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Benign nodules in post-Fontan livers can show imaging features considered diagnostic for hepatocellular carcinoma

Michael L. Wells,[1] David M. Hough,[1] Jeff L. Fidler,[1] Patrick S. Kamath,[2] Joseph T. Poterucha,[3] Sudhakar K. Venkatesh[1]

[1]Department of Radiology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA
[2]Department of Gastroenterology, Mayo Clinic, Rochester, MN, USA
[3]Department of Pediatric Cardiology, Mayo Clinic, Rochester, MN, USA

Abstract

Purpose: To describe the imaging appearance of hyperenhancing nodules arising in post-Fontan patients and to identify specific features best correlated with malignancy.
Methods: Hyperenhancing hepatic nodules visible on CT and/or MRI in post-Fontan patients were identified retrospectively and reviewed by subspecialty radiologists. Nodules with characteristic imaging findings of focal nodular hyperplasia (FNH) were defined as typical, the remainder were defined as atypical, described in detail according to LIRADS criteria, and length of stability over time was recorded. Clinical data, alpha fetoprotein levels (AFP), central venous pressures (CVP), and histopathology were recorded.
Results: 245 hyperenhancing nodules (215 typical, 30 atypical) were evaluated in 30 patients. Twenty-nine atypical nodules showed washout (portal phase in 6, delayed phase in 29), 0 showed pseudocapsule, 1 showed threshold growth, 1 showed tumor in vein, and 5 showed ancillary features favoring malignancy. Pathology confirmed hepatocellular carcinoma (HCC) in 3 atypical nodules and FNH-like histology in 3 atypical and 4 typical nodules. 2 atypical nodules were present in a patient with clinical diagnosis of HCC. 20 nodules (7 typical, 13 atypical due to washout) were studied with hepatobiliary contrast agent and all showed homogenous hepatobiliary phase retention. Atypical nodules were significantly more likely to be HCC than biopsy-proven FNH-like or stable ≥24 months when showing portal phase washout ($P < 0.001$), mosaic architecture ($P = 0.020$) or in the presence of cirrhosis ($P = 0.004$) or elevated AFP ($P = 0.004$). Atypical nodules that were HCC had higher median CVP than those that were FNH-like (19, range 16–27 vs. 13, range 12–16 mmHg, $P = 0.0003$), there was not a significant difference based on median patient age (HCC 30, range 10–41 vs. FNH-like 40 range 10–41, $P = 0.244$).
Conclusions: Benign hyperenhancing masses in Fontan patients may demonstrate washout and be mistaken for HCC by imaging criteria. Portal phase washout, mosaic architecture, elevated AFP and higher CVP were associated with HCC in the atypical nodules found in this population.

Key words: Fontan—Heart failure—Congestive hepatopathy—Focal nodular hyperplasia—Hepatocellular carcinoma—Washout

Corrective surgery for congenital heart disease may result in a spectrum of hepatic abnormalities resulting from a combination of hepatic venous congestion and ischemia [1, 2]. Patients who have undergone the Fontan operation for palliation of functional single ventricle anatomy are particularly at risk for passive congestion of the liver. Disturbances in hepatic vascular flow imposed by passive congestion and inherent low cardiac output Fontan physiology result in parenchymal changes including peri-sinusoidal and centrilobular fibrosis [3–5]. Both benign and malignant hepatic masses arising in the post-Fontan setting have been reported. Benign lesions are suspected to arise secondary to the disturbed vascular flow, whereas hepatocellular carcinoma (HCC) results from cirrhosis [1–4, 6–14].

Prior reports documenting the hepatic imaging findings of post-Fontan patients frequently describe the presence of hypervascular hepatic nodules [3, 6–8]. These

Correspondence to: Sudhakar K. Venkatesh; *email:* Venkatesh.Sudhakar@mayo.edu

nodules most commonly represent benign regenerative nodules or focal nodular hyperplasia [3, 8]. Focal nodular hyperplasia (FNH) is defined as a mass occurring in the setting of normal liver parenchyma [15]. When these nodules occur in the setting passive congestion they are often referred to as "FNH-like" due to the frequent finding of parenchymal fibrosis and parenchymal perfusion abnormalities found on imaging. Several prior reports have also documented the development of HCC in patients post-Fontan [9–14, 16–18]. Chronic liver damage and subsequent cirrhosis imposed by the Fontan circulation may predispose these patients to development of HCC.

Benign hyperenhancing nodules in the congested liver often simulate HCC and may create difficulty in making management decisions [19]. Increasing the complexity are FNH-like nodules which may demonstrate important imaging characteristics associated with HCC such as washout on portal venous and/or delayed phase imaging [20, 21]. It correspondingly has been reported that the American Association for the Study of Liver Disease (AASLD) guidelines for management of hepatocellular carcinoma may misclassify these types of nodules [20, 22, 23]. The decision of how to manage a hyperenhancing nodule in a post-Fontan patient is particularly important given the young age and co-morbidities found in this population. In particular, the tenuous cardiac and hepatic function in these patients may place them at particular risk of complications if invasive interventions are undertaken [9, 13].

The objective of our study was to describe the imaging characteristics of hyperenhancing nodules in the livers of post-Fontan patients. Specifically, we sought to define imaging features which may be reliable for differentiating benign from malignant nodules.

