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ORIGINAL ARTICLE

Clinical value of spectral CT imaging combined with AFP in identifying liver cancer and hepatic focal nodular hyperplasia

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Summary

Purpose: *To investigate the clinical value of spectral computed tomography (CT) imaging combined with alpha-fetoprotein (AFP) in identifying liver cancer and hepatic focal nodular hyperplasia (FNH).*

Methods: *A total of 132 patients with local liver space-occupying lesions, including 68 patients with liver cancer, were randomly enrolled. All the patients underwent spectral CT imaging and AFP examinations. The corresponding specificity, sensitivity, accuracy rate, positive predictive value and negative predictive value of spectral CT imaging, AFP and combined detection were recorded, respectively, with pathological findings as the gold standards. SPSS 17.0 software was used for statistical analysis. P<0.05 suggested that the difference was statistically significant.*

Results: *The diagnostic rate of spectral CT imaging was 79.5% for liver cancer and 81.3% for hepatic FNH. In arterial phase and portal venous phase, the contrast-to-noise ratio (CNR) of liver cancer was remarkably lower than that of FNH, showing a statistically significant difference, and the difference was the greatest at 70-100 keV between the two kinds of lesions. The detection rate of AFP for liver cancer was 86.8%, and the exclusive diagnostic rate of AFP for hepatic FNH was 96.9%. AFP had the highest specificity (73.2%) in identifying liver cancer and hepatic FNH. The spectral CT imaging possessed the highest sensitivity (91.7%) in identifying liver cancer and hepatic FNH. Both the sensitivity (98.1%) and accuracy (89.1%) of spectral CT imaging combined with AFP were the highest in identifying liver cancer and hepatic FNH.*

Conclusion: *The spectral CT imaging combined with AFP is conducive to improving the efficiency of differential diagnosis of liver cancer and hepatic FNH.*

Key words: *spectral CT imaging, AFP, liver cancer, hepatic focal nodule, differential diagnosis*

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer in people around the world, especially those in the Asian and Mediterranean regions. It is generally a complication of chronic liver diseases, which mostly occur in patients with liver cirrhosis. However, there are great differences in the imaging findings of HCC. Focal nodular hyperplasia (FNH) is the most common kind of benign hepatic lesion, second only to hemangioma, with an incidence rate of 1-8% in adults [1]. It is characterized by nodular hyperplasia in the liver parenchyma, surrounded by central stellate cell fibrosis regions and accompanied with abnormal arteries [2]. Typical FNH can be diagnosed by means of computed tomography (CT) or magnetic resonance imaging (MRI) [3,4]. In case of

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atypical FNH, however, weak enhancement or non-enhancement of central scars and enhancement of pseudo-capsule may be displayed on delayed images. It is fairly difficult to distinguish atypical FNH from HCC in some cases [5], so it is essential to carry out differential diagnoses for HCC and FNH due to different therapeutic methods. It has been proven that hepatectomy is a highly efficient treatment method for liver cancer, but, on the contrary, it is feasible to closely observe the patients with FNH [6,7].

After hepatic nodules are discovered in patients with liver cirrhosis, they usually need to be characterized by means of multi-detector CT, MRI, contrast-enhanced ultrasound or hepatocyte-specific MRI, diffusion-weighted (DW) MRI and positron emission tomography (PET). Each of the above-mentioned technique has advantages and disadvantages, and the selection of imaging modalities depends on multiple factors such as the number of nodules, existence of liver cirrhosis, availability, interpretation, expense and other issues.

If typical imaging characteristics occur but biopsy is not necessary, it is crucial to diagnose liver cancer through noninvasive or semi-invasive imaging, of which noninvasive examinations are more acceptable for the patients. Although the seeding rate of tracing tumor after HCC biopsy is low, it cannot be ignored. It is reported that the overall incidence rate of tumor dissemination along the needle passage after biopsy is about 2.7% or 0.9% every year. Imaging can further facilitate the observation of the lesion, vascular invasion and impacts on surrounding structures. This information is especially useful for the determination of the type of treatment, such as local ablation therapy (radiofrequency ablation, percutaneous ethanol injection or microwave ablation), resection or liver transplantation. Spectral CT imaging is a type of CT imaging modality based on fast switching between high- and low-energy datasets, which is adopted to generate material decomposition image and monochromatic spectrum image at an energy level of 40-140 keV [7]. This imaging method is also applied to many clinical practices, including preoperative discovery of insulinoma [8], identification of intense liver vascular damage [9] and diagnosis of pulmonary embolism [10].

