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ORIGINAL ARTICLE

The impact of hepatocyte phase imaging from infancy to young adulthood in patients with a known or suspected liver lesion

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Abstract
Objective Hepatocyte-specific contrast agents are used to help characterize liver lesions. However, there are no studies evaluating the utility of these agents in detecting or diagnosing pediatric liver lesions. The purpose of this study is to assess the impact of the hepatocyte phase of imaging on lesion detection, tumor staging and diagnostic confidence.
Materials and methods All patients undergoing an MRI between September 2010 and August 2012 using gadoxetate disodium as the contrast agent were included in this study. Each exam was duplicated so that one copy contained all sequences, including the hepatocyte phase of imaging, and the other copy contained all sequences *except* the hepatocyte phase of imaging. One reviewer evaluated all exams in a blinded, random fashion. Data tracked included imaging diagnosis, confidence in diagnosis, number of lesions and PRETEXT grade. The imaging diagnosis was compared to histopathology, when available. Data were analyzed for the study population as well as the subset of patients diagnosed with focal nodular hyperplasia (FNH).
Results There were 112 patients (56 male; mean age: 9.25 years) included in this study. A total of 33 patients had a malignant tumor and the remainder had either a benign lesion or no lesion. The addition of the hepatocyte phase of imaging significantly improved the diagnostic confidence for all patients ($P<0.0001$) as well as specifically for patients diagnosed with FNH ($P=0.003$). In nearly a quarter of patients, the hepatocyte phase of imaging allowed the reviewer to detect additional lesions ($P=0.005$). In the patients with a malignant tumor, the addition of the hepatocyte phase of imaging changed the PRETEXT grade in 7/30 patients although the results were not significant ($P=0.161$).
Conclusion The addition of the hepatocyte phase of imaging helps to improve lesion detection and increase the diagnostic confidence for all liver tumors, as well as for FNH in particular.

Keywords Hepatocyte-specific contrast agent · Liver tumors · Liver · Magnetic resonance imaging · Children

Introduction

Pediatric liver tumors encompass a wide range of benign and malignant etiologies, some of which are specific to children, but many of which overlap with adult diagnoses [1–5]. Because there is considerable overlap in the imaging appearance of these tumors, it is often difficult to make a specific diagnosis based purely on the imaging findings. Radiologists rely on clinical information, such as patient demographics, associated laboratory findings, history of prior malignancy, chronic liver disease or congenital disorders, to narrow their differential diagnosis [1–8].

Gadoxetate disodium (Eovist/Primavist; Bayer HealthCare, Leverkusen, Germany) is a hepatocyte-specific gadolinium-based contrast agent that is taken up by functioning hepatocytes and is partially excreted through the biliary system [9]. In adults, hepatocyte-specific contrast agents have been shown to improve detection of liver lesions, reliably distinguish hepatocellular adenomas from focal nodular hyperplasia (FNH), characterize different types of tumors, improve the detection of liver metastases and increase overall

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diagnostic confidence [10–17]. In addition, hepatobiliary agents have been used to evaluate the anatomy, function and pathology of the biliary system [10].

Initial reports describing the use of hepatocyte-specific contrast agents in the pediatric liver have shown that different tumors may have distinct imaging patterns and suggest that the combination of pre-contrast and post-contrast imaging is useful to distinguish tumor types [5, 18, 19]. Despite these reports, no large-scale studies have been performed assessing the utility of gadoxetate disodium in children. The purpose of this study was to determine if the addition of the hepatocyte phase of imaging after the administration of gadoxetate disodium helped to increase diagnostic confidence in the MR evaluation of pediatric liver tumors. In addition, we sought to determine if the use of gadoxetate disodium improved lesion detection.

Materials and methods

After IRB approval was obtained, a retrospective HIPAA compliant study was performed. The pharmacy records were queried to identify every patient who had received a dose of gadoxetate disodium between September 2010 and August 2012 at our institution. Each dosage of contrast was then correlated with the associated liver MRI creating the list of patients to be included in the study. If a patient had multiple gadoxetate disodium-enhanced MRI examinations, only the first examination for each patient was included in this study.

All MRI examinations followed our standard liver tumor protocol [5]. After a localizer sequence is performed to identify the superior and inferior extent of the liver, the following pre-contrast sequences are obtained: coronal T2-weighted fast spin echo (FSE), axial T2-weighted FSE (with and without fat suppression), axial T1-weighted, and axial T1-weighted in- and opposed-phase images. Gadoxetate disodium is then administered intravenously at a dose of 0.05 mmol/kg (0.2 mL/kg; maximum dose of 10 mL) and a rate of 1 mL/s. After contrast injection, the following sequences are performed: axial T1-weighted gradient echo images in the arterial, portal venous and late portal venous phases; axial arterial and venous 2-D time of flight; axial diffusion-weighted imaging; axial balanced steady-state free precession; and axial and coronal T1-weighted gradient echo images in the hepatocyte phase of imaging (20 min after contrast injection).

Each MRI was then duplicated so that one copy contained all sequences, including the hepatocyte phase of imaging, and the other copy contained all sequences *except* the hepatocyte phase of imaging. Both copies of each study were anonymized, cleansed of all clinical data except age, and randomized by a radiology informatics research coordinator. The exams were then placed on the research PACS in use at our institution and each study was reviewed in a random, blinded fashion during a 1-week period.

All studies were reviewed by one board-certified pediatric radiologist with 6 years of experience specializing in pediatric abdominal imaging and liver tumors (A. J. T.). The reviewer was blinded to the patient history, study indication and any prior or subsequent imaging (including MRI). For each study, the number of lesions (maximum of six lesions counted) and hepatic segments involved was recorded. The hepatic segments involved were used to determine PRETEXT staging for malignant tumors [20]. PRETEXT staging was not performed if the patient had already undergone partial or complete resection of a liver mass. Finally, the reviewer recorded the single most likely diagnosis and stated his level of confidence in that diagnosis using a 5-point Likert scale. There were no strict criteria for making a specific diagnosis. The reviewer used clinical acumen based on experience as well as published descriptions of the encountered liver pathology [5, 11–18, 21, 22]. The typical lesion characteristics used for diagnosis are described in Table 1. If no lesion was identified, no diagnostic confidence score was recorded. The final imaging diagnosis was compared to histopathology when available. If no pathology was present, final diagnosis was based on the clinical diagnosis in the electronic medical record. In addition to the data obtained from imaging, patient demographic data were recorded.

