-D SPGR hepatocyte phase	Functioning hepatocytes retain contrast —important for lesion characterization
Coronal T1-weighted 3-D SPGR hepatocyte phase	Additional imaging plane improves lesion detection/localization
	Assessment of central biliary tree

FSE, fast spin echo; *PRETEXT*, pretreatment extent of disease; *SPGR*, spoiled gradient recalled echo

the middle hepatic vein. If in doubt, it is best to attempt to follow the course of each vessel and determine the segment that each vein drains. Once segmental anatomy is determined, the involved section(s) can be more reliably determined.

- Duplicated left hepatic vein. An accessory left hepatic vein is often confused with the middle hepatic vein. The left hepatic vein can be recognized via its course to the left of the ligamentum teres. Again, if confused, segmental anatomy should first be determined. This typically allows for more reliable assessment of the hepatic section involved by tumor.
- Common junction of hepatic veins prior to insertion into the inferior vena cava. A common insertion of multiple hepatic veins into the inferior vena cava creates a challenge when determining the presence or absence of vascular involvement rather than PRETEXT determination. In this instance, the inferior vena cava can be said to begin whenever multiple hepatic veins become confluent. The course of the hepatic veins can still be used to define the hepatic sections.
- Accessory hepatic veins are typically small vessels that join the inferior vena cava inferior to the confluence of the named hepatic veins. Perhaps the most common accessory vein drains the caudate lobe. In general, the small accessory veins should not be used to define hepatic segmental anatomy.

Pedunculated tumors

Pedunculated tumors are relatively common (Fig. 5). These tumors extend inferiorly from the inferior aspect of the liver

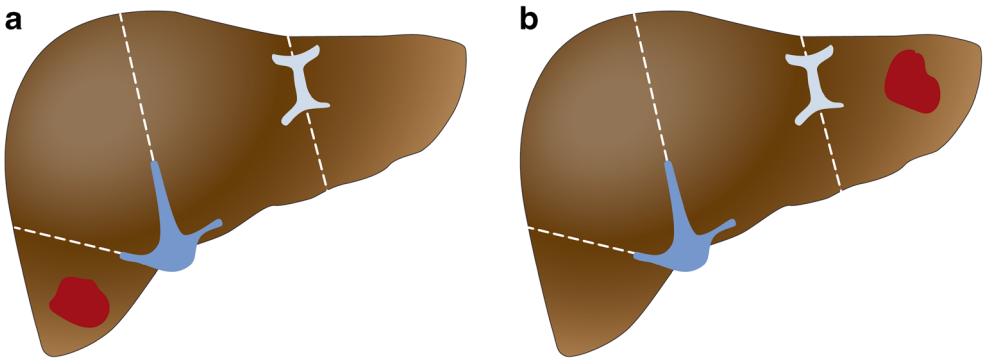

Fig. 1 PRETEXT I tumor involves only either the (**a**) right posterior section or the (**b**) left lateral section

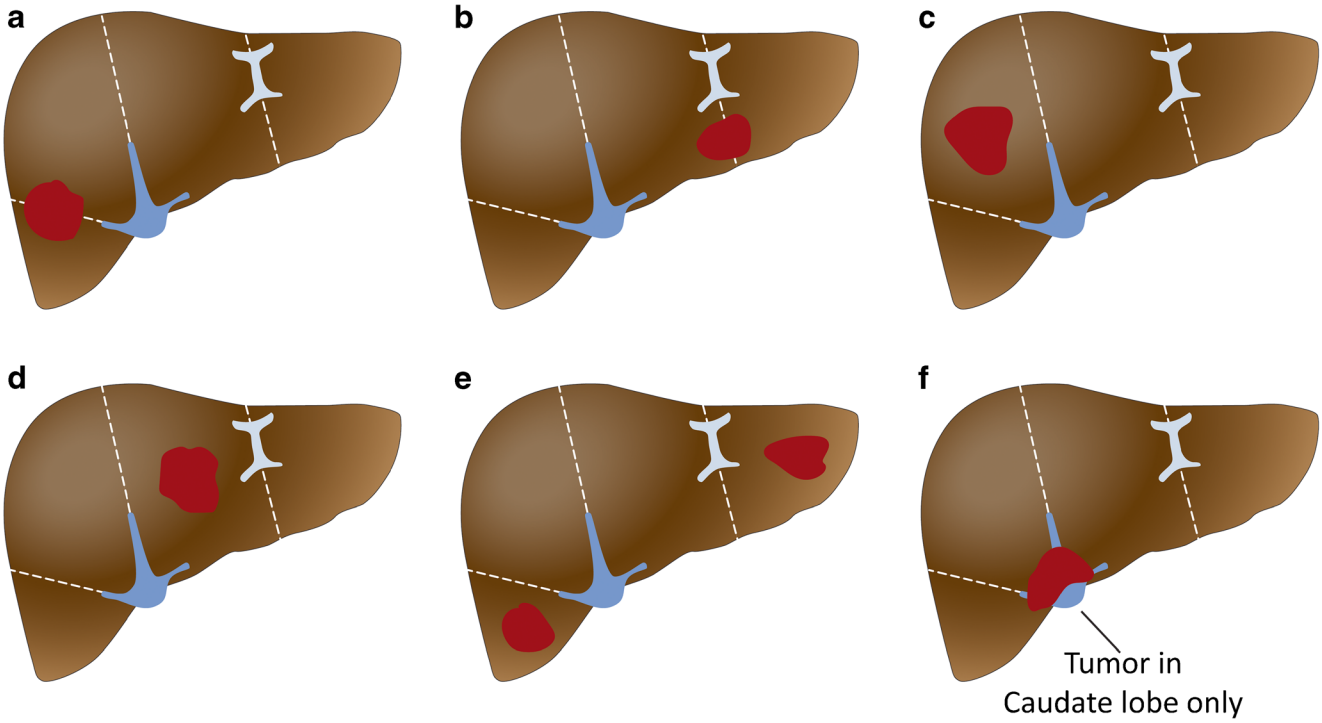

Fig. 2 PRETEXT II tumor involves one of the following sections or combinations of sections: (**a**) right anterior and right posterior sections, (**b**) left medial and left lateral sections, (**c**) right anterior section only, (**d**) left medial section only, (**e**) right posterior and left lateral sections or (**f**) the caudate lobe only

(segments 3, 4b, 5, and/or 6). It is often difficult to determine whether these tumors arise from one or more sections of the liver. In general, the reviewer should attempt to identify the stalk of the tumor. If the tumor stalk is contiguous with a section, it should be considered to arise from that section. If there is a plane between the stalk and the tumor, the tumor is likely compressing the liver at this location, and the tumor should not be considered to arise from this abutting section.

Pushing versus invasion

In the setting of large tumors, it is often very difficult to determine whether a tumor is invading a segment or rather pushing upon that segment with a compressive mass effect. In many cases, a close examination of the vessels can help to make this distinction. If the tumor remains to one side of a hepatic vein or portal vein, the tumor can be said to be compressing the segment rather than invading the segment. While this principle is helpful, it often remains difficult to assess the tumor above or below the course of the vein. In these scenarios, it is appropriate to assume that the tumor is invading the section and select the higher PRETEXT group. Typically this assessment becomes easier after neoadjuvant chemotherapy reduces the tumor size and compressive mass effect.

Effect of therapy

It is often easier to make a determination of the PRETEXT group and annotation factors during the course of neoadjuvant chemotherapy. However, in this setting the classification is termed POST-TEXT (POST-Treatment EXTent of disease).

Caudate

In the PRETEXT classification, the caudate lobe (Couinaud segment 1) is considered separately. If tumor only involves the caudate lobe, it should be considered a PRETEXT II tumor by convention. The caudate is described in more detail in the annotation factors section.

PRETEXT I

PRETEXT I tumors are uncommon and are typically small. By definition, three contiguous hepatic sections must be free of tumor. Therefore, PRETEXT I tumors can only involve either the left lateral or right posterior section (Fig. 1).