Generally, alpha-fetoprotein (AFP) is hardly detected in the serum of adults because its transcription declines dramatically after birth, so it is regarded as a major serum marker of HCC. The serum AFP level can be increased in other malignant tumors such as non-seminomatous germ cell tumor and gastric neoplasms. Besides, the elevated AFP level may also be detected in acute or chronic hepatitis, hepatic necrosis or hepatic regeneration. In contrast, benign hepatic nodules, including FNH, are associated with normal serum AFP level in adults.

This research aimed to preliminarily explore the efficacy and accuracy of spectral CT imaging combined with AFP in identifying HCC and FNH.

Methods

Clinical case data

A total of 132 patients with local liver space-occupying lesions hospitalized in our hospital from January 2017 to January 2018 were randomly enrolled. All the patients were examined with CT and AFP, and the diagnosis was pathologically confirmed. The study was approved by the Ethics Committee of our hospital and informed consents were obtained from all participants. The basic patient data are shown in Table 1.

Table 1. Clinicopathological case data of enrolled patients

Clinicopathological data	*n (%)*
Age (years)	
>50	60 (45.5)
≤50	72 (54.5)
Gender	
Male	72 (54.5)
Female	60 (45.5)
Type	
Liver cancer	68 (51.5)
Hepatic FNH	64 (48.5)
Tumor diameter, cm	
≥2	65 (49.2)
<2	67 (50.8)

Spectral CT imaging and AFP detection

The patients needed to be fasted for 6 h before CT examination. Discovery CT750 HD CT system (64 detectors) was used for unenhanced and two-phase contrast material-enhanced CT examinations. Imaging for head and neck was performed in all of the patients in supine position under a tube voltage of 120 kVp in conventional spiral scan mode, and then the unenhanced images were obtained. Next, a total of 80-100 mL nonionic contrast medium (Iopamiro 300, Shanghai BRACCO Sine Pharmaceutical, China) was injected in the antecubital vein using a power injector (Ulrich Medical, Germany) at a rate of 3-4 mL/s to perform arterial phase (AP) and portal venous phase (PP) imaging. The delay of AP imaging was determined by means of automatic image triggering software (SmartPrep; GE Healthcare). The AP imaging started 8 s after the attenuation at trigger threshold was obtained at the abdominal aorta level on the peritoneum, and then after 30 s of delay, PP imaging began.

The AP and PP imaging was performed under the spectral imaging modality, and the tube voltage was rapidly switched between 80 kVp and 140 kVp on adjacent views during single rotation. Other imaging parameters were set as follows: thickness of collimator: 0.625 mm, tube current: 600 mA, rotation speed: 0.6 s and pitch: 0.983. The CT images were reconstructed using the projection-based material decomposition software and standard reconstruction core. The following three types of images were collected and reconstructed through single-spectral CT for analysis use: conventional multi-color images acquired under 140 kVp, material decomposition images based on iodine and water and monochrome images acquired under 40-140 keV.

A total of 5 mL fasting venous blood was drawn from every subject in the morning, followed by separation of serum via centrifugation and measurement of concentration by virtue of ROCHE E170. All the kits were purchased from ROCHE.

Analysis of diagnostic efficiency

The corresponding specificity, sensitivity, accuracy rate, positive predictive value and negative predictive value of CT, AFP and combined detection were recorded, respectively, with pathological findings as the gold standard. The area under curve of receiver operating characteristic (AUC^{ROC}) was utilized to compare the diagnostic efficiency of AFP, CT and combined detection for liver cancer and hepatic FNH.