Statistical analysis was performed using SAS (Version 9.3, Cary, NC). Diagnostic confidence was compared using the nonparametric Wilcoxon rank sum test. This test was used because the confidence was not normally distributed. The diagnostic confidence levels were compared first for all liver tumors. Then, because one of the major benefits of using hepatocyte-specific contrast agents in adults is the improved diagnostic confidence in diagnosing FNH, the diagnostic confidence level for two distinct subsets of patients was compared. First, the diagnostic confidence using the hepatocyte phase of imaging was compared to the diagnostic confidence of the exam without the hepatocyte phase of imaging for patients with histologically confirmed FNH. Next, the diagnostic confidence levels were compared for the separate study types in patients who did not undergo a biopsy but were diagnosed with FNH using the hepatocyte phase as the gold standard [13]. Finally, lesion detection was compared using the paired *t*-test. *P*-values of less than 0.05 were considered to indicate statistical significance.

Results

Study population

A total of 112 patients were imaged with a hepatocyte-specific contrast agent over the course of the study. The first examination for each patient was duplicated, creating 224 studies for evaluation. The mean age of the patients was 9 years, 3 months (range: 45 days to 32 years, 7 months; median age: 8 years, 8 months). There were 11 patients older than 18 years of age. Exactly one-half of the patients were male (56/112).

Table 1 Typical MRI imaging characteristics for pediatric hepatic lesions. All signal intensities are described in relation to the background liver

Tumor type	T2	T1 noncontrast	T1 arterial phase	T1 hepatocyte phase
Malignant lesions				
Hepatoblastoma	Hyperintense (often heterogeneous)	Hypointense (often heterogeneous)	Hypointense (often heterogeneous)	Variable, usually hypointense (often heterogeneous)
Hepatocellular carcinoma	Slightly hyperintense	Hypointense	Hyperintense	Hypointense
Fibrolamellar hepatocellular carcinoma	Hyperintense with a hypointense central scar	Hypointense with a hypointense central scar	Hyperintense with a hypointense central scar	Hypointense with a hypointense central scar
Undifferentiated embryonal sarcoma	Hyperintense	Hypointense	Hypointense	Hypointense
metastases	Hyperintense	Hypointense	Variable (depends on primary tumor)	Hypointense
Benign lesions				
Hepatic hemangioma	Hyperintense	Hypointense	Nodular centripetal enhancement	Variable
Focal nodular hyperplasia	Isointense to slightly hyperintense. If present, central scar is hyperintense	Isointense to slightly hypointense. If present, central scar is hypointense	Hyperintense. If present, central scar is hypointense	Hyperintense. If present, central scar is hypointense
Hepatocellular adenoma	Hyperintense	Hypointense	Hyperintense	Hypointense
Regenerative nodule	Hypointense	Hypointense	Hypointense	Isointense to slightly hyperintense
Dysplastic nodule	Hypointense	Variable	Variable	Variable
Mesenchymal hamartoma	Hyperintense	Hypointense	Hypointense	Hypointense
Bile lake	Hyperintense	Hypointense	Hypointense	Hyperintense. May see contrast puddling
Hepatic cyst	Hyperintense	Hypointense	Hypointense	Hypointense

Pathology

Histopathology was available in 52 of the 112 patients, including 33 malignant lesions and 19 benign lesions (Table 2). The majority of the pathologically proven malignant lesions were hepatoblastoma (24/33) and the majority of the pathologically proven benign lesions were FNH (9/19).

There was no pathological diagnosis in 60 of the 112 patients. In 43 of these 60 patients, there was agreement in the imaging diagnosis between studies with the hepatocyte phase of imaging and studies without the hepatocyte phase of imaging. This included 20 patients in whom no lesion was detected and 23 patients with a variety of additional benign diagnoses, the majority of which (13/23) were thought to be FNH. In 17 of the 60 patients where histopathology was not available, there was not agreement between studies with the hepatocyte phase of imaging and studies without the hepatocyte phase of imaging. The imaging-based diagnoses in these

Table 2 Diagnosis based on histopathology or imaging

	Histopathology	Suspected by MRI without histopathology confirmation (agreement between studies without and with hepatocyte phase imaging)
Malignant		
Hepatoblastoma	24	
Hepatocellular carcinoma	4	
Metastasis	2	
Undifferentiated embryonal sarcoma	2	
Fibrolamellar hepatocellular carcinoma	1	
Total malignant	33	0
Benign		
Focal nodular hyperplasia	9	13
Hepatocellular adenoma	3	2
Hepatic hemangioma	3	2
Mesenchymal hamartoma	2	
Dysplastic nodule	1	
Nonspecific inflammation	1	
No lesion identified		20
Hepatic cyst		5
Bile duct/lake/collection		1
Total benign	19	43
Overall total	52	43

Table 3 MRI diagnoses without agreement between studies without and with hepatocyte phase of imaging

Suspected MRI diagnosis		Number of patients
Without hepatocyte phase	With hepatocyte phase	
No lesion detected	FNH	2
FNH	Hepatocellular adenoma	2
Hepatocellular adenoma	FNH	1
No lesion detected	Hepatocellular adenoma	1
FNH	Hemangioma	1
Metastases	Abscess	1
No lesion detected	Bile duct/lake/collection	1
No lesion detected	Cyst	1
FNH	Cyst	1
FNH	Dysplastic nodule	1
Dysplastic nodule	FNH	1
Hepatocellular carcinoma	No lesion detected	1
Regenerative nodule	FNH	1
Hepatoblastoma	FNH	1
Dysplastic nodule	Hepatocellular adenoma	1
	Total	17

FNH focal nodular hyperplasia

patients varied considerably (Table 3). In all cases where histopathology was not available, review of the medical records showed that not one patient was subsequently.