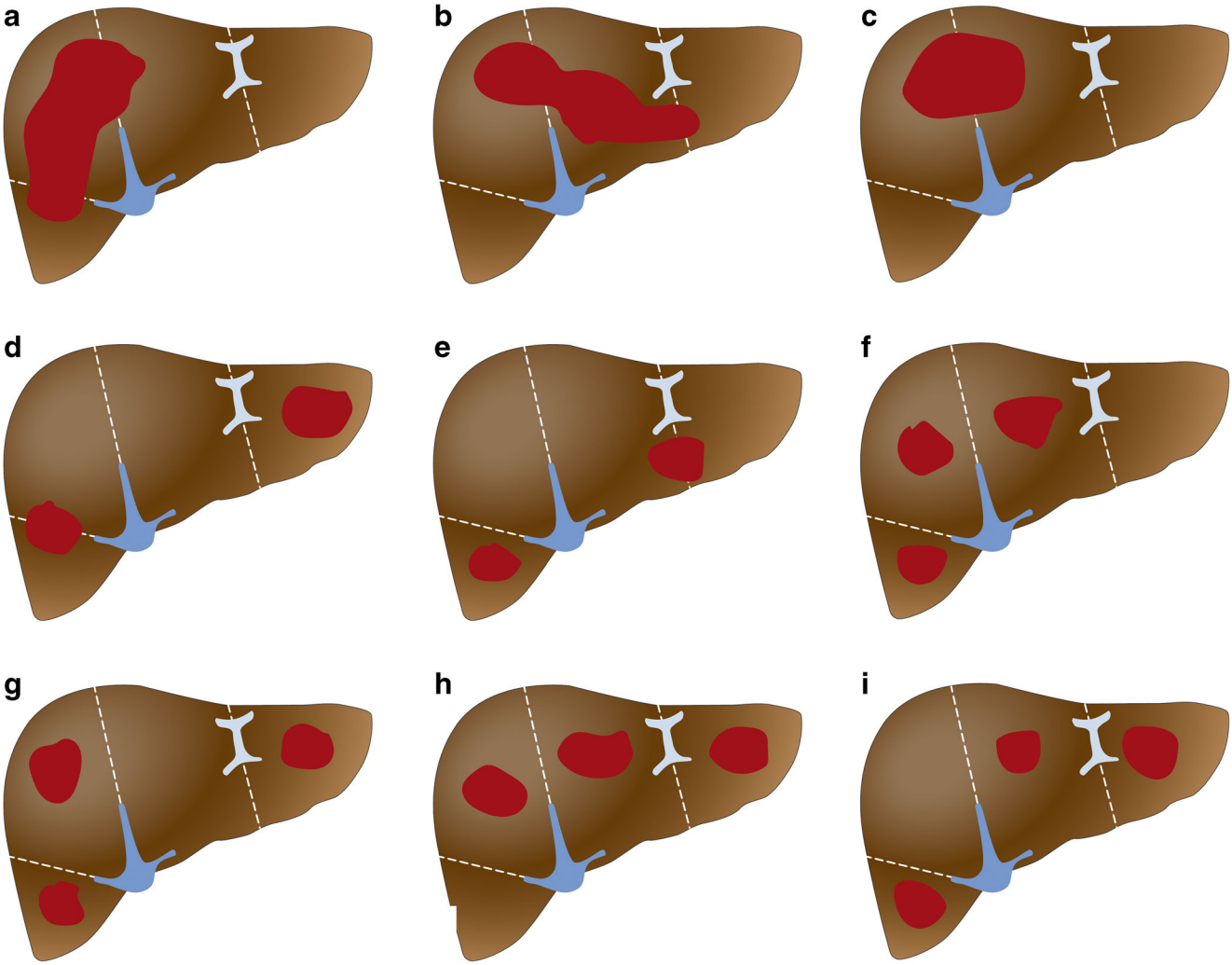

Fig. 3 PRETEXT III tumor involves one of the following combinations of sections: (**a**) left medial, right anterior and right posterior sections; (**b**) left lateral, left medial and right anterior sections; (**c**) right anterior and left medial sections; (**d**) right anterior, right posterior and left lateral sections; (**e**) right posterior, left medial and left lateral sections; (**f**) left medial, right anterior and right posterior sections (multifocal); (**g**) right anterior, right posterior and left lateral sections (multifocal); (**h**) left lateral, left medial and right anterior sections (multifocal); or (**i**) right posterior, left medial and left lateral sections (multifocal)

PRETEXT II

Almost all PRETEXT II tumors are limited either to the right lobe or the left lobe of the liver (Fig. 2). They can involve either one or two sections of the liver. If a tumor involves either the left medial or right anterior section only, it is considered a PRETEXT II tumor because either a left or right hepatectomy must be performed to resect the mass.

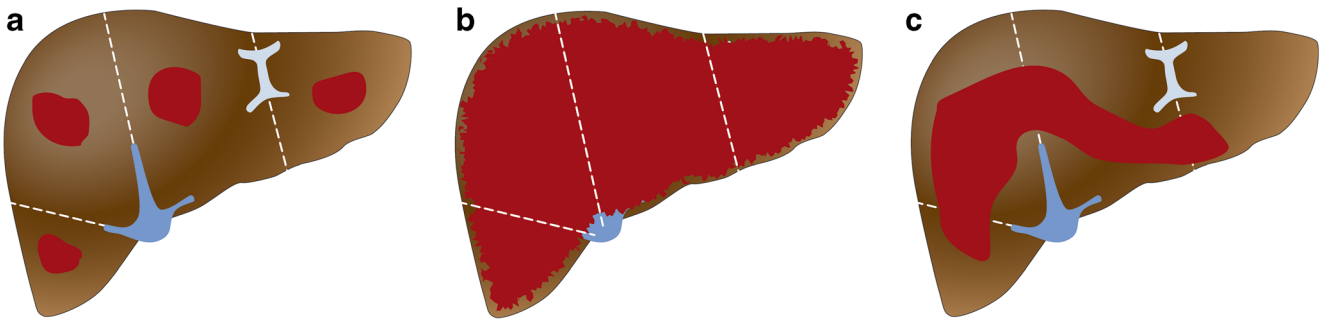

Fig. 4 PRETEXT IV tumor occurs in one of the following combinations: (**a**) multifocal tumor involving all sections, (**b**) diffuse infiltrative tumor or (**c**) one large tumor involving all four sections. Note that this last scenario is incredibly rare

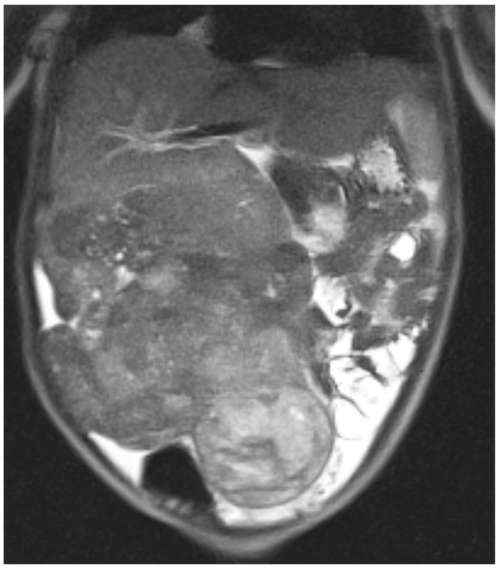

Fig. 5 Coronal T2-weighted MRI in a child with hepatoblastoma shows a pedunculated tumor extending from the inferior aspect of the segments 5 and 6. This is a PRETEXT II tumor

As stated, tumors that only involve the caudate lobe are considered to be PRETEXT II. If the tumor involves other sections in addition to the caudate, the PRETEXT determination can be made by accounting for all of the other sections involved with tumor.

PRETEXT III

PRETEXT III tumors involve portions of both the right and left lobes (Fig. 3). These tumors involve either two or three sections with only one contiguous section that is tumor-free. Central tumors that involve only the left medial *and* right anterior sections result in only one contiguous tumor-free section of liver and are considered PRETEXT III by convention.

The determination between PRETEXT II and PRETEXT III can be difficult because there is the question of tumor compression versus tumor invasion of the adjacent liver parenchyma. This is an important distinction because risk stratification might depend on the assignment. The guidelines described here can be helpful for determining this fact.

PRETEXT IV

PRETEXT IV tumors are almost always multifocal or infiltrative (Fig. 4). Because it is unlikely for a single mass to affect all four sections, careful assessment should be made before assigning the stage in the absence of a the multifocal or infiltrative pattern. Often, in cases where there is an extremely large tumor, one or more sections are being severely compressed. This can be best assessed in the coronal plane.

Table 2 can be used as a guide to determine PRETEXT grouping based on the liver sections or Couinaud segments that contain tumor.