Methods

Patient selection

This retrospective review study was approved by our Institutional Review Board. An electronic medical records database was searched to identify post-Fontan patients who had undergone contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) examinations between the dates of 01/01/2005 and 08/01/2015. The resulting list included 294 patients which were individually reviewed by a radiologist with 1 year staff level experience in hepatobiliary imaging. Cases were confirmed by manual chart review to have undergone the Fontan procedure. Both dictated reports and original images of each exam of each subject were reviewed for the presence of one or more arterial phase hyperenhancing hepatic nodules. Patients without dedicated extracellular contrast enhanced three phase (arterial, portal, and delayed phases) CT or MRI liver imaging were excluded. An additional six patients were eliminated at consensus imaging review (described below) due to inadequate protocol or timing of contrast-enhanced phases. Two additional patients were removed due to the presence of additional source of chronic liver disease discovered during review of the patient clinical information (described below). A total of 30 patients remained in the final study group.

Clinical review

Recorded clinical information for the study group included: the date of Fontan procedure, time between Fontan procedure and imaging diagnosis or pathologic diagnosis (if available) of a liver nodule, clinical diagnosis of cirrhosis, presence of chronic liver disease other than congestive hepatopathy, serum alpha fetoprotein (AFP), and central venous pressure (CVP). Diagnosis of cirrhosis was made by a gastroenterologist based on clinical features of chronic liver disease and hepatic decompensation (decreased liver function, ascites, portal hypertension) in conjunction with imaging findings of morphological changes in liver and/or biopsy results showing cirrhosis. Patients were excluded if they had an additional source of chronic liver disease than congestive hepatopathy. AFP greater than 200 ng/mL was considered elevated due to its high specificity (99.4%) for diagnosis of HCC [24, 25]. CVP greater than 8 mmHg was considered elevated. Central venous pressure was measured at cardiac catheterization and performed by cardiologist as per standard guidelines. Pathology results of liver nodules (surgical specimens and/or needle biopsies) and indications for the biopsy were reviewed.

Imaging protocol

Standard MRI protocols performed on both 1.5 and 3 T (GE, Waukesha, WI) systems at our institution included axial fat suppressed pre and post-contrast dynamic T1-weighted three dimensional (3D) gradient recalled echo, axial fat suppressed T2-weighted fast spin-echo, coronal T2-weighted single-shot fast spin-echo, axial in/opposed-phase, and diffusion-weighted imaging (b values of 0, 100, 600 s/mm^2). Abdominal post-contrast imaging was obtained using 0.1 mmol/kg gadobutrol at 1.5 mL/s injection, with three arterial phase series timed using test bolus-tracking and region of interest on the descending aorta followed by portal venous phase at 60 s and delayed phase at 180 s. If a patient had additional exams enhanced with hepatobiliary specific intravenous (IV) contrast (0.025 mmol/kg gadoxetate disodium, Eovist), delayed fat suppressed T1-weighted 3D gradient recalled echo sequences were included in the hepatobiliary phase (20 min delay). Standard liver CT protocols performed at our institution on multiple CT systems (Siemens, Erlangen, Germany) included injection of 140 mL (adjusted for patient size and renal function) iohexol 300 at 3–5 mL/s (adjusted for IV size and position); bolus-

tracking assisted timing of late arterial followed by 70 and 180 s delayed phase images. Available phases of post intravenous contrast enhancement on each CT and MRI exam were categorized at imaging review (described below). CT and MRI exams performed at other institutions were only used for liver nodule characterization if protocols were similar to that of our institution (outside studies were used for nodule characterization in two patients).

Imaging review

Images were reviewed by four staff radiologists with 1, 12, 20, and 22 years of experience in hepatobiliary imaging. Imaging review was completed in two sessions and all imaging findings were agreed upon in consensus. Definitions of primary and ancillary imaging findings were adapted from Liver Imaging Reporting and Data System (LIRADS v2014, accessed 11/13/2015). Individual series of each contrast-enhanced MRI and CT exam were inspected for adequacy of bolus timing and excluded if they did not meet LIRADS criteria. The appearance of typical FNH-like nodules on CT/MRI was defined as: homogenous in attenuation or signal intensity on all series, mild T1 hypointensity or isointensity, mild T2 hyperintensity or isointensity, mild or no restricted diffusion, late arterial phase hyperintensity/hyperattenuation with fade to isointensity/iso-attenuation on portal venous or delayed phase imaging, hepatobiliary phase hyperintensity (if MRI performed using gadoxetate disodium), and lack of threshold growth (for nodules with imaging follow-up). An example of a typical FNH-like nodule is provided in Fig. 1. The total number of nodules with a typical FNH-like appearance and the number of months of stability was recorded for each patient. Any arterial phase hyperenhancing nodule which did not have typical FNH-like appearance was labeled as "atypical," described in detail according to LIRADs descriptors and was assigned a LIRADs class (LR). Note was also made of any atypical nodule which had a central scar.

Statistical analysis

Numbers of nodules and imaging findings of nodules were primarily described using descriptive terms such as means and percentages. Mann–Whitney U test was used to compare continuous variables between atypical vs. typical nodules, between groups of patients with atypical vs. typical nodules, and between groups of atypical nodules that were HCC vs. atypical nodules that were either biopsy-proven FNH-like or stable ≥24 month of imaging follow-up. Fischer's exact test was used to compare categorical variables of atypical nodules that were HCC vs. atypical nodules that were either biopsy-proven FNH-like or stable on ≥24 months of imaging follow-up. Statistics were performed using microsoft excel (Version 14.0.7166.5000, Microsoft Office Standard 2010) and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Thirty patients (17 female) were included. Average age and years post-Fontan at diagnosis of a liver nodule was 26.0 years (±8.0, range 10–41) and 20.2 years (±5.8, range 8–29), respectively. Sixteen patients had clinical diagnosis of cirrhosis due to congestive hepatopathy. AFP was measured in 25 of the 30 study patients. AFP was elevated in 3 of the 25 patients, the remaining 22 patients had AFP levels ranging from 0.9 to 8.9 ng/mL. CVP was measured in 17 patients and was elevated in all but one patient with average of 17.1 mmHg (±5.2, range 8–27 mmHg). There was not a statistically significant difference between patients with atypical nodules and those without atypical nodules in terms of median CVP (17, range 12–27 vs. 14.5, range 8–15 mmHg, $P = 0.176$) and median number of nodules (10.5, range 1–41 vs. 2, range 1–13, $P = 0.082$). A positive but not statistically significant correlation was found between CVP and age (correlation coefficient $r = 0.371$, $P = 0.090$) and number of years post-Fontan (correlation coefficient $r = 0.266$, $P = 0.240$). A negative but not statistically significant correlation was found between CVP and

