

Atypical Enhancement Pattern of Hepatocellular Carcinoma with Portal Vein Thrombosis on Multiphase CT

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Abstract

Introduction: The 2005 American Association for Study of Liver Diseases (AASLD) diagnostic criteria allow non-invasive diagnosis of hepatocellular carcinoma (HCC) based on their enhancement pattern but we have observed a high incidence of atypical enhancement characteristics in HCC associated with portal vein thrombosis. This study seeks to examine the radiological features of this particular subgroup. **Materials and Methods:** Patients with HCC and portal vein thrombosis who underwent pre-treatment multiphase CT imaging were drawn from a surgical database. The arterial, portal venous and delayed phase images were assessed qualitatively and quantitatively (with region of interest [ROI] analysis) for lesion hypervascularity and washout. The background enhancement of the left and right lobes of the liver was also quantified by ROI analysis. **Results:** Twenty-five lesions in 25 patients were selected for analysis. Qualitative analysis showed that 10/25 (40%) lesions demonstrated arterial hypervascularity while 16/25 (64%) lesions showed washout. Ten out of 25 (40%) lesions demonstrated both arterial hypervascularity and washout. Quantitative analysis showed that the average absolute lesion enhancement from precontrast to arterial phases was 49.1 (± 17.1) HU for hypervascular lesions compared to 23.8 (± 16.6) HU for non-hypervascular lesions ($P < 0.01$). The mean absolute enhancement of the background liver parenchyma in the arterial phase was 13.79 (± 7.9) HU for hypervascular lesions compared to 36.6 (± 30.6) HU for non-hypervascular lesions ($P = 0.03$). **Conclusion:** A large proportion of HCC with portal vein thrombosis lack characteristic arterial hypervascularity, which may be secondary to compensatory increased arterial supply to the background liver. This is a potential pitfall when applying imaging criteria for diagnosis of HCC.

Ann Acad Med Singapore 2011;40:454-9

Key words: HCC, Hypervascular, Pitfall, Wash-out

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumour in the liver, and is associated with portal vein thrombosis in up to 44% of patients in an autopsy series.¹ The European Association for the Study of the Liver (EASL) and American Association for the study of Liver Disease (AASLD) diagnostic guidelines for HCC include both invasive and non-invasive criteria.^{2,3} The non-invasive criteria emphasise the characteristic appearance of HCC at dynamic contrast-enhanced imaging techniques, namely arterial phase hypervascularisation and portal venous/delayed phase washout. A number of studies have validated

these non-invasive imaging criteria.^{4,5}

There are particular situations in which the hypervascular nature is not observed, the most well reported being small HCCs less than 2 cm in size in which up to 38% are hypovascular.⁴ In our clinical experience, we have also found that HCCs with portal vein thrombosis frequently fail to meet the characteristic HCC enhancement profile despite being larger than 2 cm in size.

The aim of this retrospective study is to examine the enhancement profiles of HCCs with portal vein thrombosis on multidetector CT, in particular the frequency of

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hypervascular tumour profiles in this subgroup.

Materials and Methods

The study was approved by the IRB of our institution, with a waiver of consent obtained.

Subjects

A retrospective review of the 5 year (2004 to 2009) surgical hepatobiliary database of patients at our tertiary referral centre for diagnosis of HCC with portal vein thrombosis was performed. Only cases of HCC which fulfilled one or more of the following 2005 AASLD diagnostic criteria were included in our study: (i) cytohistological diagnosis (ii) AFP levels >200 ng/mL associated with a mass >2cm at CT examination and/or (iii) typical HCC enhancement pattern of arterial hypervascularity with washout in a cirrhotic liver. Only patients who had pre-treatment multiphasic CT images were included in the study. In patients with multifocal lesions, only the largest one was used for analysis. Thus, the study population comprised 25 patients with 25 lesions.

CT Examination

Multiphasic CT examinations were performed with 1 of 4 multidetector scanners (Somatom Sensation Cardiac, Siemens Medical Solutions, Erlangen, Germany; Dual Source Somatom Definition, Siemens Medical Solutions, Erlangen, Germany; Lightspeed VCT 64, GE Medical Systems, Milwaukee, Wisconsin, USA; MX 8000 IDT 16, Philips Medical Systems, Best, The Netherlands). Images were reconstructed at the following parameters: 3 or 5 mm section thickness and intersection gap in the arterial phase and portal venous and delayed phases, voltage, 120 kVp, tube current 180 to 230 mAs. Scans were obtained after injection of 80 to 100 mL of nonionic contrast medium (iohexol 350 mgI/mL; Omnipaque 350 or ioversol 350 mgI/mL; Optiray 350) at a rate of 3 to 4 ml/sec. Bolus tracking of the aorta at the level of the celiac axis (trigger threshold 100 to 155 HU above baseline) was used to time the arterial phase. Arterial, portal venous and delayed phases were obtained at 8 to 10 seconds, 25 to 40 seconds post trigger and 3 to 4 minutes after the start of injection, respectively. The precontrast scans (with identical imaging parameters to the portal venous phase) were also performed in 19 patients.

