Volume 18, No 4 | International Journal of Radiation Research, October 2020

CT-Value (ΔHU and CT-Value ratioin) differential diagnosis of small hepatocellular carcinoma from focal nodular hyperplasia

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[DOR: 20.1001.1.23223243.2020.18.4.4.4]

[DOI: 10.52547/ijrr.18.4.641]

► *Original article*

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Revised: September 2019
Accepted: October 2019

Int. J. Radiat. Res., October 2020; 18(4): 641-646

DOI: 10.18869/acadpub.ijrr.18.4.641

ABSTRACT

Background: The objective was to explore the value of the CT value difference (ΔHU) and CT value ratio (CVR) between the hepatic arterial (AP), portal (PP), and delayed phases (DP) to differentiate the small Hepatocellular Carcinoma (SHCC, ≤ 3 cm) from the small Focal nodular hyperplasia (SFNH, ≤ 3 cm). ***Materials and Methods:*** All the lesions were confirmed by clinically and/or pathologically and all the patients underwent triple-phase enhanced CT scans. The lesions' CT values (LCV) and the surrounding normal liver parenchyma (NCV) of the enhancement phases were measured separately, the ΔHU and CVR were calculated. ***Results:*** The median age and the male/female ratios of the SHCC and SFNH have statistically significant, and the size haven't statistically significant. The ΔHU and CVR of the AP, PP, and DP of the SHCCs and SFNHs were statistically significant, respectively. The area under curve of ΔHU and CVR of AP, PP and DP were increased gradually. When the ΔHU and CVR of the AP, PP and DP were 105.800HU vs. 1.516, -12.600HU vs. 0.949, -19.750 HU vs. 0.951, obtained the maximum You-den indexes. The corresponding sensitivity and specificity were 80.6 % and 90.1 % vs. 88.90% and 72.1%, 100% and 81.1% vs. 100% and 81.1%, 94.4 % and 96.4% vs. 94.4 % and 96.4%, respectively. ***Conclusion:*** The SHCC was highly suggested when ΔHU and CVR are no greater than 105.800HU and 1.516, -12.600HU and 0.949, -19.750 HU and 0.951 of the AP, PP, and DP in the middle-aged and elderly male patients, especially in the DP.

Keywords: *Computerized Tomography-value, Liver cancer, hepatocytes, Liver, focal nodular hyperplasia.*

INTRODUCTION

Hepatocellular carcinoma (HCC) was the most common malignant tumor of the liver and accounted for 80% of primary liver malignancy approximately [1], whereas hepatic focal nodular hyperplasia (FNH) was the second most common benign tumor after the hepatic hemangioma [2,3] and accounted for about 8% of primary hepatic tumor [4,5]. The treatment plan of HCC and FNH were completely different, the former was dominated by surgery or interventional radiology, while the latter was mainly based on conservative treatment. Therefore, the preoperative diagnostic imaging to identity of the two is very important.

Although the typical imaging features of small hepatocellular carcinoma (SHCC) and small focal nodular hyperplasia (SFNH) were different. The enhancement of the hepatic arterial phase (AP) of the former was significantly higher than that of the peripheral hepatic parenchyma, and the enhancement of the portal phase (PP), and delayed phase (DP) were lower than that of the surrounding parenchyma, that is, the "wash-in and wash-out" enhancement pattern; for

example, the latter was higher than the surrounding liver parenchyma of AP obviously, and the enhancement of PP and DP were similar or slightly lower or slightly higher to the surrounding liver parenchyma, that is, the "wash -in and slow out" enhancement mode. However, in the clinical practice, there are many atypical cases, the speed of SHCC "wash-out" was not enough and the SFNH "slow out" was too fast, so the difference between the SHCC and SFNH was difficult to judge by the naked eye simply.

How to quantify the difference between the SHCC and SFNH is an important issue for clinicians and radiologists. In addition, with the rapid development of artificial intelligence (AI), the requirements for the quantification of the image signs have become increasingly strong. There is no report on quantifying the differences between the SHCC and SFNH enhancement up to now. Our aim was to evaluate the value of the ΔHU and CT-value ratio in the differential diagnosis and to guide clinicians to formulate more reasonable treatment plan further, through investigating the ΔHU of AP, PP and DP of 111 SHCC and 36 SFNH lesions.