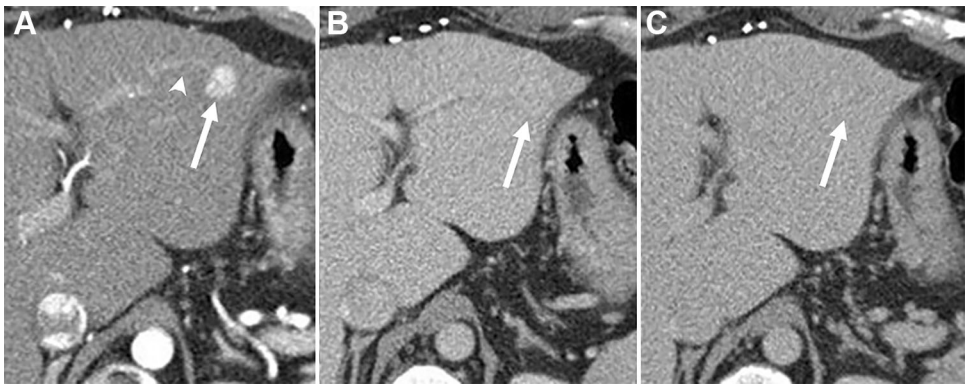

Fig. 1. Typical appearance of a benign FNH-Like lesion. Small well-circumscribed mass (*arrows*) with an associated peripheral vessel (*arrowhead*). The mass is homogenously hyperattenuating on arterial phase (**A**) and fades to isoattenuation on portal venous and delayed phase imaging (**B**, **C**).

number of nodules (correlation coefficient $r = 0.09$, $P = 0.68$).

Histology was available in four typical nodules (4 surgical specimens from 2 patients), all of which were consistent with FNH-like nodules. Histology was available in 6 atypical nodules (6 needle biopsy), including 3 HCC (3 patients; 3 LR5) and 3 FNH-like (2 patients; 1 LR4, 2 LR5). In most cases, the decision to proceed with biopsy or surgical resection was based on the presence of imaging findings suspicious for carcinoma or elevated AFP. A patient with clinical diagnosis of HCC had a 27 mm nodule with threshold growth, washout, moderate T2 signal, and serum AFP over 600 ng/mL (Fig. 2).

15 patients had CT only available for review, 6 patients had MRI only available for review, 9 patients had both CT and MRI available for review. The number of nodules per patient ranged from 1 to 41. 215 typical nodules and 30 atypical nodules were evaluated. Median diameter of atypical nodules was significantly ($P < 0.001$) larger (19 mm, range 7–41 mm) than typical nodules (8 mm, range 3–34 mm). Imaging findings of atypical nodules are summarized in Table 1. All atypical nodules that were HCC showed washout in both the portal venous and delayed phases (4 nodules), while nodules which were either biopsy-proven FNH-like or stable for ≥24 showed washout in the delayed phase in all (15 nodules) and in the portal venous phase in only 1 nodule. All nodules that were HCC showed ancillary features supportive of malignancy (4 nodules) whereas ancillary features were absent in all 15 nodules which were biopsy proven-FNH-like or stable ≥24 months. No atypical nodule showed a central scar. MRI with hepatobiliary agent was performed in four patients without histology available for review. All nodules assessed with hepatobiliary agent showed homogenous hepatobiliary phase retention (Fig. 3). This included two patients with 13 atypical nodules showing washout (9 LR4, 4 LR5); in one of these patients 11 nodules were stable for