Image Interpretation

The findings from all imaging studies were retrospectively reviewed by 2 radiologists (TYL and TCH; 3 years and 14 years experience, respectively) with consensus reached where the interpreted results differed. A lesion was considered to demonstrate arterial hypervascularity if the

most enhanced portion of the tumour was hyperattenuating to the background non-tumourous liver on the arterial phase. Washout in a lesion was defined as increased conspicuity of lesion hypoattenuation on the portal venous or delayed phases compared to the arterial phase when viewed on standard liver windows (window level 50 HU, window width 150 HU). Washout is typically defined as a hypervascular lesion becoming less dense compared to the background liver in the portal venous or delayed phases. A modification of this definition was used in this study as a large proportion of lesions were not hyperdense on the arterial phase, and hence were expected to remain hypodense to the background in the portal venous and delayed phases. The greatest diameter of each lesion and site of portal vein thrombosis (main, left or right main branch) was recorded.

A quantitative analysis of each lesion was also performed. In quantitative analysis, the CT attenuation coefficient of each tumour as well as normal background liver parenchyma was measured during each phase. The regions of interest (ROI) were chosen by one radiologist (YL). The ROI of heterogeneous lesions was evaluated in the areas where there was the most avid homogenous enhancement on the arterial phase, and not including any overtly visible vasculature, bile ducts or necrotic areas. Attempt was made to maintain the ROI area from 0.5 cm³ to 1.0 cm³. Measurements were obtained from the same areas on all phases.

Clinical data were obtained by review of the electronic medical records. The patient demographics, alpha-fetoprotein (AFP) levels nearest the time of scan, viral hepatitis carrier status, and histopathological results were extracted.

Statistical Analysis

The level of statistical significance was set a priori at 0.05. All analyses were performed using statistical software (SPSS v 14.0). The Fisher's exact test was used for correlation of categorical variables while the paired Student's t-test was used to compare mean diameters, absolute lesion enhancement and absolute background liver enhancement.

Results

Table 1 summarises the CT imaging features for the 25 patients.

Patient Demographics and Laboratory Data

Our study included 23 male patients and 2 female patients, with a mean age of 60 years (range, 41 to 85). The diagnosis of HCC was established by cytohistological proof in 5 patients, elevated AFP levels (>200ng/mL) with associated mass in a cirrhotic liver on CT in 18 patients, and typical

Table 1. Summary of CT Scan Features of Patients with HCC and Portal Vein Thrombosis

Patient No	Portal vein thrombus (L/R/M)	Tumour diameter (cm)	Hyper-vascular	Washout	Liver enhancement (HU)	Lesion enhancement (HU)
1	L	15.1	N	N	97	14
2	R, M	3.9	N	N	15	10
3	R, M	12.6	N	N	87	62
4	R	14.2	N	Y	18	16
5	R	8.3	N	Y	16	1
6	L, R	multifocal small	Y	Y	12	46
7	L, M, R	multifocal small	Y	Y	NA	NA
8	L, M, R	7.5	N	N	37	15
9	R	3	N	N	25	23
10	L, M, R	15.9	N	N	NA	NA
11	L, M, R	13	N	N	NA	NA
12	L, M, R	11	N	N	49	26
13	L, M, R	11.4	N	Y	17	26
14	L, M, R	8.5	N	Y	1	27
15	L, M, R	9.9	N	Y	NA	NA
16	L, M, R	3.9	N	Y	NA	NA
17	L, M, R	11	Y	Y	6	87
18	R, M	11.7	Y	Y	12	35
19	L, M, R	13.5	Y	Y	13	35
20	R	15.7	Y	Y	NA	NA
21	R	6.3	Y	Y	16	43
22	L, M, R	8.3	Y	Y	2	48
23	L	8.5	Y	Y	26	40
24	L	5.7	Y	Y	23	59
25	L, M, R	8.5	N	N	41	42

L: left portal vein; R: right portal vein; M: main portal vein; NA: not available as precontrast scans were not done

HCC enhancement pattern (arterial hypervascularity with subsequent washout) in 2 patients. Thirteen patients were Hepatitis B carriers and 5 patients were Hepatitis C carriers. In the 20 patients without cytohistological proof, all had pre-existing diagnosis of cirrhosis.