Diagnostic confidence

The diagnostic confidence improved in 46 patients after viewing the hepatocyte phase of imaging (Figs. 1 and 2). This difference was significant ($P<0.0001$). The frequency of di-

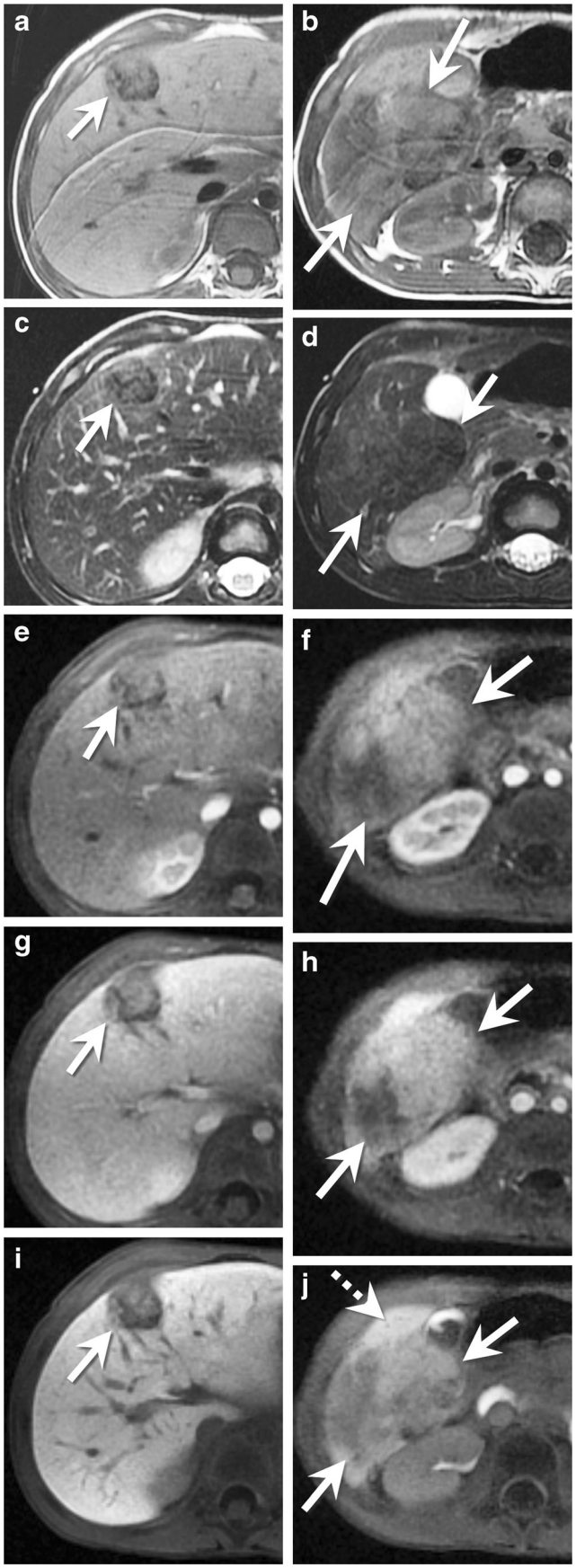

Fig. 1 A 3-year-old boy with a history of multifocal hepatoblastoma status post six cycles of chemotherapy. The mass was diagnosed on imaging as a hepatoblastoma with an initial confidence score of 1. The confidence score increased to 4 when viewing the study with the hepatocyte phase of imaging. **a** Axial T1-W image of the liver shows a hypointense mass (*arrow*) in segment 4b. **b** Axial T1-W image of the liver shows a second, larger hypointense mass (*arrows*) arising from segment 5 to 6. **c** Axial T2-W image shows the hypointense, segment 4b mass (*arrow*). **d** Axial T2-W image shows the larger mass (*arrows*) to be isointense to the background liver. **e** Axial liver acquisition with volume acceleration (LAVA) image obtained in the hepatic arterial phase of enhancement shows the segment 4b mass (*arrow*) to be hypointense to the liver. **f** Axial LAVA image obtained in the hepatic arterial phase of enhancement shows the larger mass (*arrows*) to have heterogeneous enhancement. **g** Axial LAVA image obtained in the portal venous phase of enhancement shows the segment 4b mass (*arrow*) to be hypointense compared to the background liver. **h** Axial LAVA image obtained in the portal venous phase of enhancement shows the larger mass (*arrows*) to have heterogeneous enhancement. **i** Axial LAVA image obtained in the hepatocyte phase of enhancement shows the segment 4b mass (*arrow*) to be hypointense compared to the background liver. **j** Axial LAVA image obtained in the hepatocyte phase of enhancement shows the larger mass (*arrows*) to have a heterogeneous appearance with some areas of the mass retaining contrast and others having no retention of contrast. Overall, the mass is hypointense compared to the background liver (*dashed arrow*)