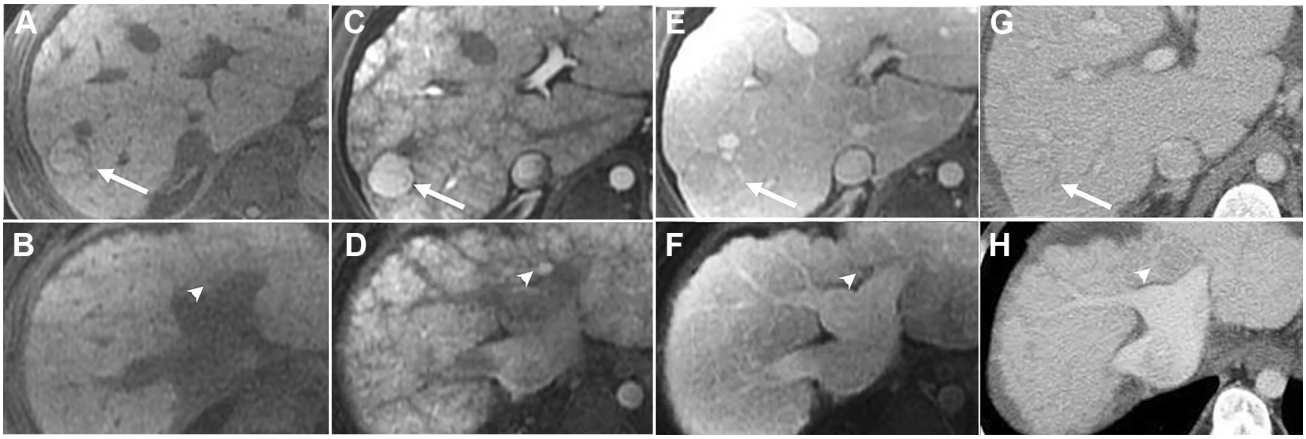

Fig. 2. Patient with development of hepatocellular carcinoma in the setting of a suspected benign hypervascular nodule. Precontrast (**A**, **B**), arterial phase (**C**, **D**), and delayed phase (**E**, **F**) MRI images demonstrate hypervascular lesions in the *right* (*arrows*; **A**, **C**, **E**) and *left* (*arrowhead*; **B**, **D**, **F**) liver with subtle washout in the delayed phase. CT images in the same patient obtained 16 months later demonstrate no change in size of the *right* hepatic lobe nodule (*arrow*, **G**), while the *left* lobe nodule (*arrowhead*, **H**) demonstrates significant interval growth from 8 to 27 mm with definite washout in the delayed phase.

Table 1. Imaging findings of atypical nodules

Atypical nodule characteristics	Biopsy-proven HCC	Clinically diagnosed HCC	Biopsy-proven FNH-like	≥24 months stable follow-up	<24 months stable follow-up	No follow-up	Total
Number	3	1	3	12	7	4	30
LIRADS							
LR4	0	0	1	8	4	3	16
LR5	3	1	2	4	3	1	14
Washout	3	1	3	12	6	4	29
Portal phase	3	1	1	0	0	1	6
Delayed phase	3	1	3	12	6	4	29
Pseudocapsule	0	0	0	0	0	0	0
Threshold growth	0	1	0	0	0	0	1
Tumor in vein	1	0	0	0	0	0	1
Ancillary features	3[a]	1[b]	0	0	1[c]	0	5

[a] Mosaic architecture in 3 nodules, moderate T2 signal in 1, restricted diffusion in 1
[b] One nodule with moderate T2 signal
[c] One nodule with mosaic architecture

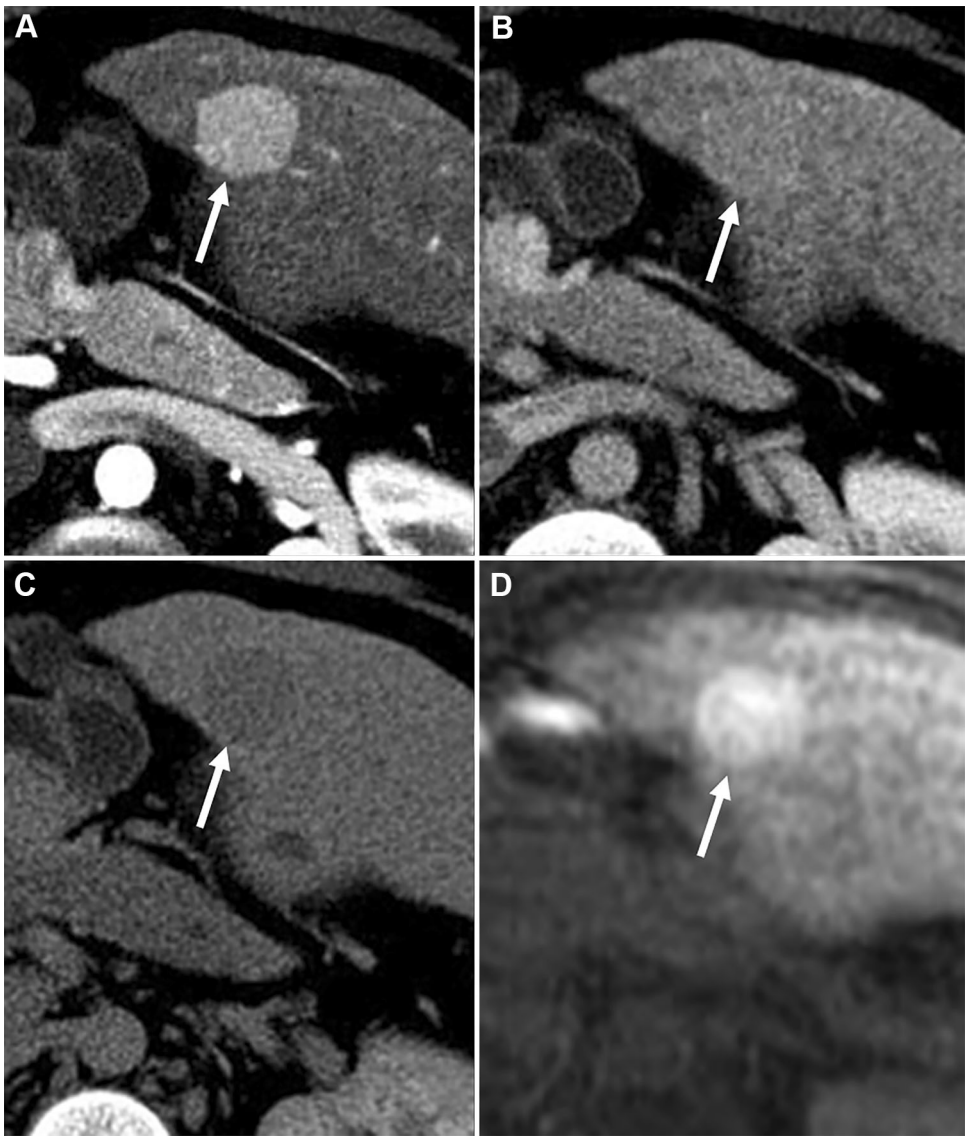

Fig. 3. Hypervascular lesion (*arrow*, **A**) fades to isointensity on portal venous phase (*arrow*, **B**) and shows washout (*arrow*, **C**) on delayed CT images. Subsequent MRI imaging with gadoxetate disodium in the hepatobiliary phase shows homogenous retention of contrast (*arrow*, **D**). This patient had numerous hyperenhancing lesions with washout which were all stable on 25 months of imaging follow-up.