Tumour Size and Location of PV Thrombus

Twenty-five lesions in 25 patients were analysed. The mean lesion maximum diameter was 9.9 (\pm 3.8) cm and all lesions were larger than 2 cm (range, 3.0 to 15.9 cm). Nineteen lesions were located in the right hepatic lobe, 4 lesions in the left lobe, and 2 cases were multifocal with lesions in both hepatic lobes. There was involvement of the main portal vein and both left and right portal vein branches in 13 lesions, involvement of the main portal vein and right portal vein in 3 lesions, involvement of the left and right portal veins without involvement of the main portal vein in 1 lesion, involvement of the right portal vein only in 5

lesions, and involvement of the left portal vein only in 3 lesions. In all lesions, at least the ipsilateral portal vein branch was thrombosed.

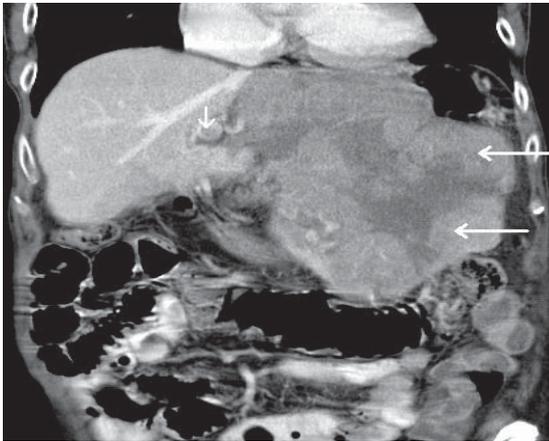
Enhancement Pattern

On the arterial phase, 10/25 lesions (40%) were hyperdense (arterial hypervascularity), 6/25 (24%) lesions were isodense to the liver and 9/25 lesions (36%) were hypodense to the liver (Fig. 1). Sixteen out of 25 lesions (64%) showed wash-out of contrast on the portal-venous or delayed phases. Ten out of 25 lesions (40%) demonstrated both arterial hypervascularity and washout. There was no correlation between lesion hypervascularity and AFP levels ($P = 0.8904$). The mean diameter of hypervascular lesions (10.1 ± 3.5 cm) was not significantly different from the mean diameter of non-hypervascular lesions (9.8 ± 4.1 cm) (2 tailed t-test $P = 0.852$).

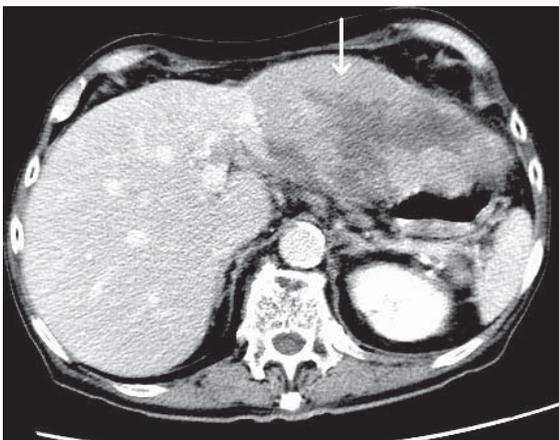
Fig. 1. An 85-year-old man with jaundice and AFP level of 15963 ng/mL.



A. Axial CT in the arterial phase shows hypodense/isodense (non-hypervascular) appearance of the large left liver mass (arrow), even in the non-necrotic portion.



B. Reconstructed coronal image in the portal venous phase shows expansile thrombus within the left portal vein (small arrow) and continued hypodense attenuation of the left liver mass (arrows).



C. Axial CT in the delayed phase shows hypodense appearance of the mass (arrow). Typical washout is difficult to appreciate because of the tumour's hypodense appearance on all phases.