PRETEXT annotation factors (V, P, E, F, R, C, N, M)

While the cooperative groups have applied the PRETEXT group in a consistent manner across trials, the same cannot be said for the annotation factors. The non-standard definitions have become problematic as it has become increasingly clear that certain annotation factors such as vascular involvement (both hepatic venous and portal venous), extrahepatic disease, multifocal tumor and tumor rupture place the child at higher risk [9, 10]. In the upcoming PHITT trial, these annotation factors are to be used to help risk-stratify patients. In the next portion of this manuscript we review each of the annotation factors and describe the differences (if any) among the cooperative groups' definitions, and then describe the new consensus definition.

Hepatic venous/inferior vena cava involvement (V)

One key difference between the definitions used in the most recent SIOPEL and COG trials centers on the definitions of various degrees of vascular involvement. In the SIOPEL studies, the hepatic veins or inferior vena cava are said to be involved if they are completely obstructed or circumferentially encased, or there are findings of tumor invasion [7]. In the COG study, the definitions were divided into more nuanced degrees of involvement designed to aid in the planning of surgical resection [8]. Thus, tumors that were within 1 cm of the intrahepatic inferior vena cava, abutted the inferior vena cava, or compressed the inferior vena cava were also said to have some degree of vascular involvement.

Gradation of hepatic venous or inferior vena cava involvement is made more difficult by the attempt to assess the number of vessels involved. In the SIOPEL system, the number of obstructed, encased or invaded veins is specifically noted. For example, if the tumor is said to be V2, this means that two hepatic veins are obstructed, encased or invaded. If the tumor is said to be V3, all three hepatic veins are obstructed, encased or invaded [7].

In the COG system, the tumor was only said to be V positive if all three hepatic veins or the inferior vena cava met one of the following criteria: V0 – tumor within 1 cm of vessel, V1 – tumor abutting vessel, V2 – tumor compressing vessel, V3 – intravascular tumor thrombus [8].

To address these differences, a consensus definition was created that includes information from both the SIOPEL and COG approaches (Table 3). Therefore, in the new

Table 2 PRETEXT group assignments based on the hepatic sections containing tumor; an x in a cell means that that section of the liver contains tumor

Sections affected by tumor					
C	RP	RA	LM	LL	PRETEXT
	x				1
				x	1
	x	x			2
		x			2
			x		2
			x	x	2
x					2
x	x				2
x		x			2
x	x	x			2
x			x		2
x			x	x	2
x				x	2
	x			x	2
	x	x	x		3
		x	x		3
		x	x	x	3
x	x	x	x		3
x		x	x		3
x		x	x	x	3
		x		x	3
	x		x		3
	x		x	x	3
	x	x		x	3
x		x		x	3
x	x			x	3
x	x		x		3
x	x		x	x	3
x	x	x		x	3
x	x	x	x	x	4
	x	x	x	x	4

Section name	Sections	Segment
Caudate	C	1
Left lateral	LL	2
Left lateral	LL	3
Left medial	LM	4a
Left medial	LM	4b
Right anterior	RA	5
Right anterior	RA	8
Right posterior	RP	6
Right posterior	RP	7

collaborative international approach for the upcoming PHITT trial each patient will be assigned a V-status: either V-negative or V-positive (Figs. 6, 7 and 8). A tumor is said to be V-positive if it meets any of the following criteria:

1. The tumor obliterates (meaning that the lumen is no longer visible) all three first-order hepatic veins or the intrahepatic inferior vena cava. It is recognized that failure to identify the lumen on cross-sectional imaging does not imply functional obstruction of the inferior vena cava, and the presence of enlarged collateral venous pathways (azygos and/or hemiazygos veins) or clinical signs (e.g., lower body edema) is not required to confirm this finding.
2. The tumor encases (by more than 50% or 180°) all three first-order hepatic veins or the intrahepatic inferior vena cava.
3. There is tumor thrombus in any one (or more) first-order hepatic vein or the intrahepatic inferior vena cava.

If the tumor does not meet any of these criteria, it should be assigned a V-negative.

Table 3 Hepatic venous/inferior vena cava involvement (V); a tumor is considered V-positive if all three lighter gray cells are selected or if any one darker gray box is selected

Extent of hepatic venous involvement	Right hepatic vein [a]	Middle hepatic vein [a]	Left hepatic vein [a]	Intrahepatic inferior vena cava [b]
Tumor obliterating [c] vein(s) or encasing [d] >50% or 180°				
Intravascular tumor thrombus [e]				

[a] *Hepatic vein* is defined as the hepatic vein between the confluence of the three hepatic veins (at the inferior vena cava) and the most central major branch of the hepatic vein

[b] *Intrahepatic inferior vena cava* is defined as the portion of the inferior vena cava surrounded more than 50% or 180° by liver parenchyma. Typically this occurs between the right atrium and the inferior aspect of the caudate

[c] *Obliterating* is defined as tumor compressing the vein so that the lumen is not visible

[d] *Tumor encasement* is defined as the tumor touching and surrounding the vein by more than 50% or 180°

[e] *Tumor thrombus* is defined as any thrombus within a first-order hepatic vein or the inferior vena cava

The following definitions are important to help assess hepatic venous/inferior vena cava involvement:

1. First-order hepatic vein. The portion of hepatic vein between its confluence with the inferior vena cava and its most central branch.
2. Intrahepatic inferior vena cava. The inferior vena cava is said to be intrahepatic if it is surrounded more than 50% or 180° by liver parenchyma. Typically this occurs between the right atrium and the inferior aspect of the caudate.
3. Tumor thrombus. For the purpose of PRETEXT classification, any type of thrombus within a first-order hepatic vein or the inferior vena cava should be considered tumor thrombus. Generally tumor thrombus appears as an expansile, enhancing mass within a vessel on CT or MRI. Color Doppler ultrasound might reveal the presence of small vessels within the thrombus.

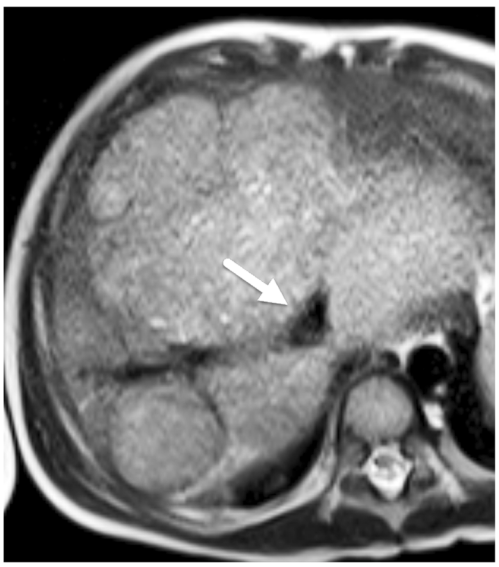

Fig. 6 Example of V-positive disease (encasement). Axial T2-weighted MRI of the liver in a child with hepatoblastoma shows that the inferior vena cava (*arrow*) is encased by tumor more than 180°

Perhaps the biggest challenge in determining hepatic venous involvement is in the setting of variant anatomy. Three common variants can cause challenges:

1. Common origin of the middle hepatic vein and either the right or left hepatic vein. In children with central tumors (particularly those that occupy segments 4a and 8), it is often difficult to identify the middle hepatic vein. In these cases it is not possible to distinguish a common origin of the middle hepatic vein and either the right or left hepatic vein. The new definitions for hepatic venous involvement should limit the importance of this scenario.
2. Four hepatic vein branches joining to form the inferior vena cava. In this scenario the same rules apply for determining hepatic venous involvement with the exception