25 months and in the other patient two nodules were stable for 50 months. The remaining two patients had a total of 7 typical nodules, one patient had 6 nodules without any follow-up imaging and the other patient had 1 nodule which was stable for 29 months.

MRI was available for review in two of the patients with atypical nodules. Of the nodules in these patients, 1 clinically diagnosed HCC nodule demonstrated moderate T2 hyperintensity, while 1 nodule stable for 22 months and 7 nodules stable for 25 months demonstrated T2 hypointensity (Fig. 4). The livers of two patients with biopsy-proven HCC had numerous additional typical nodules (Fig. 5). Atypical nodules were significantly more likely to be HCC than either biopsy-proven FNH-like or stable ≥24 months without biopsy, when showing portal venous phase washout ($P < 0.001$), mosaic architecture ($P = 0.020$) or in the presence of cirrhosis ($P = 0.004$) or elevated AFP ($P = 0.004$); there was not a difference between the groups based on gender ($P = 0.576$). Atypical nodules that were HCC had higher median CVP than those that were FNH-like or stable ≥24 months (19, range 16–27 vs. 13, range 12–16 mmHg, $P = 0.0003$), there was not a statistical difference based on median patient age (HCC: 30, range 10–41 vs. FNH-like: 40, range 10–41, $P = 0.244$).

Discussion

The principle findings of our study show that benign and stable (≥24 months) arterially enhancing nodules in the post-Fontan population may show portal venous or delayed phase washout, potentially mimicking HCC. The biopsy-proven benign and stable nodules with washout in our study all had a homogenous appearance without additional imaging findings favoring malignancy. Nodules which show stability ≥24 months of time are much less likely to represent malignancy and this stability is considered an ancillary finding favoring benignity by the