MATERIALS AND METHODS

The CT scan parameters

Instrument: Philips Brilliance 64 slices Spiral CT Scanner (Brilliance, Japan). CT scan parameters: 120 kV, 90 mA, pitch: 0.914 vs 1, layer thickness: 5 mm, layer distance: 5 mm, bed speed: 12 mm/s. The CT-enhanced scan using the non-ionic contrast agent-iohexol (300 mgI/ mL), the dose was 80 to 100 mL, the rate was 3 mL/s, and it is injected through the cubital vein using a high-pressure syringe; underwent AP, PP and DP scan after injected 25 ~ 30 seconds, 60 ~ 70 seconds, and 90 ~ 120 seconds, respectively.

Material collection

Retrospective analysis was performed for the SHCC and SFNH from January 2014 to December 2016. Enrollment criteria: a) all the patients underwent three-phase enhancement Multidetector computed tomography (MDCT) scan; b) the maximum diameter of lesion was no more than 3cm; and c) all the SHCC were confirmed by histopathological immunohistochemistry, 10 cases of SFNH were confirmed by pathologically and the other 23 cases by typical imaging whose clinical performance were stable, and the lesion size of the image were constant or reduce in the 2 years follow-up [6,7]. Exclusion criteria: fatty liver [8]. Obtained 111 SHCC lesions in 108 patients which contain 88 males and 20 females with a median age of 58 years old; 36 SFNH lesions in 33 patients which contain 9 males and 24 females with a median age of 35 years old finally.

Image measurement

The images were analyzed by a resident physician who had been working for 3 years and determined the size and location of the region of interest (ROI). The ROI was drawn in a region with a more uniform density of the lesion and the area was 15 ~ 35 mm^2. The CT values of each enhancement phase were measured at the same position of the solid component of the lesion, and the necrosis area and vascular structure were avoided. The ROI of the adjacent normal liver parenchyma was 3-5 cm from the lesion, avoided the big vessels and the size was consistent with the ROI of the lesion. The CT values of each ROI were measured twice which were two months apart, and a mean CT value was obtained for each ROI.

Data analysis

The data were analyzed by SPSS 23.0, it did not meet the normal distribution, so used the quartile M (P25 ~ P75) to describe. The ΔHU and CVR of the SHCC and SFNH were analyzed by Wilcoxon rank sum test and receiver operating curve (ROC); gender was used for chi-square test, age and lesion size were tested by Wilcoxon rank sum test; $P < 0.01$ was considered statistically significant.

RESULTS

General conditions

Among the 108 patients of 111 SHCC lesions,

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[DOI: 10.52547/ijrr.18.4.641]

105 patients single mass with 105 lesions and 3 patients of double hair with 6 lesions; and among the 33 patients of 36 SFNH lesions, there are 30 single lesions in 30 patients and another 6 lesions in 3 patients. The difference of the sex ratio and age of the SHCC and SFNH were statistically significant, male and female ratio were (88 vs. 20) and (9 vs. 24) (P = 0.000 < 0.01), and the age were 58 (51.25 ~ 64) and 35 (31 ~ 48) years old (P = 0.000 < 0.01); while the size was not statistically significant, which were 2.4 (1.8 to 3.0) cm and 2.0 (1.5 to 2.88) cm respectively (P = 0.12).

The ΔHU and CVR of AP, PP and DP

Among the 108 patients of 111 SHCC and 33 patients of 36 SFNH lesions, the ΔHU and CVR of AP, PP and DP of the two were gradually decreased; the ΔHU of the AP, PP and DP of the SHCC were significant lower than the SFNH, which were 66.60 (48.00 ~ 97.60) vs. 126.70 (110.05 ~ 162.53) (Z = -7.106, P = 0.000 < 0.000), -33.60 (-51.40 ~ -19.90) vs. 18.15 (6.50 ~ 30.93) (Z = -7.439, P = 0.000 < 0.000), -38.40 (-51.90 ~ -25.60) vs. 5.60 (-0.03 ~ 12.10) (Z = -8.829, P = 0.000 < 0.000) , respectively (table 1). And the CVR of the AP, PP and DP of the SHCC lesions were significant lower than the SFNH, which were 1.43 (1.26 ~ 1.61) vs 1.77(1.63 ~ 1.90) (Z = -6.086, P = 0.000 < 0.000)，0.84 (0.76 ~ 0.90) vs 1.09 (1.03 ~ 1.16) (Z = -7.446, P = 0.000 < 0.000), 0.79 (0.73 ~ 0.88) vs 1.03 (1.00 ~ 1.06) (Z = -8.838, P = 0.000 < 0.000), respectively (table 1).