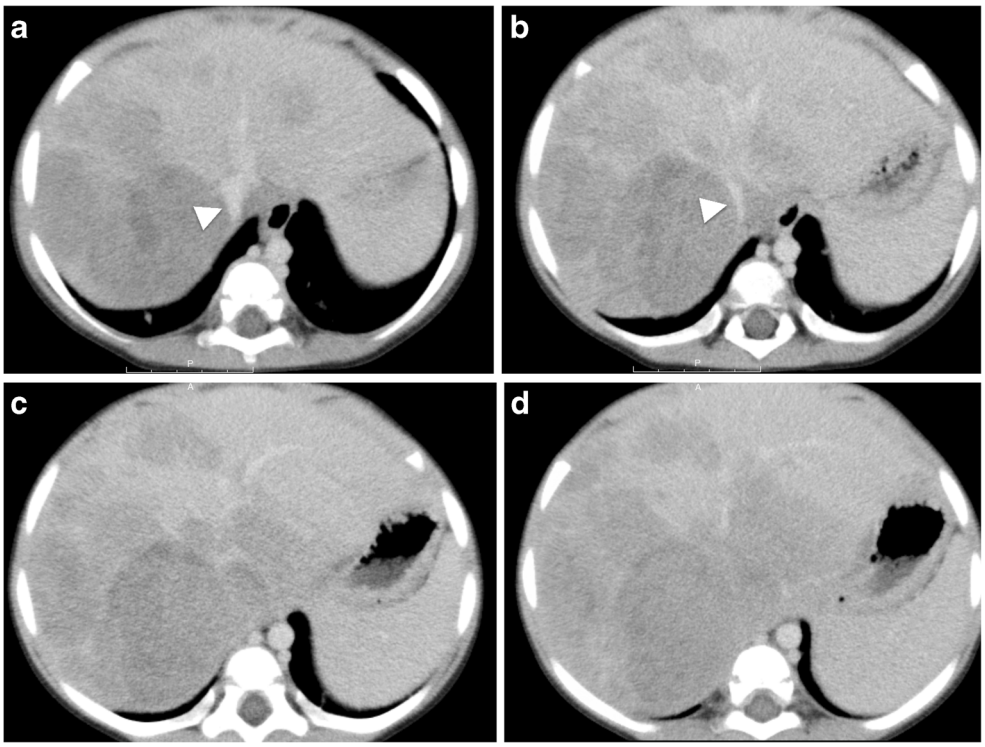

Fig. 7 Example of V-positive disease (obliteration). Four sequential axial contrast-enhanced CT images of the liver from superior (**a**) to inferior (**d**) in a child with hepatoblastoma show the inferior vena cava (*arrowheads*) is compressed (**a, b**) and then obliterated (**c, d**) by tumor

that instead of the tumor affecting three vessels, it must affect all four hepatic vein branches.

3. Accessory veins (such as a caudate branch) that join the inferior vena cava below the main confluence of the hepatic veins. In these children there is no change in the rules for determining hepatic venous involvement. Specifically, the accessory vein does not need to be affected by tumor in order for the tumor to be considered V-positive.

Portal venous involvement (P)

Portal venous involvement definitions have also been different in the recent SIOPEL and COG trials. In SIOPEL studies, the definition of portal vein involvement is the same as for the hepatic veins [7]. However the annotation number can only extend to two, owing to the fact that the portal vein has only two main branches rather than the three hepatic veins.

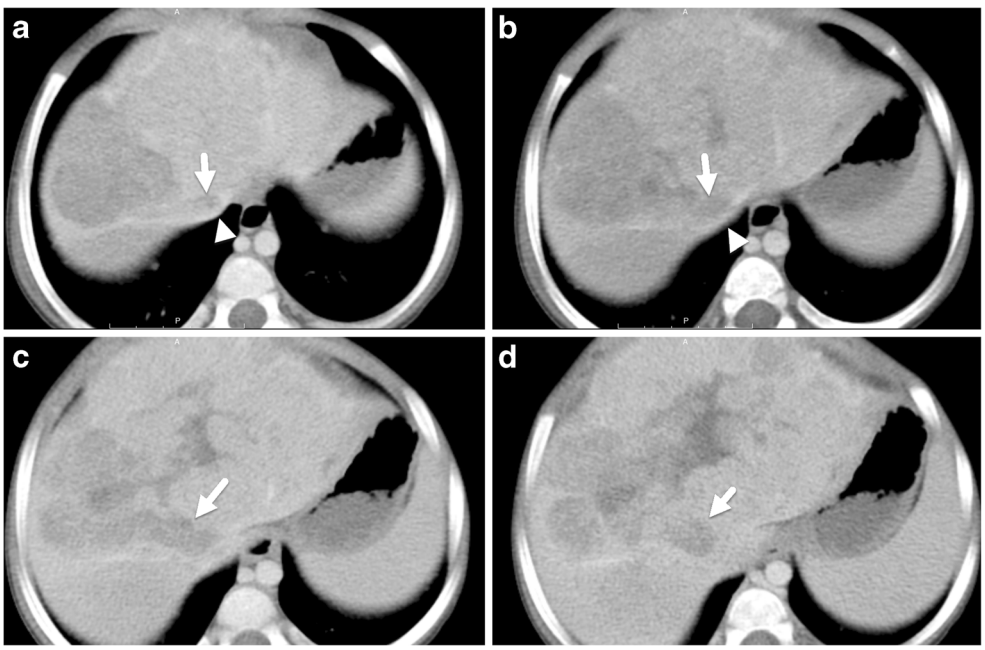

Fig. 8 Example of V-positive disease (tumor thrombus). Four sequential axial contrast-enhanced CT images from superior (**a**) to inferior (**d**) of the liver in a child with hepatoblastoma show tumor thrombus (*arrows*) extending from the right and middle hepatic veins to the inferior vena cava (*arrowheads*)

Table 4 Portal vein involvement (P); a tumor is considered P-positive if both lighter gray cells are selected or if any one darker gray box is selected

Extent of portal venous involvement	Right portal vein [a]	Left portal veins [a]	Main portal vein [a]
Tumor obliterating [b] vein(s) or encasing [c] >50% or 180°			
Intravascular tumor thrombus [d]			

[a] *Portal vein* branches are defined as extending from the bifurcation of the main portal vein to the first major branch of the vein (i.e. on the right, the right anterior and right posterior portal vein; on the left, the umbilical portion of the portal vein and the branch supplying segment 2)

[b] *Obliterating* is defined as tumor compressing the vein so that the lumen is not visible

[c] *Tumor encasement* is defined as the tumor touching and surrounding the vein by more than 50% or 180°

[d] *Tumor thrombus* is defined as any thrombus within a first-order portal vein or the inferior vena cava

Therefore if both first-order branch portal veins were obstructed/encased/invaded, the child would be said to have P2 portal venous involvement [7].

The COG AHEP 0731 study used more nuanced degrees of portal venous involvement, again in an attempt to define anticipated ease of surgical resection. The tumor was considered P-positive if both the right and left portal veins or the main portal vein met one of the following criteria: P0 – tumor within 1 cm of the main portal vein, the right and left portal veins, or the portal vein bifurcation; P1 – tumor abutting the main portal vein, the right and left portal veins, or the portal vein bifurcation; P2 – tumor compressing the main portal vein, the right and left portal veins, or the portal vein bifurcation; P3 – intravascular tumor thrombus within the main portal vein, the right and left portal veins, or the portal vein bifurcation [8].

The new international collaborative definitions are shown in Table 4 and Figs. 9, 10 and 11. Like the definitions for the V-status, the P-status has been simplified. Tumors are considered either P-negative or P-positive. A tumor is said to be P-positive if it meets any of the following criteria:

1. The tumor obliterates (meaning that the lumen is no longer visible) either both first-order portal veins or the main portal vein.
2. The tumor encases (by more than 50% or 180°) either both first-order portal veins or the main portal vein.
3. There is tumor thrombus in either or both the right and left portal veins, or the main portal vein.

If the tumor does not meet any of these criteria, it should be assigned a P-negative.

The following definitions are important to help assess portal venous involvement:

1. First-order portal vein. A portal vein is said to be involved by tumor if the tumor is affecting the vessel between the bifurcation of the main portal vein and the first major branch of the vein.
2. Tumor thrombus. For the purpose of PRETEXT classification, any type of thrombus within either the right or left portal vein, or the main portal vein should be considered tumor thrombus. Cavernous transformation should be considered as evidence of tumor thrombus.