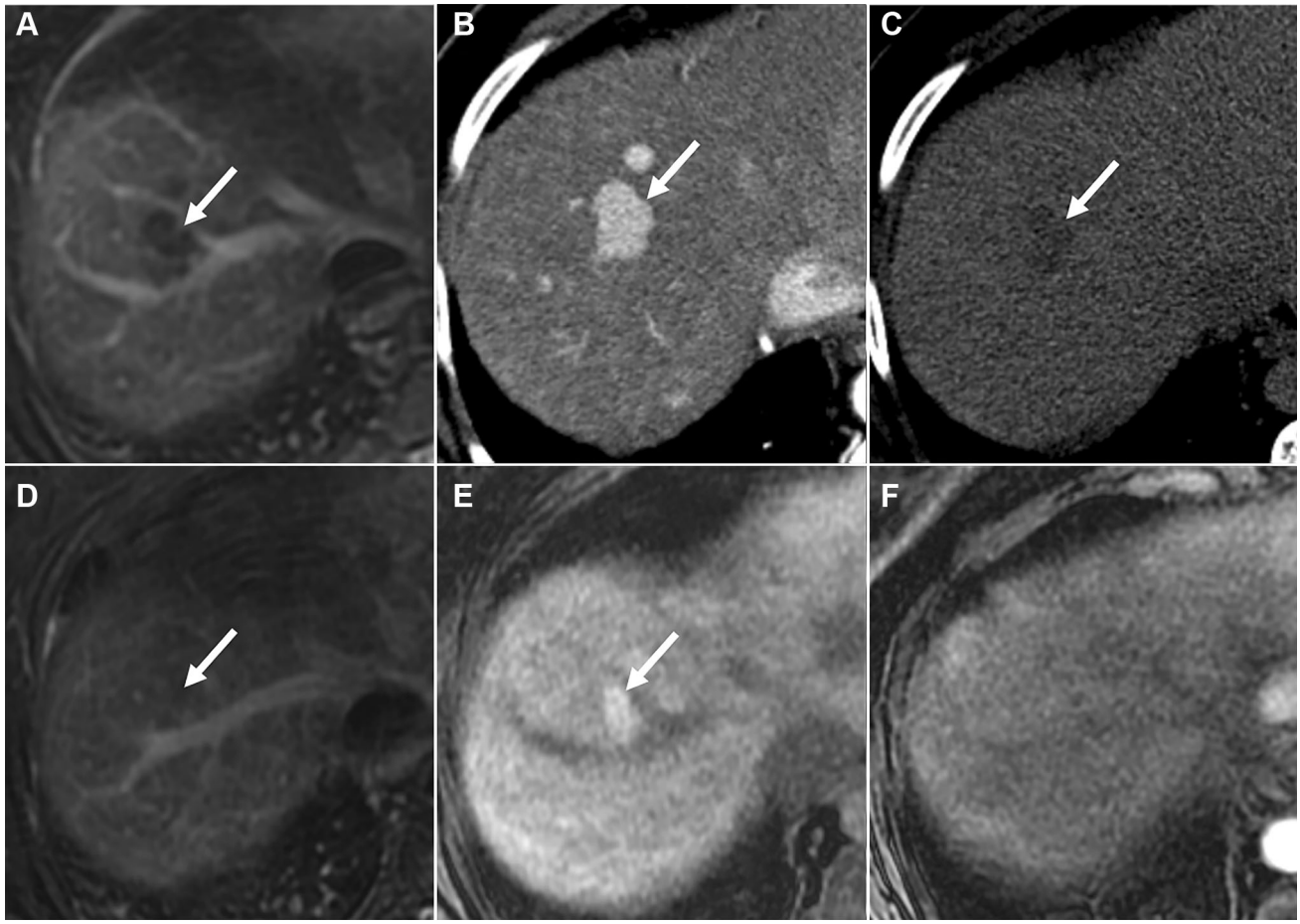

Fig. 4. Patient with multiple T2 hypointense masses, one of which is shown (*arrow*, **A**). Nodules in this patient showed arterial phase hyperintensity (*arrow*, **B**) and delayed phase washout (*arrow*, **C**) on CT scan obtained near the time of the initial MRI (MRI was enhanced with gadoxetate disodium making assessment of delayed phase washout unreliable). This patient had numerous follow-up exams over 25 months of imaging follow-up which demonstrated resolution of both the T2 hypointensity (*arrow*, **D**) and delayed phase washout (not shown), possibly reflecting a change in the composition of the background liver parenchyma. The nodule remained present when imaged in the arterial phase and with extracellular contrast agent or in the hepatobiliary phase with intracellular contrast agent (*arrow*, **E**). A precontrast image (**F**) from the study performed in image (**E**) is provided for reference.

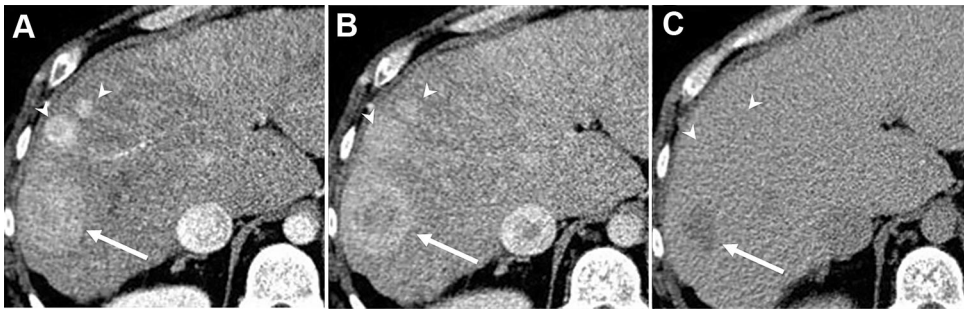

Fig. 5. Biopsy-proven hepatocellular carcinoma (*arrow*, **A**) in a patient with numerous hypervascular nodules, two of which are shown (*arrowheads*, **A**–**B**). The HCC was unique due to its size and heterogenous washout on portal venous and delayed phase images (*arrows*, **B**–**C**), while the remaining hepatic nodules fade to iso-attenuation on delayed phase images (*arrowheads*, **C**).

LIRADS criteria [26–28]. Washout characteristics are uncommon but can occur in FNH-like nodules. In a series of 84 patients with FNH and FNH-like nodules reported by Choi et al., approximately 10% of nodules demonstrated washout on delayed phase [20]. This included nine patients with risk factors for HCC, of which, three would have been wrongly classified by the AASLD guidelines. The three FNH-like nodules that could have been mis-classified included patients with Budd–Chiari syndrome, cardiac cirrhosis secondary to constrictive pericarditis and alcoholic cirrhosis. Lee et al. similarly showed that FNH-like nodules in the setting of alcoholic cirrhosis could show washout on delayed phase [21]. However, in 4 prior reports of presumed benign hyperenhacing nodules in post-Fontan patients comprising 31 patients, a LIRADS washout pattern was not reported [3, 6–8].

The finding of delayed phase washout was not specific for HCC in our patient population. While portal venous phase washout was more specific than delayed phase washout for HCC in our cohort, it was also seen in one benign nodule. The cause for washout appearance of benign nodules in the post-Fontan patient is unknown but we speculate that it may be related to the abnormal background parenchymal congestion, fibrosis, or from a predominant hepatic arterial supply (as in malignant nodules). Recent work has shown that increased extracellular space related to fibrosis increases parenchymal retention of contrast in the delayed phase [29–31]. Hepatic congestion results in sinusoidal dilation and fluid retention; the associated increase in extracellular space could also be a contributor to parenchymal contrast retention [31, 32]. Therefore, the imaging finding of washout may not be related to an abnormality of the nodule itself but a reflection of the background parenchymal contrast retention. In the two patients with nodules showing washout and having MRI available for review, the nodule with washout and moderate T2 hyperintensity was HCC, while nodules with washout and T2 hypointensity were stable on imaging follow-up suggesting benign nature. We speculate that this finding could be related to abnormal increased T2 signal of the background liver due to increased extracellular space and/or fluid content. The utility of T2 signal intensity in the setting of a nodule with washout in this patient population is uncertain and requires further evaluation.

In our study, all HCC had concerning imaging features in addition to washout. Literature review reveals 14 patients previously reported to have had HCC develop in the post-Fontan setting [9–14, 16–18]. Seven patients in which a description of imaging was included reported clearly concerning findings such as a large or heterogenous mass, portal thrombus and tumoral necrosis. Serum AFP was elevated in 10 of 11 patients in which it was reported, supporting the finding in our study that elevated AFP was significantly associated with development of HCC. AFP has relatively poor sensitivity and specificity for HCC screening but should represent a helpful addition to diagnostic evaluation in a post-Fontan patient with a suspicious nodule [22]. Cirrhosis was present in 8 of 10 patients in which it was reported. This finding is concordant with our study in which all patients with HCC carried a diagnosis of cirrhosis and atypical nodules were significantly more likely to be HCC when cirrhosis was present.