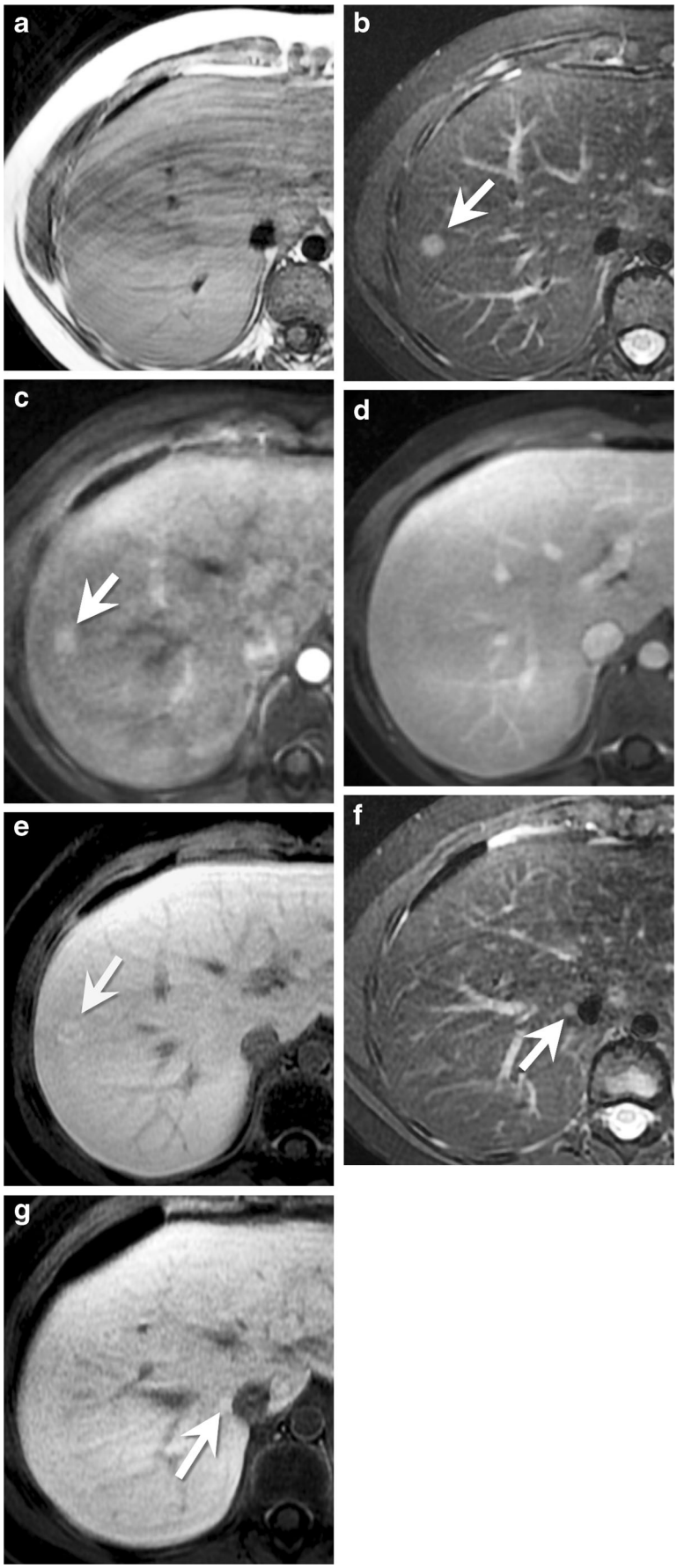

Fig. 2 A 10-year-old girl with a history of treated stage IV neuroblastoma and bone metastases diagnosed 4 years earlier, now off therapy. The mass was diagnosed on imaging as focal nodular hyperplasia with an initial confidence score of 2. The confidence score increased to 5 when viewing the study with the hepatocyte phase of imaging. **a** Axial T1-W image is limited by artifact; however, no lesion is identified. **b** Axial T2-W image shows a small, hyperintense lesion (*arrow*) in segment 8 of the liver. **c** Axial LAVA image obtained in the hepatic arterial phase of enhancement shows faint enhancement of the small lesion (*arrow*). **d** Axial LAVA image obtained in the portal venous phase of enhancement shows that the lesion is isointense to the background liver. **e** Axial LAVA image obtained in the hepatocyte phase of enhancement shows that the lesion (*arrow*) is hyperintense to the background liver with a central stellate scar that is hypointense. **f** Axial T2-W image shows a second, smaller hyperintense lesion (*arrow*) adjacent to the inferior vena cava. **g** Axial LAVA image obtained in the hepatocyte phase of enhancement shows that the second lesion (*arrow*) is also hyperintense to the background liver

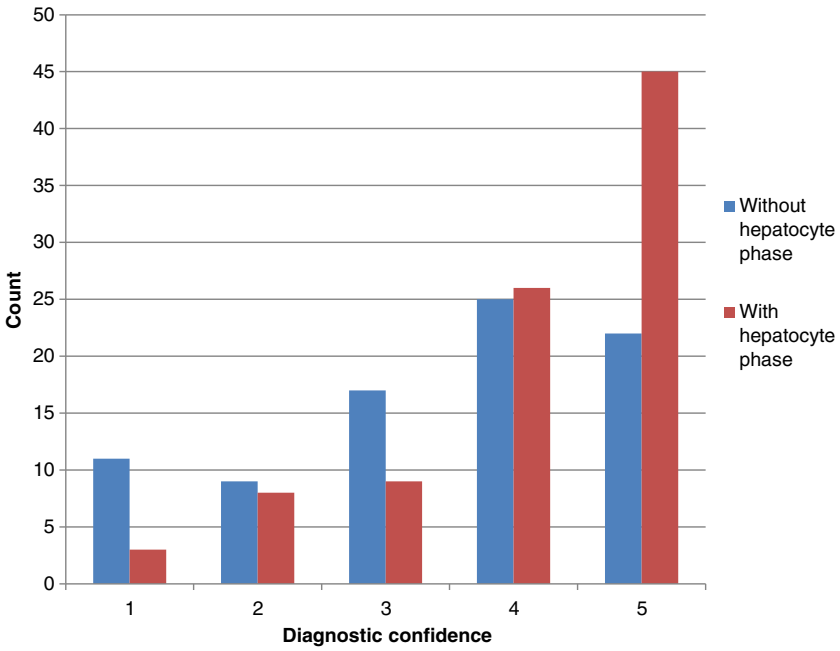

Fig. 3 Graph shows the distribution of confidence scores without (blue) and with (red) the hepatocyte phase of imaging

agnostic confidence scores without and with the hepatocyte phase of imaging is shown in Fig. 3. When just the cases of biopsy-proven FNH were evaluated, the diagnostic confidence was significantly increased ($P<0.003$). This increase in diagnostic confidence was also present in patients diagnosed with FNH by imaging alone ($P<0.001$). The frequency of diagnostic confidence scores for both subsets of patients diagnosed with FNH is shown in Fig. 4.

Lesion detection

In 25 instances (22.3% of all patients [$n=112$]; 27% of patients with an identified liver lesion [$n=92$]), the hepatocyte phase of imaging allowed the reviewer to detect additional lesions (Figs. 5 and 6). Using the paired *t*-test, this was statistically significant ($P=0.005$). This included ten patients with an additional lesion, four patients with two additional lesions, and 11 patients with three to six additional lesions.

There were seven instances where fewer lesions were identified on the study that included the hepatocyte phase of imaging. While reviewing the data, these cases were reread. In six of these seven cases, the hepatocyte phase of imaging provided additional information that could be used to classify the potential lesions. In three patients, potential lesions identified on the study without hepatocyte phase

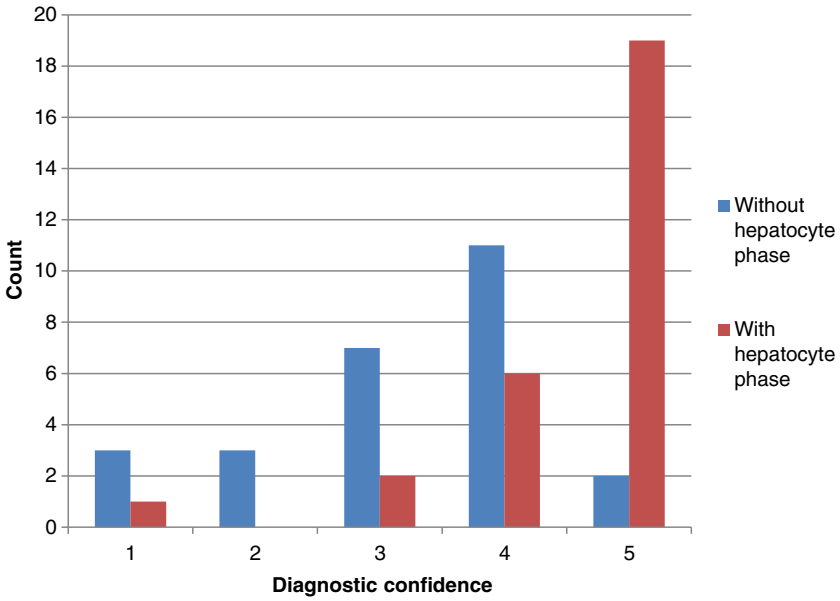

Fig. 4 Graph shows the distribution of confidence scores without (*blue*) and with (*red*) the hepatocyte phase of imaging in patients diagnosed with focal nodular hyperplasia