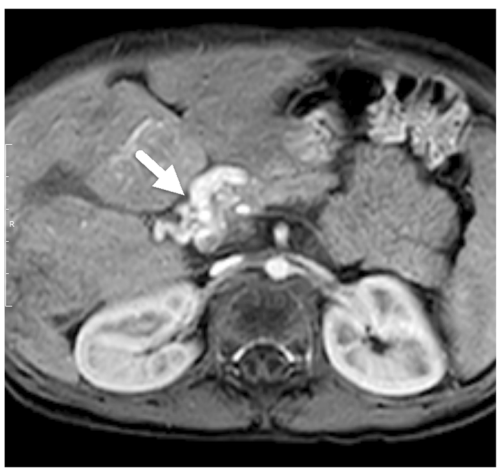

Fig. 9 Example of P-positive disease. Axial T1-weighted MR image obtained in a child with hepatoblastoma in the portal venous phase of enhancement shows cavernous transformation (*arrow*) of the main portal vein. Portal vein thrombosis/tumor thrombus should be inferred

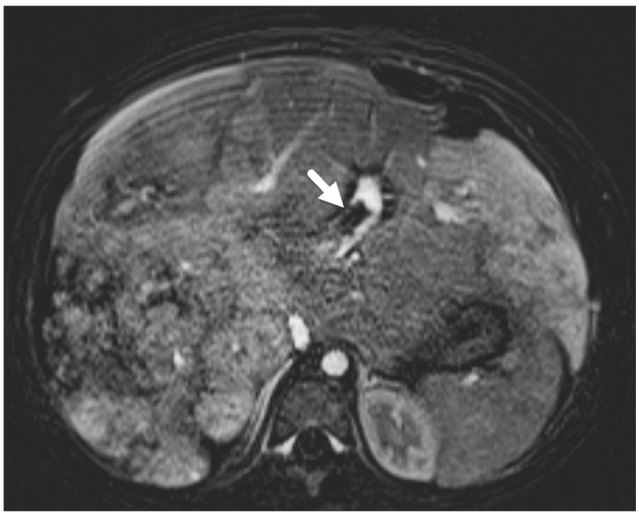

Fig. 10 Example of P-positive disease. Axial T1-weighted MRI of the abdomen obtained in the portal venous phase of enhancement in a child with hepatoblastoma shows thrombus within the left portal vein. The main portal vein and right portal vein were patent (not shown)

Although anatomical variation occurs less frequently in the portal vein, it can occur. Two common portal vein variants can affect assessment of portal vein involvement [35]:

1. Trifurcation of the portal vein with the right anterior and right posterior portal veins each arising at the trifurcation. In this scenario, the same rules apply for determining portal venous involvement with the exception that instead of the tumor affecting two vessels, it must affect all three portal vein branches.
2. Early branching of the right posterior branch of the portal vein prior to the bifurcation of the right and left portal veins. Like the previous scenario, the same rules apply for determining portal venous involvement with the exception that instead of the tumor affecting two vessels, it must affect all three portal vein branches.

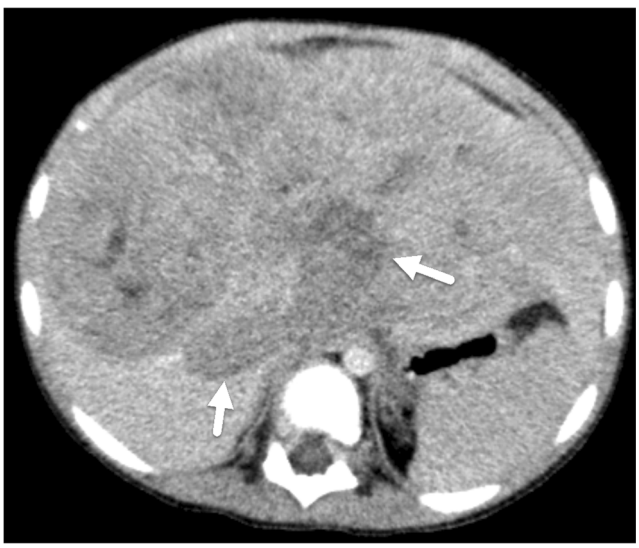

Fig. 11 Example of P-positive disease. Axial contrast-enhanced CT of the abdomen in a child with hepatoblastoma shows tumor thrombus (*arrows*) in the right and left portal veins

Extrahepatic disease contiguous with the main liver tumor (E)

The assessment of contiguous extrahepatic disease was one of the most confusing aspects of the original PRETEXT classification [7]. The definition of extrahepatic disease was improved in the 2005 revision [7, 36]. That revision defined extrahepatic disease as being present if there were findings of direct extension of tumor (E1) through the diaphragm or other organs or if there were peritoneal deposits (E2) [7, 36].

Even with a simplified definition, diagnosis of contiguous extrahepatic disease remains difficult. Frequently a large tumor is seen to abut the diaphragm or abdominal wall causing a loss of the plane between the affected structure and the tumor. Therefore for extrahepatic disease to be present, one of the following criteria must be met (Table 5):

1. Tumor is seen to cross boundaries/tissue planes, i.e. tumor is seen both above and below the diaphragm or extending through the abdominal wall.
2. Tumor is seen to be surrounded by normal tissue by >180° (Fig. 12). Note that this definition does not apply to intrahepatic tumor surrounded by normal hepatic parenchyma.
3. Peritoneal nodules (not lymph nodes) are present so that there is at least one nodule measuring ≥10 mm or two or more nodules measuring ≥5 mm (Fig. 13).

Fortunately, extrahepatic disease is uncommon, occurring in less than 5% of patients with hepatoblastoma [37]. Most times, tumor is seen to be abutting and displacing nearby structures, not invading them. Tumor extension and peritoneal deposits are more common in children with hepatocellular carcinoma. The following factors are important in the assessment of extrahepatic disease:

1. Ascites. Ascites is relatively common in the setting of liver tumors. Simple ascites is not considered extrahepatic disease.
2. Biopsy tracks. It is often difficult to assess for tumor within a biopsy track. In this instance, tumor should not be considered as present unless there is a discreet tumor nodule.

Table 5 PRETEXT annotation factors E, F, R, C, N and M

Factor	Annotation	Positive definition
Extrahepatic spread of disease	E	Any one of the following criteria is met: 1. Tumor crosses boundaries/tissue planes 2. Tumor is surrounded by normal tissue more than 180° 3. Peritoneal nodules (not lymph nodes) are present so that there is at least 1 nodule measuring 10 mm or larger or at least 2 nodules measuring 5 mm or larger
Multifocality	F	Two or more discrete hepatic tumors with normal intervening liver tissue
Tumor rupture	R	Free fluid in the abdomen or pelvis with one or more of the following findings of hemorrhage 1. Internal complexity/septations within fluid 2. High-density fluid on CT (>25 HU) 3. Imaging characteristics of blood or blood degradation products on MRI 4. Heterogeneous fluid on ultrasound with echogenic debris 5. Visible defect in tumor capsule -OR- Tumor cells are present within the peritoneal fluid -OR- Rupture diagnosed pathologically in patients who have received an upfront resection
Caudate involvement	C	Tumor involving the caudate
Lymph node metastases	N	Any one of the following criteria is met: 1. Lymph node with short-axis diameter of >1 cm 2. Portocaval lymph node with short-axis diameter >1.5 cm 3. Spherical lymph node shape with loss of fatty hilum
Distant metastases	M	Any one of the following criteria is met: 1. One non-calcified pulmonary nodule greater than or equal to 5 mm in diameter 2. Two or more non-calcified pulmonary nodules, each greater than or equal to 3 mm in diameter 3. Pathologically proven metastatic disease

CT, computed tomography; *HU*, Hounsfield units; *MRI*, magnetic resonance imaging

3. Imaging protocol. The coronal or sagittal planes should be used to assess for diaphragmatic disease and other extrahepatic disease.

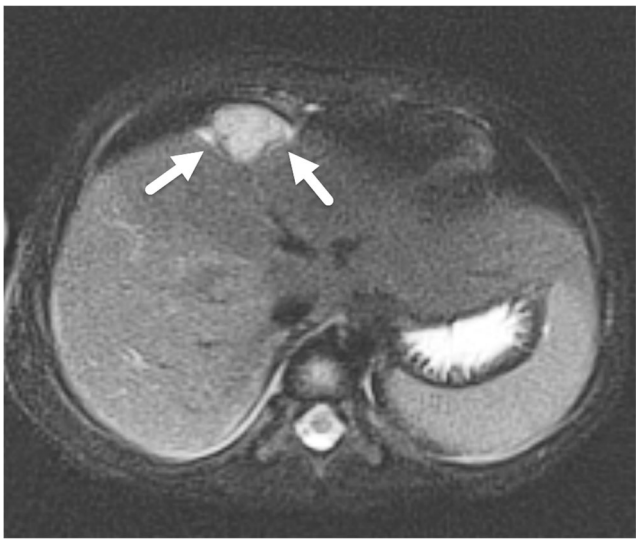

Fig. 12 Tumor surrounded by normal tissue. Axial T2-weighted MRI in a child with hepatoblastoma shows extrahepatic/peritoneal spread of tumor (*arrows*). The tumor, a diaphragmatic metastasis, is surrounded more than 180° by a small amount of fluid and normal liver. A clear plane is seen between the tumor and the liver