Table 1. The ΔHU and CVR of AP, PP, and DP of the SFNH and SHCC.

Group	Number	AP		PP		DP	
		ΔHU	CVR	ΔHU	CVR	ΔHU	CVR
SFNH	36	126.7 (110.05 ~ 62.53)	1.77 (1.63 ~ 1.90)	18.15 (6.50 ~ 30.93)	1.09 (1.03 ~ 1.16)	5.6 (-0.03 ~ 12.10)	1.03 (1.00 ~ 1.06)
SHCC	111	66.6 (48.00 ~ 97.60)	1.43 (1.26 ~ 1.61)	-33.6 (-51.40~ -19.90)	0.84 (0.76 ~ 0.90)	-38.4 (-51.90 ~ -25.60)	0.79 (0.73 ~ 0.88)
Z-value		-7.106	-6.086	-7.439	-7.446	-8.829	-8.838
P-value		0.000	0.000	0.000	0.000	0.000	0.000

ROC curve

The area under curve (AUC) of the ΔHU of the AP, PP and DP were increased gradually, which were 0.895 (95%CI: 0.828 ~ 0.962), 0.913 (95% CI: 0.867 ~ 0.960), and 0.990 (95%CI: 0.979 ~ 1.000), respectively (table 2, figure 1). The area under curve (AUC) of the CVR of the AP, PP and DP were increased gradually, which were 0.838 (95%CI: 0.765 ~ 0.911), 0.914 (95%CI: 0.867 ~ 0.960), and 0.991 (95%CI: 0.980 ~ 1.00), respectively (table 2, figure 1). The typical CT-value measurement of the AP, PP and DP of the SHCC and SFNH are shown in figures 2 and 3 respectively.

Optimal threshold for differential diagnosis

When the ΔHU of the AP, PP and DP were 105.800HU, -12.600HU, and -19.750 HU, obtained the maximum You-den indexes which were 0.707, 0.811, and 0.908, respectively; besides, the corresponding sensitivity and specificity were 80.6 % and 90.1 %, 100% and 81.1%, 94.4 % and 96.4%, respectively (table 3). And when the CVR of the AP, PP and DP were 1.516, 0.949, and 0.951, obtained the maximum You-den indexes which were 0.610, 0.811, and 0.908, respectively; besides, the corresponding sensitivity and specificity were 88.90% and 72.1%, 100% and 81.1%, 94.4 % and 96.4%, respectively (table 3).

Table 2. The AUC values of the SFNH and SHCC groups.

	AUC		*P*		95%CI (Lower limit~ Upper limit)	
	ΔHU	CVR	ΔHU	CVR	ΔHU	CVR
AP	0.895	0.838	0.000	0.000	0.828~0.962	0.765~0.911
PP	0.913	0.914	0.000	0.000	0.867~0.960	0.867~0.960
DP	0.990	0.991	0.000	0.000	0.979~1.000	0.980~1.000

AUC: area under curve, CVR: CT value ratio, ΔHU: CT value difference, AP: arterial phase, PP: portal phase, DP: delayed phase.

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[DOI: 10.52547/ijrr.18.4.641]

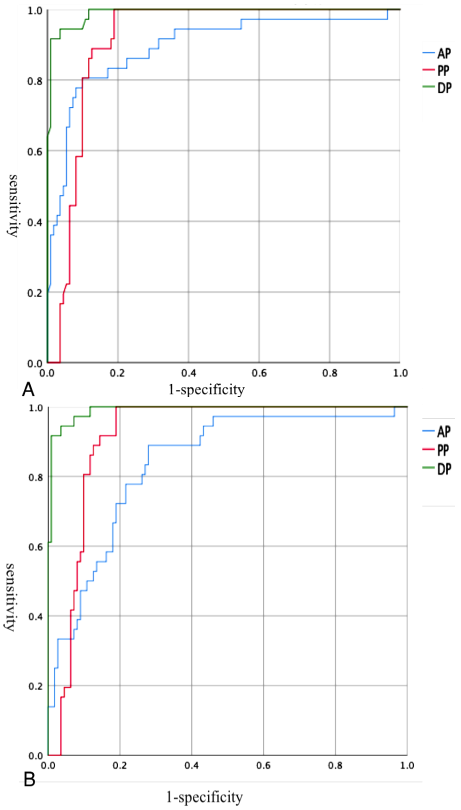


Figure 1. The ROC curves of the CVR for SHCC and SFNH groups, the figure A is the ROC of ΔHU, the figure B is CVR. ROC: receiver operating curve, CVR: CT value ratio, SHCC: small Hepatocellular Carcinoma, SFNH: small Focal nodular hyperplasia, ΔHU: CT value difference.