Quantitative Analysis

In the 19 cases where pre-contrast scans were available (8 hypervascular lesions and 11 non-hypervascular lesions), we analysed the absolute arterial-phase enhancement in terms of Hounsfield units (HU) of both the lesion as well as the normal background liver parenchyma. The average absolute lesion enhancement was $49.1 (\pm 17.1)$ HU for hypervascular lesions compared to $23.8 (\pm 16.6)$ HU for non hypervascular lesions (2 tailed $P = 0.0058$). The average absolute enhancement of the background liver was $13.75 (\pm 7.9)$ HU in hypervascular lesions and $36.6 (\pm 30.6)$ HU in nonhypervascular lesions ($P = 0.0357$). There was significantly greater background liver enhancement ($P < 0.05$) for the non-hypervascular compared to the hypervascular group.

Discussion

The AASLD guidelines provide invasive and non-invasive diagnostic criteria allowing confident diagnosis of hepatocellular carcinoma in the cirrhotic patient.³ Where possible, a non-invasive radiological diagnosis is always preferable given the attendant risks of percutaneous or surgical biopsy in these patients who are at risk of coagulopathy. The typical pattern of arterial hypervascularity has been shown in up to 84% of HCCs larger than 2 cm, whereas small HCC (lesions smaller than 2 cm) show a conclusive hypervascular pattern in only 44%.⁴ A diagnosis of HCC associated with portal vein thrombosis implicates a dismal prognosis with a 1-year survival rate of only 37.5% despite treatment.⁶

In our study involving hepatocellular carcinomas with portal vein thrombosis, all lesions exceeded 2 cm but only 40% of these showed arterial hypervascularity on multiphasic CT. Although we do not have a control group in this study, this result is markedly lower than that reported in literature (up to 84% for lesions larger than 2 cm). We postulate this is due to altered inflow to the liver secondary to thrombosis of the portal vein.

The normal liver has a dual blood supply and receives 75% of blood flow from the portal venous system and 25% from the hepatic artery.^{7,8} However, when the portal vein or lobar branch is thrombosed, there are 2 compensatory mechanisms activated that supplement the compromise of the portal vein's contribution to liver blood flow. The first is reflex arterial vasodilatation of the hepatic artery and the second is rapid development of venous collaterals to bypass the obstruction.^{8,9} The compensatory increase in hepatic arterial flow has been previously demonstrated radiologically both at dynamic CT and angiographically.¹⁰

HCCs are hypervascular neoplasms which receive their predominant supply from the hepatic artery, resulting in

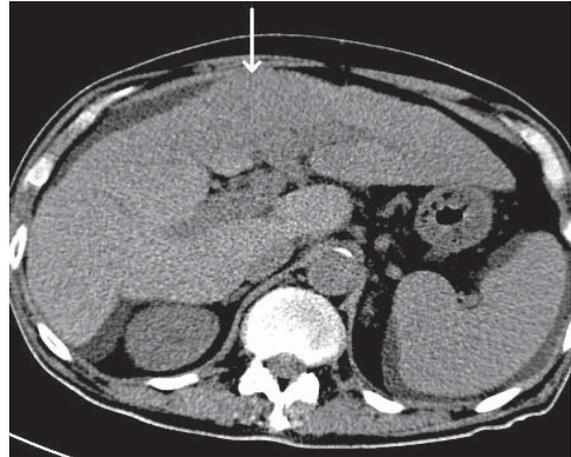
relative enhancement of the lesion best seen on late arterial phase imaging.¹¹ Most HCCs are appreciably hyperdense on the arterial phase because enhancement of the lesion on this phase exceeds enhancement of the background hepatic parenchyma. However when the portal vein or lobar branch is thrombosed, the compensatory increase in hepatic arterial supply to that lobe would intuitively imply that there will be greater enhancement of the hepatic parenchyma on the arterial phase, possibly at some expense to tumour blood supply.

This postulation seems borne out in our results when we examine the absolute enhancement of tumours as well as background liver. Our findings demonstrated hypervascular lesions show significantly greater magnitude of absolute lesion enhancement compared to nonhypervascular lesions (49.1 HU vs 23.8 HU, $P < 0.05$). Interestingly we also found the absolute enhancement of the background liver trended towards a greater magnitude in nonhypervascular lesions compared to hypervascular lesions (36.6 HU vs 13.75 HU, $P < 0.05$). Thus the inability to detect hypervascularity of the tumours could be due to 2 factors: firstly, decreased enhancement of the tumour due to “arterial steal” by the hepatic parenchyma, and secondly, an increase in absolute enhancement of background hepatic parenchyma on the arterial phase which results in diminished detection of lesion relative enhancement (Fig. 2).