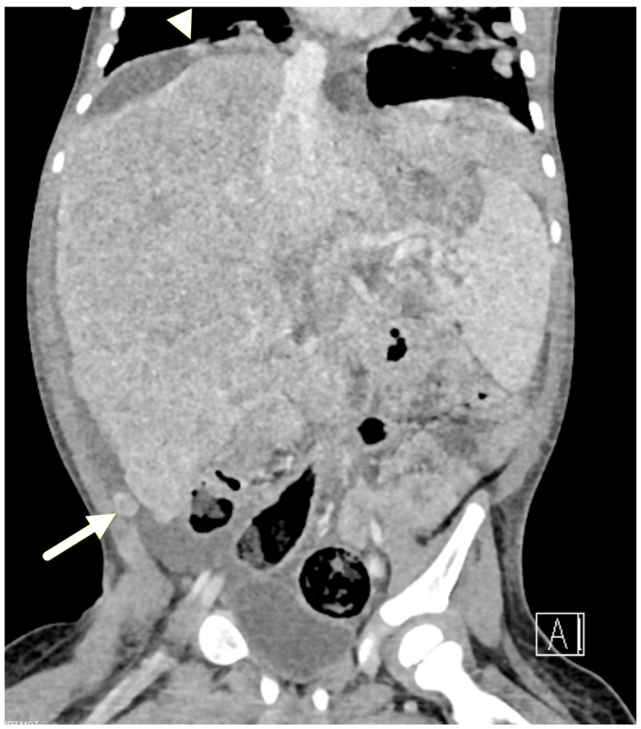

Fig. 13 Peritoneal nodules. Coronal contrast-enhanced CT of the abdomen in a child shows a large infiltrative hepatoblastoma. In addition, there are multiple peritoneal nodules. The largest nodule (*arrow*) is in the right lower quadrant and measures 10 mm in longest diameter. A peritoneal nodule abutting the right hemidiaphragm (*arrowhead*) measures 8 mm

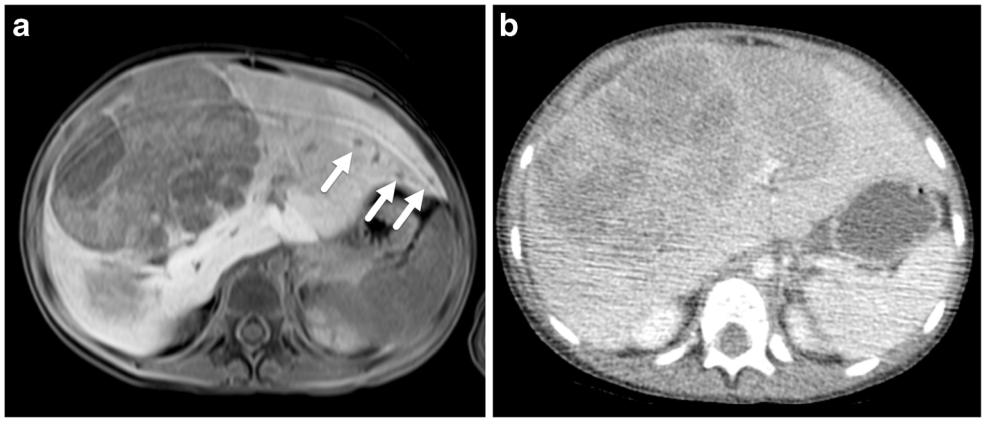

Fig. 14 Multifocal disease on MRI and CT. **a** Axial T1-weighted MRI obtained in the hepatocyte phase after administration of a hepatocyte-specific contrast agent in a child with hepatoblastoma shows a dominant mass in the right lobe of the liver. Note the multifocal disease in the left lateral section (*arrows*). The finding of multifocal disease in this child changed the staging from PRETEXT III to PRETEXT IV disease. **b** Axial contrast-enhanced CT in the same child shows the dominant central tumor but not the multifocal disease in the left lateral section

Multifocality (F)

Multifocal tumor is present in nearly 20% of patients with hepatoblastoma [37]. Multiple studies have shown that patients with multifocal disease have a worse outcome than those with a solitary focus of disease [10, 22, 37].

Tumor multifocality (F) is defined as two or more discrete hepatic tumors with normal intervening liver tissue. At times, this distinction can be difficult. This is most pronounced when there are multiple tumor nodules in close proximity. With tumor shrinkage in the setting of neoadjuvant chemotherapy, it is thus possible for a unifocal tumor to "become multifocal." In this instance the PRETEXT annotation might be unifocal and the POST-TEXT annotation multifocal.

Studies have shown that imaging is not reliable in detecting multifocal disease after neoadjuvant chemotherapy and tumor shrinkage [38, 39]. This could be because of the modality and contrast selection. Anecdotally, we have identified cases where multifocal disease was seen on MRI but not CT (Fig. 14). In addition, one recent study has shown that MRI with a hepatocyte-specific contrast agent is able to detect more hepatic tumors than MRI performed with conventional contrast agents [18].

Tumor rupture (R)

Occasionally, children with hepatoblastoma and hepatocellular carcinoma present with tumor rupture. Since the SIOPEL 4 study, those with tumor rupture have been stratified to the high-risk arm [7, 40]. The recent CHIC analysis confirmed that tumor rupture portends a worse prognosis in children with hepatoblastoma [9].

The new PHITT trial defines tumor rupture (R) as free fluid in the abdomen or pelvis at diagnosis with one or more of the following findings of hemorrhage (Figs. 15 and 16):

1. Internal complexity/septations within fluid
2. High-density fluid on CT (>25 Hounsfield units)
3. Imaging characteristics of blood or blood degradation products on MRI
4. Heterogeneous fluid on ultrasound with echogenic debris
5. Visible rupture/hepatic capsular defect on imaging.

It should be noted that while tumor rupture is most commonly diagnosed via imaging, it can also be diagnosed after laparotomy/laparoscopy or paracentesis. While laparotomy/laparoscopy or aspiration of peritoneal fluid is not required,

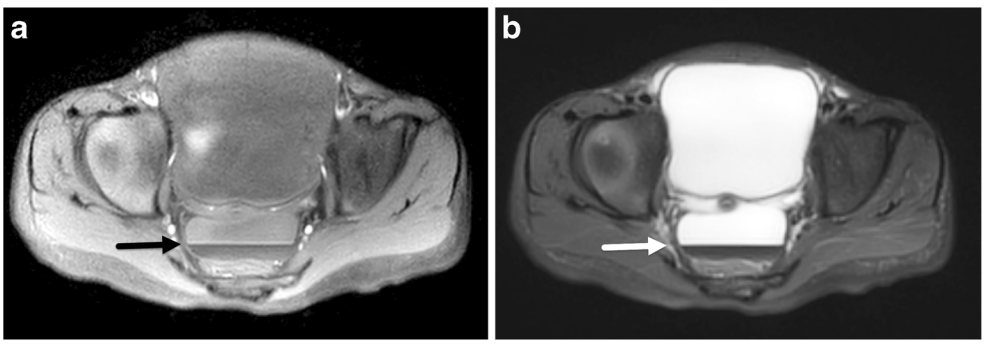

Fig. 15 Tumor rupture. Axial (**a**) T1-weighted and (**b**) T2-weighted MR images in a child with hepatoblastoma show layering fluid (arrows) in the pelvis. The fluid-fluid level is caused by blood breakdown products from tumor rupture

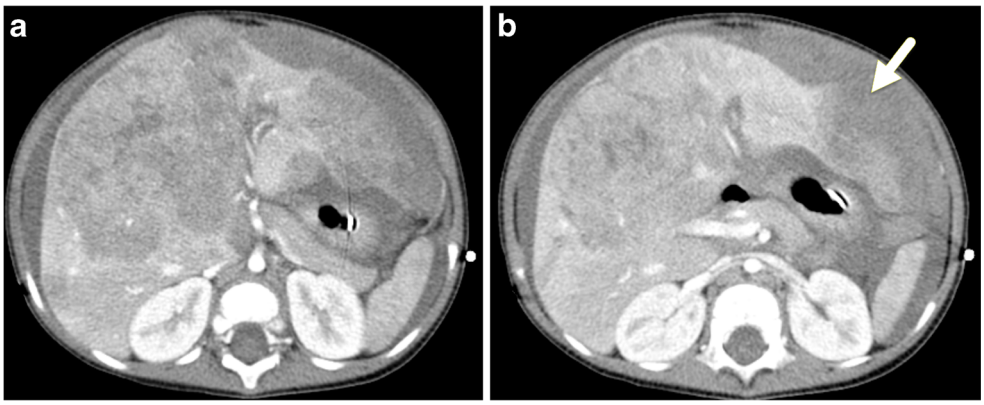

Fig. 16 Tumor rupture. Axial contrast-enhanced CT images in a child with hepatoblastoma show tumor rupture. In (**a**), the tumor capsule is contiguous. In (**b**), there is a defect (*arrow*) in the tumor capsule. The fluid adjacent to the liver measures 33 Hounsfield units

if it is performed, tumor rupture is diagnosed if tumor cells are present within the peritoneal fluid. It should also be noted that while tumor rupture can be diagnosed at pathology, the timing of this rupture cannot be determined. Therefore it cannot be assigned as a PRETEXT factor unless upfront surgery is performed (before initiation of chemotherapy). Instead, rupture identified at resection after chemotherapy would be considered a POST-TEXT factor.