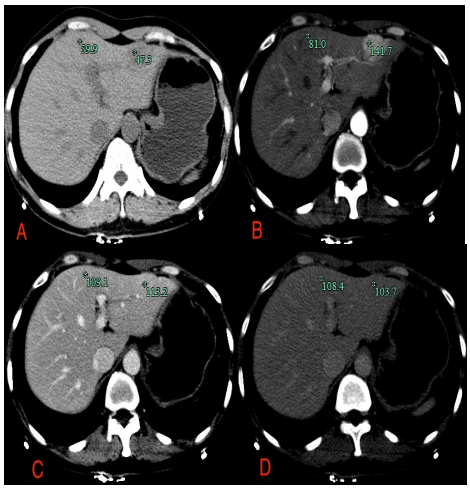


Figure 3. Images in a 39-year-old man with FNH. The CT enhanced scan of liver: there is a round slightly low-density lesion with a size of approximately 3.0 cm * 2.1 cm, uniform density, and clear boundaries in the hepatic II segment; and the lesion in AP(B) was obviously uniform enhanced with high-density (ΔHU =60.70HU, CVR=1.75), theenhancement was reduced in PP (C) and DP (D) to iso-density, and the ΔHU are 4.10HU, -4.70HU and CVR are 1.04, 0.96, respectively. FNH: Focal nodular hyperplasia, CVR: CT value ratio, ΔHU: CT value difference, AP: arterial phase, PP: portal phase, DP: delayed phase.

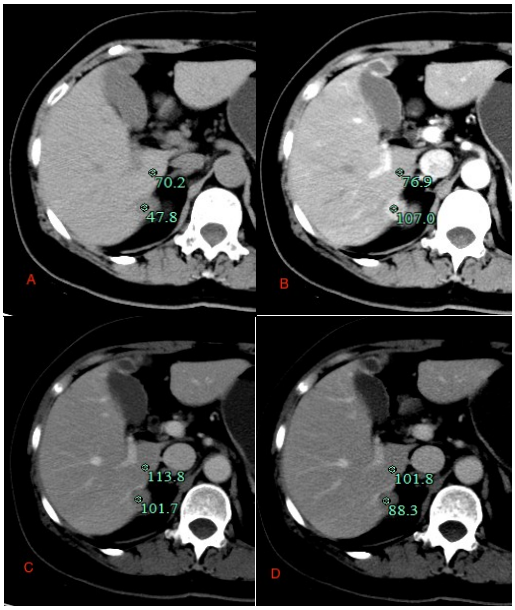


Figure 2. Images in a 55-year-old man with SHCC. The CT enhanced scan of liver shows: there is a round low - density lesion with the size of approximately 1.5 cm * 1.5 cm, uniform density, a clear boundary in the hepatic VI segment; and the lesion of AP **(B)** is obviously uniform enhanced with high - density (ΔHU =30.10HU, CVR=1.39), the enhancement was reduced in PP **(C)** and DP **(D)** to low-density, and the ΔHU are -12.10HU, -13.50HU and CVR are 0.89, 0.87, respectively. CVR: CT value ratio, SHCC: small Hepatocellular Carcinoma, ΔHU: CT value difference, AP: arterial phase, PP: portal phase, DP: delayed phase.