Occasionally, HCC can arise in the setting of other hypervascular nodules which may be benign. Two patients in our study had a single biopsy-proven HCC which demonstrated multiple concerning features while numerous remaining nodules had a typical FNH-like appearance. The patient with clinical diagnosis of HCC had cirrhosis with a nodule which increased in size from 8 to 27 mm over 16 months, demonstrated moderate T2 hyperintensity and washout in the portal venous phase along with progressively rising AFP to over 600. A nodule with these imaging features in the presence of AFP >400 is almost certainly HCC [33]. The liver of this patient also contained an additional hyperenhancing nodule which was stable on 16 and 22 month follow-up exams and showed washout only in the delayed phase. The patient was presumed to have multifocal HCC and the stable nodule was treated with radioembolization. The patient died from complications before more therapy or biopsy could be performed. The findings in our study indicate that not all hypervascular nodules with delayed phase washout can be considered malignant. Additional efforts are necessary in these patients to determine specifically which nodules represent HCC and should be targeted for treatment.

Further evaluation of nodules with delayed phase washout and absence of additional concerning imaging findings with hepatobiliary agent enhanced MRI may be helpful. While approximately 5%–10% of HCC retain hepatobiliary agent to some extent, the presence of homogenous retention in a nodule of a post-Fontan patient should dramatically increase the likelihood that the nodule is benign [34–36]. Short-term imaging follow-up and biopsy are also viable options. Given the frequency of nodules showing washout in our study, further evaluation with hepatobiliary agent enhanced MRI or imaging follow-up may be preferable to invasive methods. This is particularly true for patients in which multiple nodules show delayed phase washout and a single nodule does not demonstrate findings to indicate a higher likelihood of malignancy than others.

Several limitations of our study are acknowledged. This is a retrospective study which creates risk for bias in patient selection and prevents the gathering of data such as incidence of hyperenhancing nodules or HCC in the post-Fontan population. Three of the 13 post-Fontan patients with atypical nodules showing washout in our study did not have a clinical diagnosis of cirrhosis. Use of

LIRADS imaging criteria in noncirrhotic patients may result in higher rate of false positive diagnosis of HCC due to the lower pretest probability of HCC. The limited number of biopsy-proven cases is another limitation of the study. Performing biopsy of all nodules was not possible and not clinically indicated. A significant number of our patients were followed with imaging to establish stability of the nodules. We acknowledge the possibility of an early HCC in a few of these patients cannot be excluded. Future studies with a larger patient populations and longer duration of follow-up will help to expand on our findings.

Conclusion

Hyperenhancing nodules in the post-Fontan patient with typical FNH-like imaging findings do not require immediate additional workup and routine clinical follow-up would be sufficient. Atypical hyperenhancing nodules demonstrating washout should be approached with caution and may need further evaluation. Specifically, a hyperenhancing nodule with washout in the delayed phase only and no additional findings supportive of malignancy may represent an FNH-like nodule. Further evaluation of these nodules either by imaging with a hepatobiliary agent, short-term (3–6 months) imaging follow-up, or biopsy should be considered prior to making an imaging diagnosis of HCC as most of these tend to be benign as demonstrated in our study. Malignancy should be strongly considered when the liver is cirrhotic and a nodule shows portal venous phase washout, mosaic architecture, or when the serum AFP is elevated. It is important to note that in the setting of elevated AFP and multiple hyperenhancing nodules in the liver of a post-Fontan patient, all nodules cannot be assumed malignant.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