The following factors are important in the assessment of tumor rupture:

1. Biopsy. Hemorrhage related to tumor biopsy is not considered tumor rupture for the purposes of PRETEXT classification.
2. Surgical rupture. Surgical rupture is not considered as tumor rupture for the purposes of PRETEXT classification.
3. Ascites. Simple (i.e. non-hemorrhagic) ascites is common in the setting of hepatoblastoma and hepatocellular carcinoma. This type of peritoneal free fluid is not considered tumor rupture.
4. Subcapsular fluid. Fluid collections beneath the liver capsule, even if hemorrhagic, are not considered to represent tumor rupture.

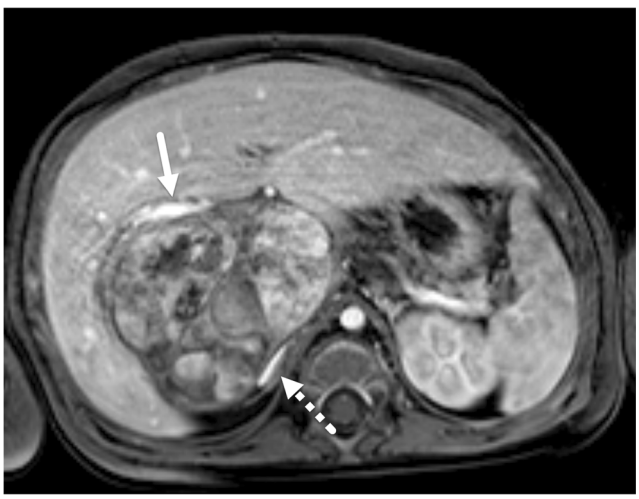

Fig. 17 Caudate involvement. Axial T1-weighted MR image obtained in the portal venous phase of imaging after administration of a hepatocyte-specific contrast agent in a child with hepatoblastoma shows a tumor arising from the caudate. The tumor is situated between the portal vein (*arrow*) and the inferior vena cava (*dashed arrow*). This tumor would be classified as PRETEXT II. Even though the inferior vena cava and portal vein are compressed, the tumor is considered V-negative and P-negative because the lumen is not obliterated and the tumor does not encase the vessel more than 180°

Caudate (C)

Involvement of the caudate lobe (Couinaud segment 1) has implications for surgical planning. As described, if the caudate lobe is involved, the tumor is said to be at least PRETEXT II by convention. Because the caudate lobe can be resected with either a right or a left hepatectomy, it is still important to determine the true extent of the tumor (Fig. 17). Even though modern surgical techniques have made resection of the caudate safer, complications are encountered with some frequency and can be significant. Thus, caudate involvement remains a distinct annotation factor, even though it is not used to risk-stratify patients.

To determine whether the caudate is truly involved with tumor, it is important to understand the boundaries of the caudate (Fig. 18). For the purpose of PRETEXT staging, the caudate is defined as the part of the liver that extends along the posterior surface of the liver between the portal vein and intrahepatic inferior vena cava. The following are used as the borders of the caudate:

- The right margin is a line drawn along the right lateral border of the inferior vena cava, perpendicular to the inferior vena cava.
- The left margin is the ligamentum venosum.
- The anterior margin is the porta hepatis and ligamentum teres.
- The superior margin is the dome of liver.
- The inferior margin is where liver passes between main portal vein and inferior vena cava.

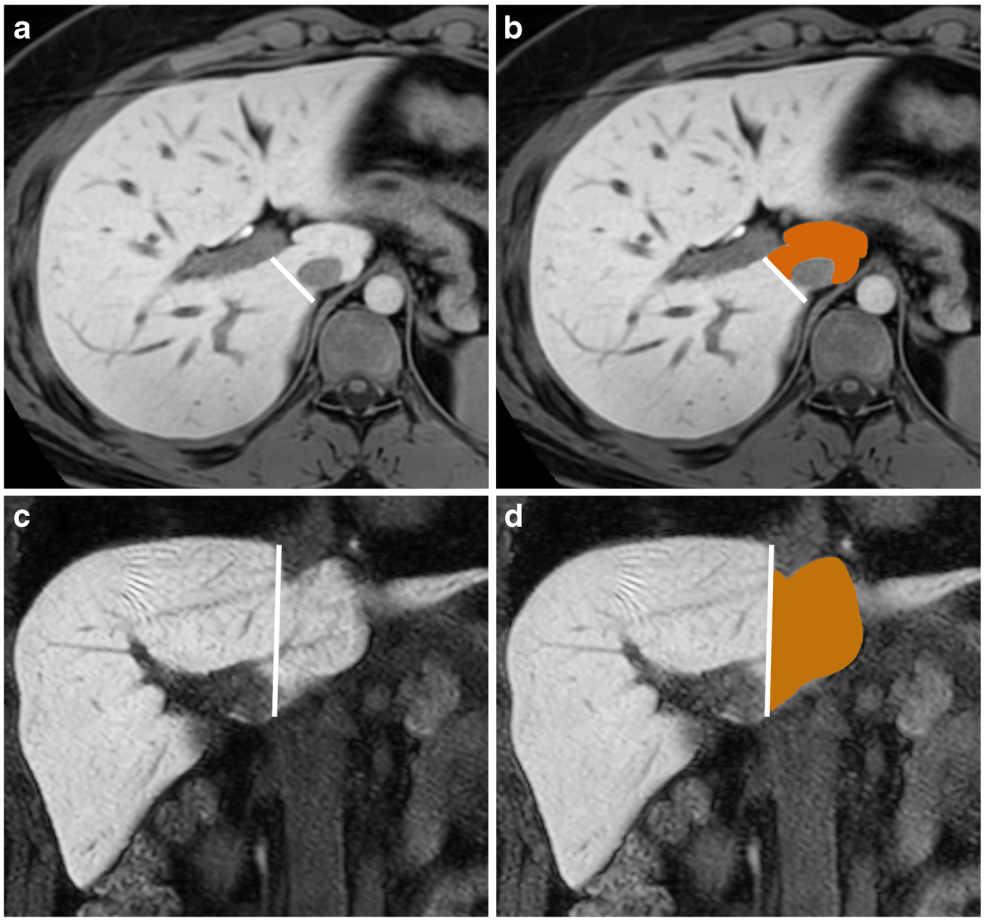

Fig. 18 Caudate boundaries. Axial (**a, b**) and coronal (**c, d**) T1-weighted MR images of a normal liver obtained in the hepatocyte phase of imaging show the boundaries of the caudate lobe. On the axial images, note the white line drawn perpendicular to the axis of the caudate lobe along the right lateral margin of the inferior vena cava. The colored portion of the image in (**b**) highlights the extent of the caudate lobe on the axial image. On the coronal images, the white line is drawn along the right lateral margin of the inferior vena cava and represents the medial border of the caudate lobe. The colored portion of the image in (**d**) highlights the extent of the caudate lobe in the coronal plane

Lymph node metastases (N)

Lymph node metastases are extremely uncommon in the setting of hepatoblastoma but are much more common in hepatocellular carcinoma [28]. It can be difficult to diagnose lymph node metastases. While biopsy is not required to diagnose lymph node metastases, it might be needed in certain instances where imaging is equivocal or in children in whom a decision to transplant requires certainty regarding lymph node status.

In young children, traditional diameter-based cutoffs can be problematic because there are no agreed upon standards. Therefore for PRETEXT staging, nodal metastases are considered to be present if one of the following criteria is met (Fig. 19):

1. Lymph node with a short-axis diameter of >1 cm or a portocaval lymph node with short-axis diameter >1.5 cm, or
2. Spherical lymph node shape with loss of fatty hilum.