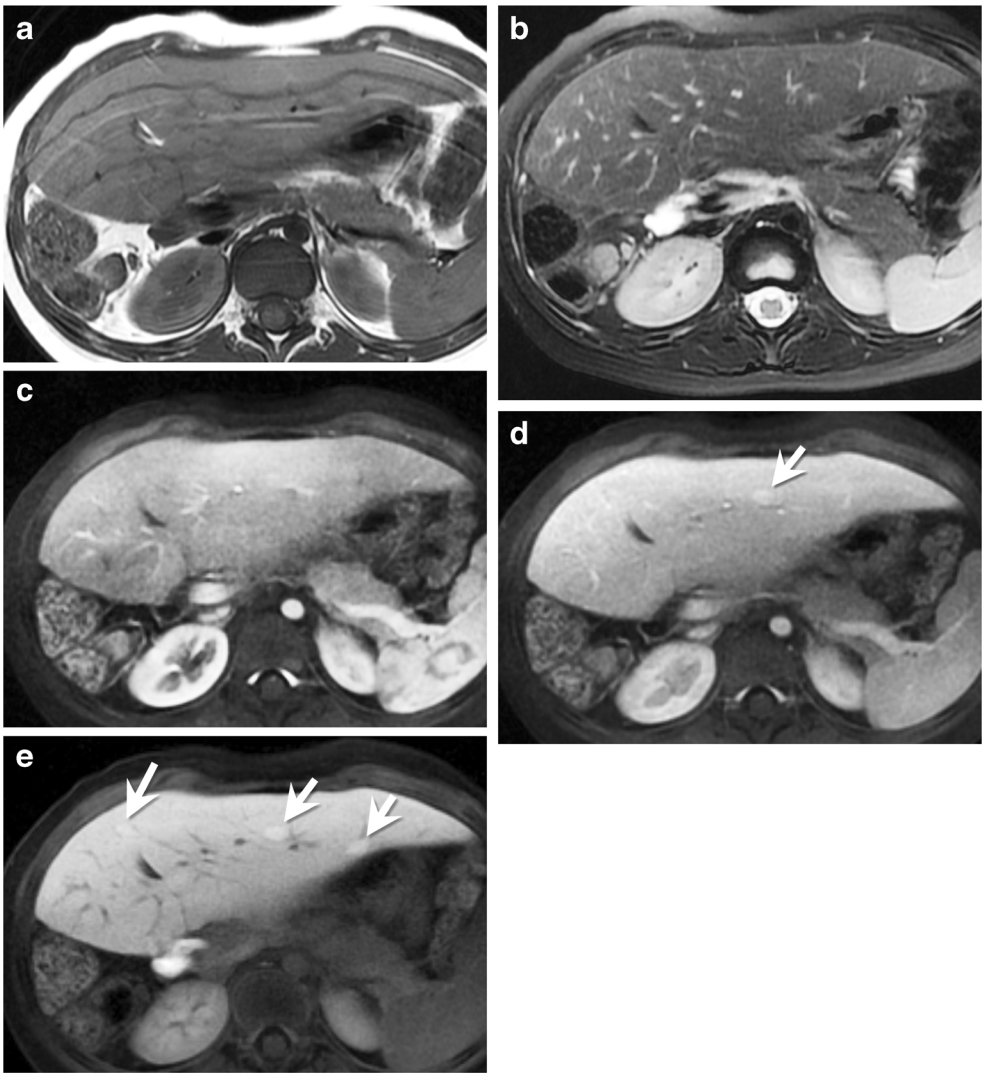

Fig. 5 A 5-year-old girl with a history of hepatoblastoma and familial adenomatous polyposis status post chemotherapy and right hepatectomy 3 years earlier. The lesions have not been biopsied and are thought to represent either focal nodular hyperplasia or β-catenin activated hepatic adenomas [23]. **a** Axial T1-W image, (**b**) axial T2-W image, and (**c**) axial LAVA image obtained in the hepatic arterial phase of enhancement all show no discrete lesion. **d** Axial LAVA image obtained in the portal venous phase of enhancement shows a single hyperintense lesion (*arrow*) in segment 2. **e** Axial LAVA image obtained in the hepatocyte phase of enhancement shows three distinct lesions (*arrows*) that are all hyperintense to the background liver. Other lesions were identified throughout the liver and were only visible on the hepatocyte phase of imaging

imaging were not thought to represent true lesions when the hepatocyte phase of imaging was included; in two patients, malignant tumors that were thought to be multifocal were found instead to be unifocal but multilobulated on the hepatocyte phase of imaging; and finally in one patient, a suspected mass was confirmed to be extrahepatic on the hepatocyte phase of imaging. There was only one patient in whom a lesion was not identified on the study that included the hepatocyte phase of imaging. On review of this study, a 3-mm hyperintense lesion was present on the hepatocyte phase of imaging. This lesion was thought to be missed on the study with the hepatocyte phase of imaging due to its small size and proximity to the inferior vena cava (Fig. 2).

PRETEXT evaluation

Of the 33 patients with a malignant tumor in this study, there were three patients in whom PRETEXT staging could not be performed due to a prior liver resection. PRETEXT staging was performed in the remaining 30 patients. In this cohort, there was no change in the PRETEXT stage between studies without the hepatocyte phase of imaging and the studies with the hepatocyte phase of imaging in 23 patients. In the remaining seven patients (23.3% of PRETEXT patients who could be evaluated), the PRETEXT stage changed with the addition of the hepatocyte phase of imaging (Fig. 6). While this represents a large percentage of patients, the results did not reach significance (P=0.161). Table 4 shows the distribution of changes in the PRETEXT scores between the two imaging studies. It should be noted that the PRETEXT score increased with the addition of the hepatocyte phase of imaging in five patients and decreased in two patients.