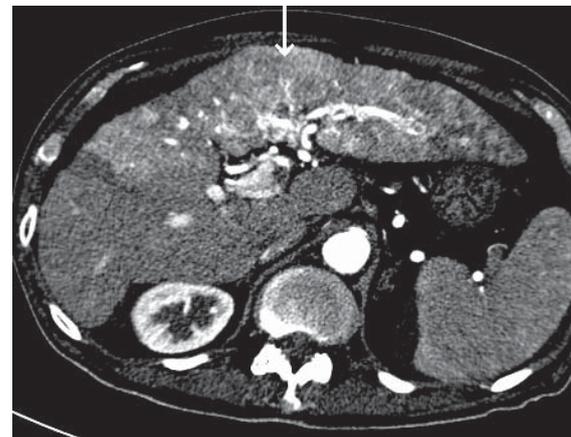
The utility of portal phase and delayed phase washout in characterisation of hepatocellular carcinoma regardless of lesion size has been established in previous studies¹²⁻¹⁴ and has been incorporated into the AASLD 2005 guidelines. In our subgroup of HCCs with portal vein thrombosis, we have also shown contrast washout to be a more consistent finding compared to arterial hypervascularity (64% vs 40%). The presence of washout kinetics is an indicator that the tumour has higher intravascular space compared to interstitial space and may be present in situations where the arterial flow may not be sufficient to result in arterial hypervascularity in a vascular tumour.^{15,16}

We acknowledge that there are several limitations in our retrospective study. Firstly, there was no control group in this study but we feel that the literature regarding hypervascularity in the vast majority of HCCs larger than 2 cm was already well established.^{11,17} Secondly, the studies were not all performed on a single scanner and there were slight differences in scan parameters between scanners. However all studies were performed on at least 16 slice multi-detector CT with fairly standard liver protocols described above which were optimised for each scanner. Thirdly, retrospective bias was introduced as the investigators were aware that cases were all pre-selected for HCC. Lastly, the study population was small. We acknowledge that the population size was limited by the need to explicitly fulfill

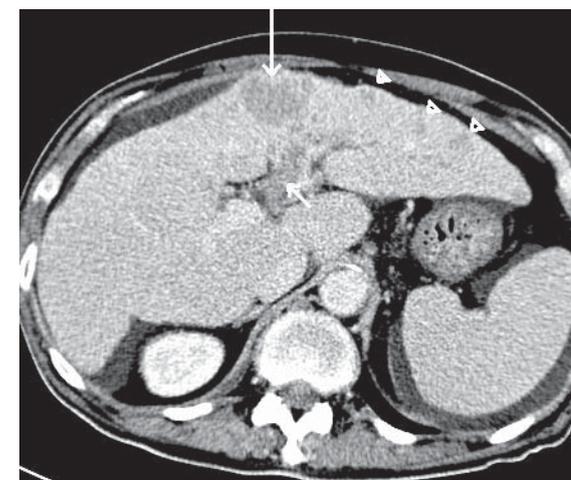
Fig. 2. A 78-year-old man with chronic Hepatitis C.



A. Precontrast axial CT shows nodular liver outline in keeping with cirrhosis. There is a subtle exophytic hypodensity in the left lobe (long arrow).



B. Arterial phase CT shows increased enhancement of the entire left lobe. It is difficult to discern the boundaries of the lesion.



C. Delayed phase CT shows lesion washout (long arrow), as well as smaller foci of HCC in the left lobe (arrowheads). Note thrombosis of the left portal vein (short arrow). Needle biopsy confirmed HCC.

the 2005 AASLD criteria for HCCs examined in this study.

Data collection for the study was performed before release of the recently revised AASLD 2010 guidelines¹⁸ and thus the AASLD 2005 diagnostic criteria were utilised in the study. We are aware the AASLD has recently revised its guidelines and elevation of AFP is no longer accepted as a criteria for non-invasive diagnosis of HCC, due to the small but significant incidence of intrahepatic cholangiocarcinoma which is also associated with cirrhotic livers. A substantial number of our cases would not qualify as HCC under the new criteria. However, as the lesions occurred in livers with risk factors for HCC and the incidence of intrahepatic cholangiocarcinoma is much lower than HCC as acknowledged in the new guidelines, it is very likely that they represent true cases of HCC, as was proposed in the 2005 AASLD criteria.

Conclusion

In summary, our study demonstrates that characteristic hypervascularity is absent in the majority of HCCs with portal venous thrombosis. This potential imaging pitfall in the non-invasive diagnosis of hepatocellular carcinoma should be recognised by radiologists and clinicians.

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