Table 3. The ΔHU and CVR, sensitivity, and specificity of the AP, PP, and DP of SFNH and SHCC groups when the You-den index is maximum.

groups	You-den index$_{max}$		Sensitivity (%)		Specificity (%)	
	ΔHU	CVR	ΔHU	CVR	ΔHU	CVR
AP	0.707	0.610	80.6%	88.90%	90.1%	72.1%
PP	0.811	0.811	100.00%	100.00%	81.1%	81.1%
DP	0.908	0.908	94.4%	94.4%	96.4%	96.4%

DISCUSSION

The age and gender of the HCC and FNH were quite different, the former occurs in elderly men and was associated with men which as a risk factor of HCC [9,10]; and the latter occur predominantly in young women and the reasons was unclear which may be related to long-term oral contraceptives and hormone therapy [11]. This study supported these characteristics, the median age of SHCC and SFNH was 58 vs. 35 and the male to female gender ratio were (88 vs. 20) and (9 vs. 24). Among the 111 SHCC and 36

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SFNH lesions in this study, the median ΔHU and CVR of the AP, PP, and DP were statistically significant, these values are decreasing gradually respectively. It can be seen that the HCC complied with the "wash-in and wash-out" intensifying mode and the FNH complied with the "wash-in and slow out" enhancement model, which were in line with the literature-based enhancement model [12,13], but the literatures did not analyze the diagnostic efficiency. The AUC of the ΔHU and CVR of AP, PP and DP were increased gradually in this study, suggested that the ΔHU and the CVR of the three-phase enhancement scan have differential significance of the two diseases, especially in the DP. When the You-den indexes are at its maximum, we obtained the best sensitivity and specificity. With the increasing of the ΔHU and the CVR, the sensitivity is decrease and the specificity increase. All in all, when the ΔHU≤105.800HU or CVR≤1.516 of the AP, ΔHU≤-12.600HU or CVR≤0.949 of the PP, and ΔHU≤-19.750 HU or CVR≤0.951 of the DP in the middle-aged and elderly male patients respectively, the SHCC was highly indicated, especially the DP.

Zhen *et al.* [14] used T1 mapping to diagnose HCC and FNH, they think there were significant differences of T1 relaxation times of pre-contrast and on hepatobiliary phase images at 20 minute after contrast the reduction of T1 relaxation time on hepatobiliary and the per-centage reduction between FNH and HCC ($P < 0.001$); Ma Luo et al. [15] found Intravoxel incoherent motion provided a new modality to differentiate the HCC and FNH, pure diffusion coefficient, pseudo-diffusion coefficient, and apparent diffusion coefficient were significantly lower in the HCC group than in the FNH group; Kitao et al. [16] found the apparent diffusion coefficient was lower in hyper-intense HCC than in FNH. FNH at dynamic CT were significantly different from HCC at arterial phase enhancement and washout pattern. There was a report about CVR that affected the prognosis of patients with HCC, SY. Gao *et al.* [17] thought the tumor-to-liver CT value ratio were risk factors contributing to survival in the arterial phase and portal venous phase, and when tumor-to-liver CT value ratio < 0.85 predicted a poor outcome for HCC patients after radical hepatectomy. There were reports about identifying liver diseases quantitatively by CT value. For example, the single parameter for differentiating intrahepatic mass-forming cholangiocarcinoma (IMCC) from small liver abscess (LA) was CT value at 90 keV, with sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 89.1%, 86.5%, 87.9%, 89.1%, and 86.5%, respectively [18]; the CT value of hyper-vascular intrahepatic Cholangiocarcinoma (HICC) was lower in the unenhanced phase (UP) and higher in the equilibrium phase (EP) in comparison to HCC, The E/U ratio (the mean CT value of the tumor in the EP to that in the UP) of > 2.3 was independent diagnostic factor for differentiating HICC from HCC [19]; these all suggested that the CT value could be used to diagnose and identify diseases quantitatively. Though there were a couple of previous studies identified the HCC than in FNH using different methods, but there no reports about quantifying the differences between the HCC and FNH up to now, not to mention the ΔHU and/or CVR.

There were some limitation in this study: Firstly, the physical condition of each patient was different, for example, partial patients with cardiopulmonary insufficiency, which may lead to different time of three phases of the scanning. Secondly, this was a retrospective study, and there may be a selective bias inevitably.

CONCLUSION

In conclusion, the CT-value (ΔHU and/or CVR) had important value in distinguishing the SHCC and SFNH, especially the DP, and it was easy to operate and apply in clinical practice. It also could provide important support for the development of AI in imaging diagnosis.

ACKNOWLEDGMENTS

The authors thank our collaborators who collected the data of the patients.

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[DOR: 20.1001.1.23223243.2020.18.4.4.4]
[DOI: 10.52547/ijrr.18.4.641]

Funding

This report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

***Conflicts of interest*:** *Declared none.*

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