Focal nodular hyperplasia

There were nine cases of histologically proven FNH. These were correctly diagnosed seven out of nine times on both study examinations. In all but one of the seven correctly

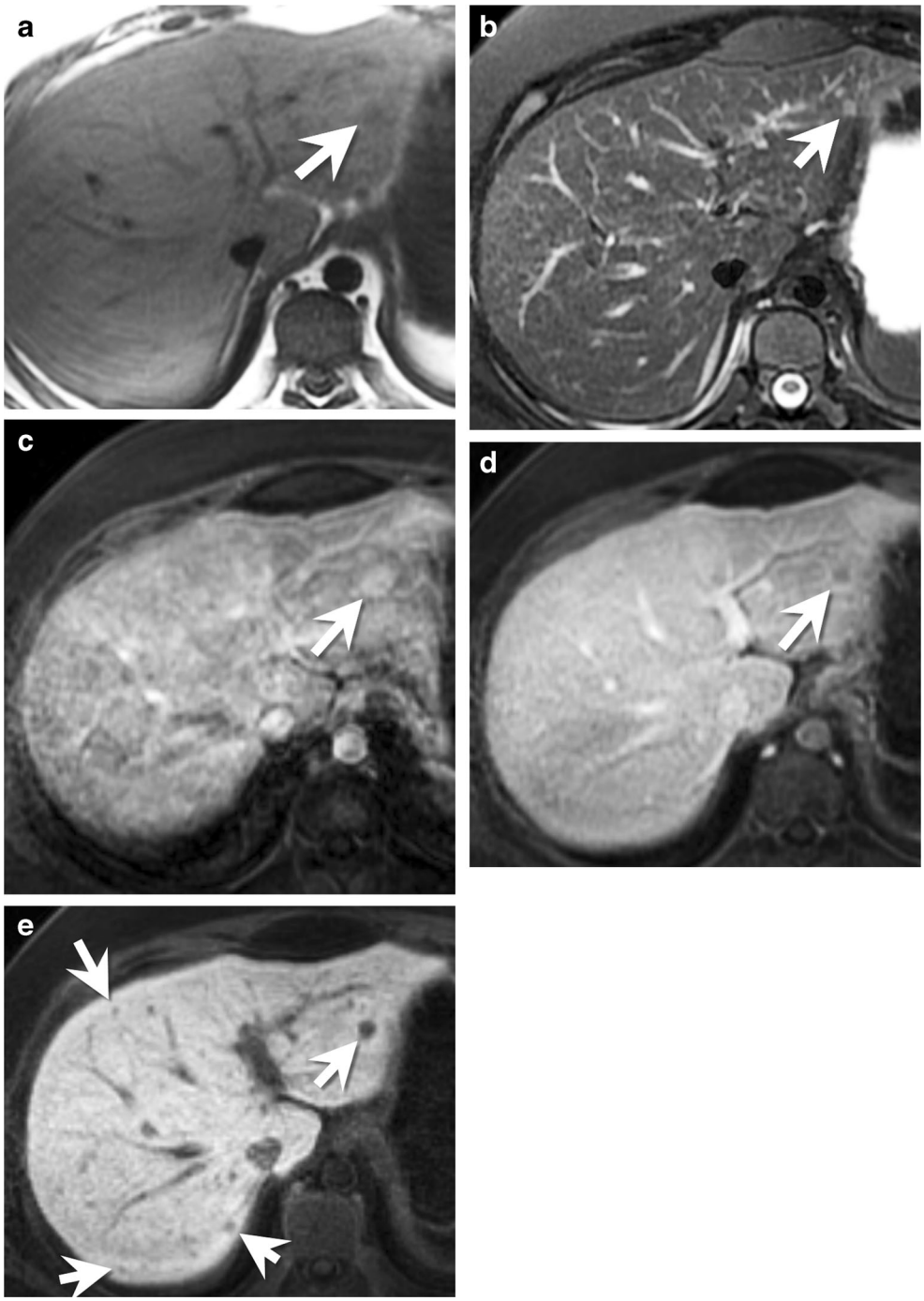

Fig. 6 A 12-year-old boy with a history of biopsy-proven metastatic pancreatic neuroendocrine tumor. The patient is status-post distal pancreatectomy. The imaging-based diagnosis was incorrect on both the initial study (where the lesions were diagnosed as focal nodular hyperplasia) and the study with the addition of the hepatocyte phase of imaging (where they were diagnosed as adenomas). **a** Axial T1-W image shows a slightly hypointense lesion (*arrow*) in segment 2 of the liver. **b** Axial T2-W image shows the lesion (*arrow*) is hyperintense to the background liver. **c** Axial LAVA image obtained in the hepatic arterial phase of enhancement shows the lesion (*arrow*) to be mildly hyperenhancing compared to the background liver. Overall, the liver has heterogeneous enhancement. **d** Axial LAVA image obtained in the portal venous phase of enhancement shows a single hypointense lesion (*arrow*). **e** Axial LAVA image obtained in the hepatocyte phase of enhancement shows multiple tiny hypointense lesions (*arrows*) throughout the liver

diagnosed FNHs, the confidence in diagnosis was higher with the addition of the hepatocyte phase of imaging. In the other correct diagnosis, the confidence level stayed the same. In the two cases where FNH was not diagnosed correctly, neither the non-hepatocyte phase study nor the hepatocyte phase study suggested it as the diagnosis. One case was read as adenoma on the non-hepatocyte phase study and hepatocellular carcinoma on the hepatocyte phase study. The other case was read as deposition on the non-hepatocyte phase study and a regenerative nodule on the hepatocyte phase study (Fig. 7). In both cases, the lesions were atypical for FNH and the diagnostic confidence was three or less for all imaging evaluations.

In addition to the nine patients with histologically proven FNH, there were 19 patients who were diagnosed with FNH based on the exam containing the hepatocyte phase of imaging. In these patients, the diagnostic confidence was higher with the addition of the hepatocyte phase in 14 of the 19

Table 4 Distribution of changes in the PRETEXT scores between studies without the hepatocyte phase of imaging and those with the hepatocyte phase of imaging

	Without hepatocyte phase
No change	23
Increase by 1	3
Increase by 2	1
Increase by 3	1
Decrease by 1	2

An increase means that the PRETEXT score increased by the corresponding number with the addition of the hepatocyte phase of imaging (e.g., the staging changed from PRETEXT 1 to PRETEXT 2 after the addition of the hepatocyte phase of imaging)

A decrease means that the PRETEXT score decreased by the corresponding number with the addition of the hepatocyte phase of imaging (e.g., the staging changed from PRETEXT 2 to PRETEXT 1 after the addition of the hepatocyte phase of imaging)

patients. In the remaining five patients, the diagnostic confidence was the same.