References

1. Asrani SK, Asrani NS, Freese DK, et al. (2012) Congenital heart disease and the liver. Hepatology 56(3):1160–1169. doi:10.1002/hep.25692
2. Rychik J, Veldtman G, Rand E, et al. (2012) The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 33(7):1001–1012. doi:10.1007/s00246-012-0315-7
3. Bryant T, Ahmad Z, Millward-Sadler H, et al. (2011) Arterialised hepatic nodules in the Fontan circulation: hepatico-cardiac interactions. Int J Cardiol 151(3):268–272. doi:10.1016/j.ijcard.2010.05.047
4. Kendall TJ, Stedman B, Hacking N, et al. (2008) Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. J Clin Pathol 61(4):504–508. doi:10.1136/jcp.2007.052365
5. Dai DF, Swanson PE, Krieger EV, et al. (2014) Congestive hepatic fibrosis score: a novel histologic assessment of clinical severity. Mod Pathol 27(12):1552–1558. doi:10.1038/modpathol.2014.79
6. Bulut OP, Romero R, Mahle WT, et al. (2013) Magnetic resonance imaging identifies unsuspected liver abnormalities in patients after the Fontan procedure. J Pediatr 163(1):201–206. doi:10.1016/j.jpeds.2012.12.071
7. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. (2007) Hepatic changes in the failing Fontan circulation. Heart 93(5):579–584. doi:10.1136/hrt.2006.094516
8. Wallihan DB, Podberesky DJ (2013) Hepatic pathology after Fontan palliation: spectrum of imaging findings. Pediatr Radiol 43(3):330–338. doi:10.1007/s00247-012-2531-y
9. Asrani SK, Warnes CA, Kamath PS (2013) Hepatocellular carcinoma after the Fontan procedure. N Engl J Med 368(18):1756–1757. doi:10.1056/NEJMc1214222
10. Ewe SHT, Ju L (2009) Hepatotocellular carcinoma—a rare complication post Fontan operation. Congenit Heart Dis 4(2):103–106. doi:10.1111/j.1747-0803.2009.00255.x
11. Ghaferi AA, Hutchins GM (2005) Progression of liver pathology in patients undergoing the Fontan procedure: chronic passive congestion, cardiac cirrhosis, hepatic adenoma, and hepatocellular carcinoma. J Thorac Cardiovasc Surg 129(6):1348–1352. doi:10.1016/j.jtcvs.2004.10.005
12. Rajoriya N, Clift P, Thorne S, Hirschfield GM, Ferguson JW (2014) A liver mass post-Fontan operation. QJM 107(7):571–572. doi:10.1093/qjmed/hcu020
13. Rosenbaum J, Vrazas J, Lane GK, Hardikar W (2012) Cardiac cirrhosis and hepatocellular carcinoma in a 13-year-old treated with doxorubicin microbead transarterial chemoembolization. J Paediatr Child Health 48(3):E140–E143. doi:10.1111/j.1440-1754.2010.01932.x
14. Saliba T, Dorkhom S, O'Reilly EM, et al. (2010) Hepatocellular carcinoma in two patients with cardiac cirrhosis. Eur J Gastroenterol Hepatol 22(7):889–891. doi:10.1097/MEG.0b013e32832e2bec
15. Wanless IR (1995) Terminology of nodular hepatocellular lesions. Hepatology 22(3):983–993
16. Josephus Jitta D, Wagenaar LJ, Mulder BJ, et al. (2016) Three cases of hepatocellular carcinoma in Fontan patients: review of the literature and suggestions for hepatic screening. Int J Cardiol 206:21–26. doi:10.1016/j.ijcard.2015.12.033
17. Yamada K, Shinmoto H, Kawamura Y, et al. (2015) Transarterial embolization for pediatric hepatocellular carcinoma with cardiac cirrhosis. Pediatr Int 57(4):766–770. doi:10.1111/ped.12619
18. Elder RW, Parekh S, Book WM (2013) More on hepatocellular carcinoma after the Fontan procedure. N Engl J Med 369(5):490. doi:10.1056/NEJMc1306854
19. Wells ML, Fenstad ER, Poterucha JT, et al. (2016) Imaging findings of congestive hepatopathy. Radiographics 36(4):1024–1037. doi:10.1148/rg.2016150207
20. Choi JY, Lee HC, Yim JH, et al. (2011) Focal nodular hyperplasia or focal nodular hyperplasia-like lesions of the liver: a special emphasis on diagnosis. J Gastroenterol Hepatol 26(6):1004–1009. doi:10.1111/j.1440-1746.2011.06659.x
21. Lee YH, Kim SH, Cho MY, Shim KY, Kim MS (2007) Focal nodular hyperplasia-like nodules in alcoholic liver cirrhosis: radiologic-pathologic correlation. AJR Am J Roentgenol 188(5):W459–W463. doi:10.2214/AJR.05.1998
22. Bruix J, Sherman M (2011) Management of hepatocellular carcinoma: an update. Hepatology 53(3):1020–1022. doi:10.1002/hep.24199
23. Libbrecht L, Cassiman D, Verslype C, et al. (2006) Clinicopathological features of focal nodular hyperplasia-like nodules in 130 cirrhotic explant livers. Am J Gastroenterol 101(10):2341–2346. doi:10.1111/j.1572-0241.2006.00783.x
24. European Association For The Study Of The L, European Organisation For R, Treatment Of C (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56(4):908–943. doi:10.1016/j.jhep.2011.12.001
25. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. (2001) Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in pa-

tients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 34(4):570–575
26. Kubota K, Ina H, Okada Y, Irie T (2003) Growth rate of primary single hepatocellular carcinoma: determining optimal screening interval with contrast enhanced computed tomography. Dig Dis Sci 48(3):581–586
27. Taouli B, Goh JS, Lu Y, et al. (2005) Growth rate of hepatocellular carcinoma: evaluation with serial computed tomography or magnetic resonance imaging. J Comput Assist Tomogr 29(4):425–429
28. Furlan A, Marin D, Agnello F, et al. (2012) Hepatocellular carcinoma presenting at contrast-enhanced multi-detector-row computed tomography or gadolinium-enhanced magnetic resonance imaging as a small (≤2 cm), indeterminate nodule: growth rate and optimal interval time for imaging follow-up. J Comput Assist Tomogr 36(1):20–25. doi:10.1097/RCT.0b013e31823ed462
29. Varenika V, Fu Y, Maher JJ, et al. (2013) Hepatic fibrosis: evaluation with semiquantitative contrast-enhanced CT. Radiology 266(1):151–158. doi:10.1148/radiol.12112452
30. Zissen MH, Wang ZJ, Yee J, et al. (2013) Contrast-enhanced CT quantification of the hepatic fractional extracellular space: correlation with diffuse liver disease severity. AJR Am J Roentgenol 201(6):1204–1210. doi:10.2214/AJR.12.10039
31. Bandula S, Punwani S, Rosenberg WM, et al. (2015) Equilibrium contrast-enhanced CT imaging to evaluate hepatic fibrosis: initial validation by comparison with histopathologic sampling. Radiology 275(1):136–143. doi:10.1148/radiol.14141435
32. Wells ML, Fenstad ER, Poterucha JT, et al. (2016) Imaging findings of congestive hepatopathy. Radiographics. doi:10.1148/rg.2016150207
33. European Association For The Study Of The Liver (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56(4):908–943. doi:10.1016/j.jhep.2011.12.00
34. Choi JY, Lee JM, Sirlin CB (2014) CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. Radiology 273(1):30–50. doi:10.1148/radiol.14132362
35. Hope TA, Fowler KJ, Sirlin CB, et al. (2015) Hepatobiliary agents and their role in LI-RADS. Abdom Imaging 40(3):613–625. doi:10.1007/s00261-014-0227-5
36. Suh YJ, Kim MJ, Choi JY, et al. (2011) Differentiation of hepatic hyperintense lesions seen on gadoxetic acid-enhanced hepatobiliary phase MRI. AJR Am J Roentgenol 197(1):W44–W52. doi:10.2214/AJR.10.5845