It should be noted that studies have shown that morphologic criteria, such as in criterion 2, are less sensitive for detection of metastases [41, 42]. Therefore this criterion should be used

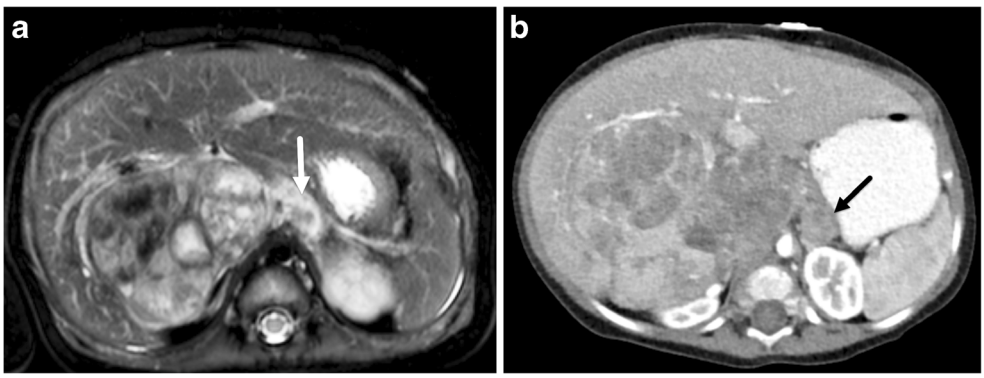

Fig. 19 Lymph node metastases. Axial (**a**) T2-weighted image and (**b**) contrast-enhanced CT image in a child with hepatoblastoma show a lymph node metastasis (*arrow*) that measured 13 mm in its short axis. This was confirmed to be a metastatic lymph node by pathology at resection

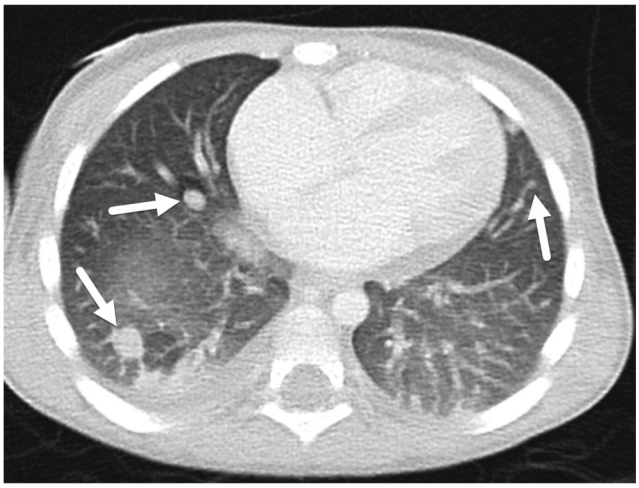

Fig. 20 Pulmonary metastases. Axial chest CT in a child with hepatoblastoma shows multiple pulmonary metastases (*arrows*). The largest nodule in the right lower lobe measures approximately 1 cm in diameter

with some caution. Definitive involvement of lymph nodes is confirmed at histological examination.

Distant metastases (M)

The lungs are the most common site of distant metastases in children with hepatoblastoma and hepatocellular carcinoma. Pulmonary metastases are present in 17% of children with hepatoblastoma at diagnosis [9]. CT is the imaging modality of choice to diagnose pulmonary metastases and should be performed in all pediatric patients with a liver tumor at the time of diagnosis. There is controversy regarding the best method to image the lungs of infants and young children. New CT scanners can image the entire chest in several tenths of a second during quiet respiration. With this technology, it might be possible to perform high-quality chest CT imaging without the need for general anesthesia. However, given the importance of detecting pulmonary metastases, it is recommended that most infants and children be imaged under general anesthesia with suspended respiration. The use of intravenous contrast agent is also controve rsial when imaging the chest. However, many pediatric practices recommend performing at least the first CT with intravenous contrast to better demonstrate hilar vessels and pleural or perihilar nodules. In addition to administering intravenous contrast agent, the following reconstructed images are recommended in order to improve nodule detection: thin slices (1 mm or less), sliding maximum-intensity projection images, and coronal plane images.

It can be difficult to diagnose pulmonary metastases. Factors that favor metastases include multiple lesions and a spherical shape (Fig. 20). In many parts of the world, a single rounded lung lesion with a diameter of >5 mm in a child with a primary liver tumor is very likely to be a metastasis. However, non-metastatic nodules might be present, especially in locations with endemic tuberculosis, or histoplasmosis. Since data analysis from the current COG AHEP0731 trial, the definition of metastatic pulmonary nodules has been modified slightly [43]. The definition of pulmonary metastasis in this revision of PRETEXT is the same as the risk stratification threshold in the forthcoming PHITT trial. To qualify as M-positive, a child must have at least one non-calcified pulmonary nodule greater than or equal to 5 mm in diameter; or two or more non-calcified pulmonary nodules, each greater than or equal to 3 mm in diameter. Like tumor rupture, metastases can be diagnosed via pathology. While children with characteristic imaging findings of pulmonary metastatic disease do not require biopsy, those with equivocal findings might require biopsy because this finding significantly changes therapy.

Because hepatoblastoma is more common in premature infants, particularly those with a very low birth weight, concomitant chronic lung disease of prematurity is often present. Also, because infants often require general anesthesia for imaging, atelectasis might be present. Both of these issues can make it difficult to fully evaluate the lungs. Several imaging factors can help to improve visualization of the lungs:

1. In children who are imaged under sedation or general anesthesia, chest CT should be performed before abdominal imaging.
2. If the child is intubated, positive pressure should be used to better inflate the lungs.
3. Prone imaging can be used to better image the lung bases in children with persistent atelectasis.

Although the lungs are the most common site of metastasis in the setting of hepatoblastoma, metastases occur to other locations. Case reports have documented bone and brain metastases [, 44]. Because these other sites of disease are uncommon, routine imaging beyond chest CT should not be performed in attempt to identify distant metastases. Prior SIOPEL and COG protocols have recommended studies such as bone scan or brain MRI. These imaging studies are no longer recommended unless the child is symptomatic or there is an unexplained rise in the serum alpha-fetoprotein level.

It should be noted that patients with hepatoblastoma sometimes have fractures at the time of diagnosis [45]. Additionally, some patients have a paraneoplastic osteopenia leading to abnormal bone metabolism and abnormal bone scans [46, 47]. Therefore bone pain in the setting of newly diagnosed hepatoblastoma might be more likely to represent a fracture or a paraneoplastic process rather than metastases. Biopsy is thus recommended to confirm a diagnosis of bone metastases.

Imaging after initiation of chemotherapy

Children with hepatoblastoma and hepatocellular carcinoma will continue to be imaged during their neoadjuvant chemotherapy. Fortunately, the imaging algorithm can be simplified after the time of diagnosis. Most children only require a CT or MRI of the abdomen and pelvis. Like imaging at diagnosis, MRI with a hepatocyte-specific contrast agent is the preferred imaging study for its superior detection of multifocal disease. However, CT with intravenous contrast agent or MRI with a conventional gadolinium-based contrast agent can be used at the institution's preference. If a CT is performed, imaging is only needed during the portal venous phase for hepatoblastoma. However, arterial-phase and portal venous phase imaging are recommended in children with hepatocellular carcinoma. Ultrasound with Doppler interrogation of the hepatic veins, inferior vena cava, and portal veins is not routinely required but might be needed in some cases of complex vascular involvement where some surgeons use this imaging modality as an adjunct to CT/MRI vascular imaging in their preoperative assessment of vascular involvement. During routine follow-up, chest CT is only required if the child had pulmonary metastases at diagnosis. However, in the setting of progressive disease, a rising serum alpha-fetoprotein level, or suspected infection, chest CT is an important tool used to diagnose new metastases or pneumonia.

The PRETEXT group (I, II, III and IV) and all PRETEXT annotation factors (V, P, E, F, R, C, N, M) should be reassessed during each imaging time point. After diagnosis, these are referred to as POST-TEXT (POST-Treatment EXTent of disease) factors. After the tumor has been surgically resected, the POST-TEXT factors no longer apply.

Conclusion

We have sought to provide medical practitioners the updated version of PRETEXT staging that will be utilized in the forthcoming coming Trial to Pediatric Hepatic International Tumor Trial (PHITT). In this manuscript we sought to clearly define and articulate the selective and specific criteria to be utilized to risk-stratify and treat children with hepatoblastoma and hepatocellular carcinoma.

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