Discussion

Hepatocyte-specific contrast agents are widely used for the characterization of liver tumors in adults and are increasingly being used in children [5, 9–18, 21, 22]. There are several reported advantages of imaging liver masses during the hepatocyte phase of imaging as compared to traditional extracellular contrast agents. These advantages include improved characterization of liver lesions, improved detection of metastases, better evaluation of the relationship of tumors to the biliary tree and differentiation of FNH from liver metastases [10–17]. While these advantages have been confirmed in adults, they have not been evaluated in children. The major disadvantage of using hepatocyte-specific contrast agents is their additional cost and additional time required for imaging. While we have not analyzed the cost-effectiveness of this strategy, we believe that the benefits described in this paper justify the added cost. In our routine clinical practice, we attempt to mitigate the additional time required for hepatocyte phase imaging by performing the axial arterial and venous 2-D time of flight, axial diffusion-weighted imaging, and axial balanced steady-state free precession sequences during the 20-min wait for the hepatocyte phase imaging.

Confidence level

The addition of the hepatocyte phase of imaging significantly increased the diagnostic confidence for all studies as well as specifically for the diagnosis of FNH. These results are comparable to similar studies in adults, which have shown that hepatocyte-specific contrast agents increase the diagnostic confidence for FNH [12–14] and metastases [15–17] through better characterization of the lesion(s).

The increased diagnostic confidence of a lesion can have a profound effect on a patient. Long-term survivors of childhood malignancies have an increased risk of developing FNH [6, 7]. In these patients, there are usually multiple enhancing lesions. These tumors are smaller in size than sporadic FNH and are less likely to have a central stellate scar [24]. As the differential diagnosis for these lesions includes metastases and FNH in these patients, they may undergo biopsy for definitive characterization. Because the imaging characteristics of FNH and metastases are different on the hepatocyte phase of imaging (FNH is isointense to hyperintense compared to the liver while metastases are hypointense), the radiologist is often able to confidently and correctly diagnose the lesions, and thus obviate the need for biopsy.

In our study, the use of the hepatocyte phase of imaging significantly improved the confidence of diagnosing FNH. In addition to improving the diagnostic confidence, the hepatocyte phase of imaging helped to identify the lesion in two patients and refine the diagnosis in two patients. While some of this data must be tempered by the lack of biopsy proof, studies in adults have also shown that the addition of the hepatocyte phase improves diagnostic confidence as well as diagnostic accuracy in diagnosing FNH [12–14].

Detecting and staging lesions

Tumors that lack functioning hepatocytes will not retain contrast on the hepatocyte phase of imaging. These lesions are hypointense compared to the enhancing background liver and are more readily apparent on the hepatocyte phase of imaging as compared to the other phases of contrast enhancement [9, 10]. In our study, the use of hepatocyte-specific contrast agents significantly increased the ability of the reviewer to detect additional lesions (P=0.005). In addition, in the instances where fewer lesions were detected on the hepatocyte phase of imaging, it was felt that the hepatocyte phase of imaging provided additional information, altering the lesion characterization.

In adults, it has been shown that delayed imaging with hepatocyte-specific contrast agents can increase the sensitivity for detecting metastases [15–17]. This allows for oncological staging and appropriate treatment determination such as resection vs. palliative treatments. While liver metastases are more commonly seen in adults, they do occur in children. There were two patients in our study with hepatic metastases. In one patient, significantly more lesions were identified on the delayed hepatocyte phase compared to the non-hepatocyte phase study (>6 vs. 1) (Fig. 6). In the other patient, the same number of metastases was detected in both studies (4 on both studies).

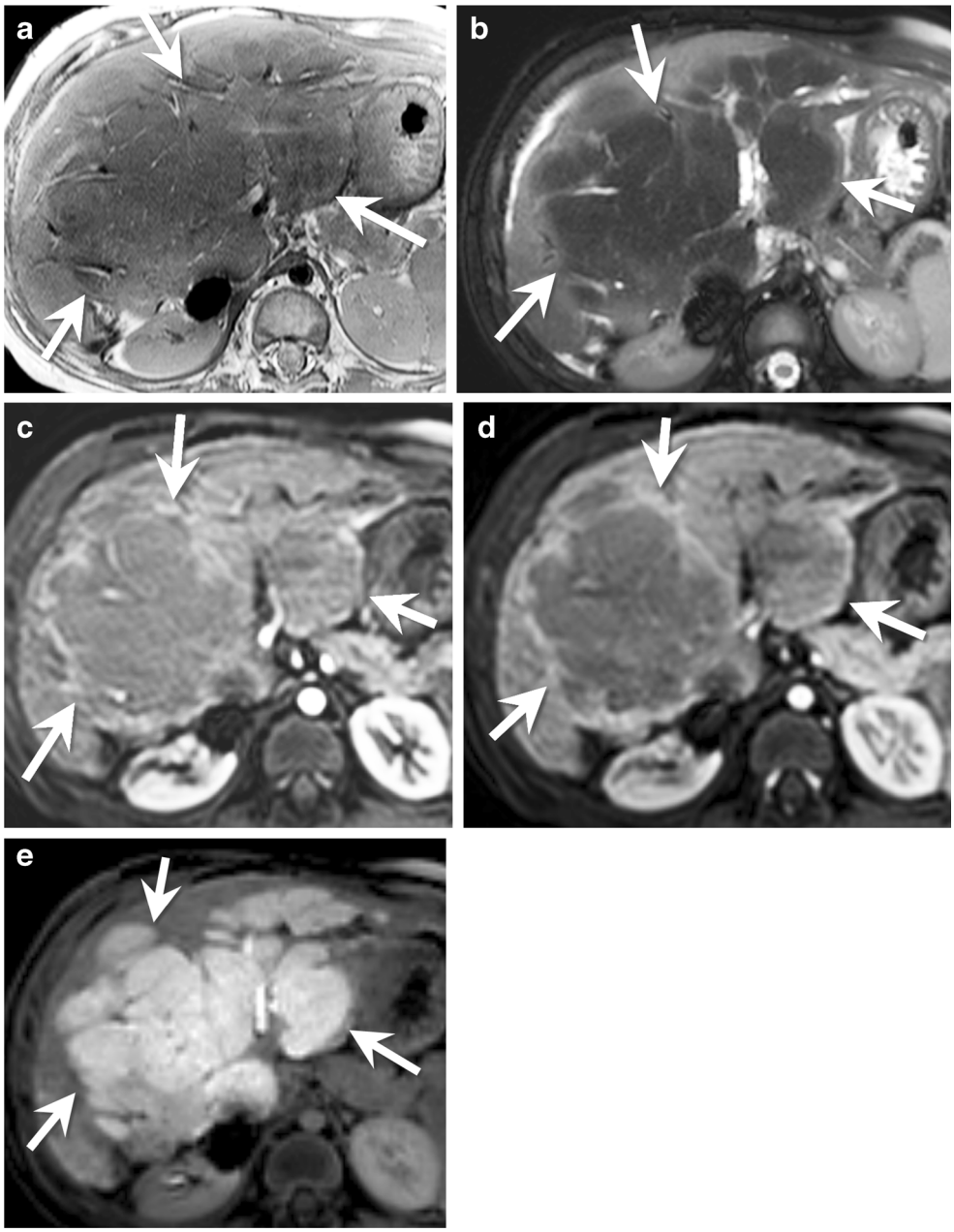

Fig. 7 A 3-year-old girl status-post heart transplant with biopsy-proven focal nodular hyperplasia. The imaging-based diagnosis was incorrect on both the initial study (where the lesion was diagnosed as deposition) and the study with the addition of the hepatocyte phase of imaging (where they were diagnosed as regenerative nodules). **a** Axial T1-W image shows a lobulated, hypointense mass (*arrows*) arising from segments 3, 4b and 5. **b** Axial T2-W images show the mass (*arrows*) to be hypointense compared to the background liver. **c** Axial LAVA images obtained in the hepatic arterial phase and (**d**) portal venous phase of enhancement show the mass (*arrows*) to be hypointense to the background liver with a peripheral rim of enhancement. **e** Axial LAVA image obtained in the hepatocyte phase of enhancement shows the mass (*arrows*) to be markedly hyperintense to the background liver

Malignant pediatric hepatic tumors are staged using the PRETEXT staging system [20]. In this staging system, cross-sectional imaging (CT or MRI) is used to define the location of tumor and the number of anatomical sections involved by tumor. The PRETEXT number is obtained by subtracting the number of contiguous tumor-free sections of the liver from four [20]. This number represents the number of liver sections that need to be resected to excise the tumor. The detection of additional lesions in separate segments of the liver can change the PRETEXT stage of the tumor and thus have major implications on the medical or surgical options. This is particularly important in the setting of multifocal hepatoblastoma and hepatocellular carcinoma. Of the 30 patients in whom PRETEXT staging was possible, the PRETEXT number changed in seven patients after the hepatocyte phase of imaging. While this number did not reach statistical significance (P=0.161), the fact that the hepatocyte phase allowed the reviewer to identify significantly more lesions suggests that the study was underpowered to answer the question regarding PRETEXT staging. The potential to change PRETEXT staging was most dramatically shown in the patient with more liver metastases detected on the hepatocyte phase of imaging. In this patient, the PRETEXT staging changed from a 1 to 4 (Fig. 6). It is interesting to note that there were two cases where the PRETEXT number decreased after reviewing the hepatocyte phase of imaging. In both

cases, the portal vein was thrombosed resulting in poor enhancement of the liver and tumor on all phases of imaging. Additional studies should be performed using a larger cohort of patients with malignant liver tumors to determine if imaging with hepatocyte specific contrast agents truly affects the PRETEXT stage. While we believe that this study shows hepatocyte-specific contrast agents should be used to evaluate every liver lesion, proving that the addition of these agents significantly affects PRETEXT staging would provide further confirmation of our opinion.

There are several limitations of our study. First, because the study was retrospective in nature, the potential for recall bias existed. We attempted to limit this bias by blinding the reviewer to all patient identifiers and clinical history. The fact that no clinical data were available, while helping to limit the potential for recall bias, also created an artificial setting for interpretation. Several factors are pertinent to providing a reasonable differential diagnosis for a pediatric liver mass such as patient age, prior history of malignancy and any prior treatment including chemotherapy or transplantation, history of chronic liver disease or congenital disorder, and laboratory values such as liver enzymes and alpha fetal protein. The lack of this information affected the reviewer's ability to make certain diagnoses. For example, the two patients with metastases in our cohort were incorrectly diagnosed. Because liver metastases from solid pediatric tumors are relatively uncommon, they were not correctly diagnosed in this review. In one patient, the metastases were thought to represent multifocal hepatocellular carcinoma on both imaging studies, while the other patient was thought to have multiple FNH lesions on the study without the hepatocyte phase of imaging and multiple adenomas on the study with the hepatocyte phase of imaging (Fig. 6). It is thought that in both cases, if the history of malignancy had been available, these would have been correctly diagnosed.

Another limitation of this study was the lack of histopathological correlation for all cases, particularly for benign lesions. Of the 40 patients (60 total patients – 20 with no lesion detected on either imaging study) who had a liver lesion that was not biopsied, there were no instances where the lesion was presumed to be malignant on both imaging sets. While we cannot confirm the exact pathology of each of these lesions, the fact that they were not biopsied highlights two points. First, in a clinical setting, radiologists are able to confidently state that a lesion is benign, and second, oncologists and surgeons trust this opinion and do not biopsy the identified lesions.

Perhaps the largest limitations of this study are that there was only one reviewer and the relative subjective nature of grading diagnostic confidence. Having one reviewer makes it hard to generalize the findings of this study to others. The subjective grading of diagnostic confidence introduces the possibility of confirmation bias into this study. It is possible that because the reviewer believed that hepatocyte-specific contrast agents were useful, he was more likely to assign a higher diagnostic confidence level to studies that contained the hepatocyte phase of imaging. This potential bias is amplified by having a single reviewer. This limitation was mitigated as much as possible by randomizing the studies and having a large number of studies in the trial. Because of this, it would be hard for the reviewer to remember the score for one study as compared to its pair.

There are several strengths of this study. First, the study design allowed the reviewer to review studies independently without and with the hepatocyte phase of imaging. By duplicating the studies and removing the sequences containing the hepatocyte phase of imaging, anonymizing the patient information, and randomizing the studies for review, we were able to limit recall bias and confirmation bias, thus forcing the reviewer to evaluate the liver based only on the images. In addition to the strong study design, we believe that this study represents the largest cohort of liver lesions in children imaged with a hepatocyte-specific contrast agent.

Conclusion

The results of our study suggest that gadoxetate disodium is a useful contrast agent for imaging hepatic lesions in children. The addition of the hepatocyte phase of imaging helps to improve lesion detection and increase the diagnostic confidence for all tumors, as well as for FNH in particular. These features can have a profound effect on patient care by helping to guide oncologists and surgeons to more appropriate therapies.

Conflicts of interest None

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