Statistics

SPSS 17.0 software was used for statistical analyses. Data were presented as mean±SD. T-test was used for intergroup comparison, and x^2 test for numerical data. Continuous data from multiple groups were analyzed using one-way ANOVA with Tukey's *post hoc* test. Pearson's correlation analysis was applied to analyze the correlation between standardized uptake $value_{max}$ and the size of primary foci. P<0.05 suggested that the difference was statistically significant.

Results

Detection of liver cancer and hepatic FNH via spectral CT imaging

The diagnostic rate of spectral CT imaging for liver cancer was statistically higher than that of hepatic FNH (p<0.05;Table 2). The contrast-to-noise ratio (CNR) of liver cancer and hepatic FNH was significantly different at varying energy levels, which declined gradually along with the increase in energy. The CNR of liver cancer was notably lower than that of FNH in AP, with statistically significant difference. Moreover, the difference in the CNR between the two lesions was the greatest at 70-100 keV (Table 3). Similarly, the greatest differ-

Table 2. Diagnosis of liver cancer and hepatic FNH via spectral CT imaging

Clinical diagnosis	*Spectral CT imaging diagnosis*		*x^2*	*p*
	Positive n (%)	*Negative n (%)*		
Liver cancer	49 (72.1)	19 (27.9)		
Hepatic FNH	35 (54.7)	29 (45.3)	4.299	0.038

Table 3. Comparisons of spectrum curve slopes of liver cancer and hepatic FNH at various energy intervals in AP

	40-70 keV	*70-100 keV*	*100-140 keV*
Liver cancer	3.6±1.1	0.6±0.1	0.3±0.1
Hepatic FNH	7.4±1.6	2.3±0.6	1.0±0.3
t	0.518	3.378	2.08
p	0.615	0.003	0.044

Table 4. Comparisons of spectrum curve slopes of liver cancer and hepatic FNH at various energy intervals in PP

	40-70 keV	*70-100 keV*	*100-140 keV*
Liver cancer	1.3±0.2	1.2±0.4	0.9±0.4
Hepatic FNH	1.0±0.2	0.5±0.1	0.6±0.3
t	2.82	2.88	0.398
p	0.006	0.007	0.602

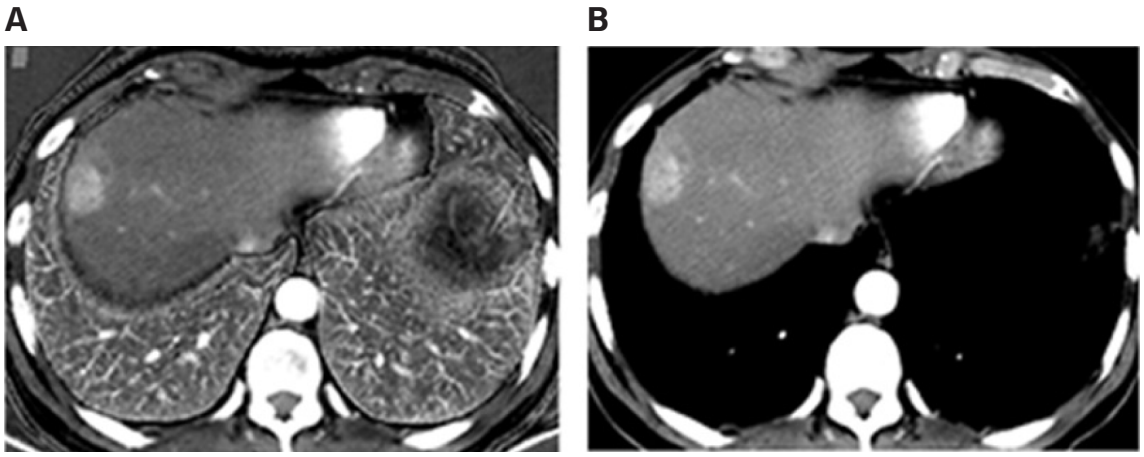

Figure 1. A male patient aged 58 years, with an HCC of 2.5 cm under the liver capsule. **A:** Locally and excessively weakened lesions are clearly displayed on the material decomposition image base on iodine. **B:** The lesions in AP are not clearly displayed on conventional multi-color image.

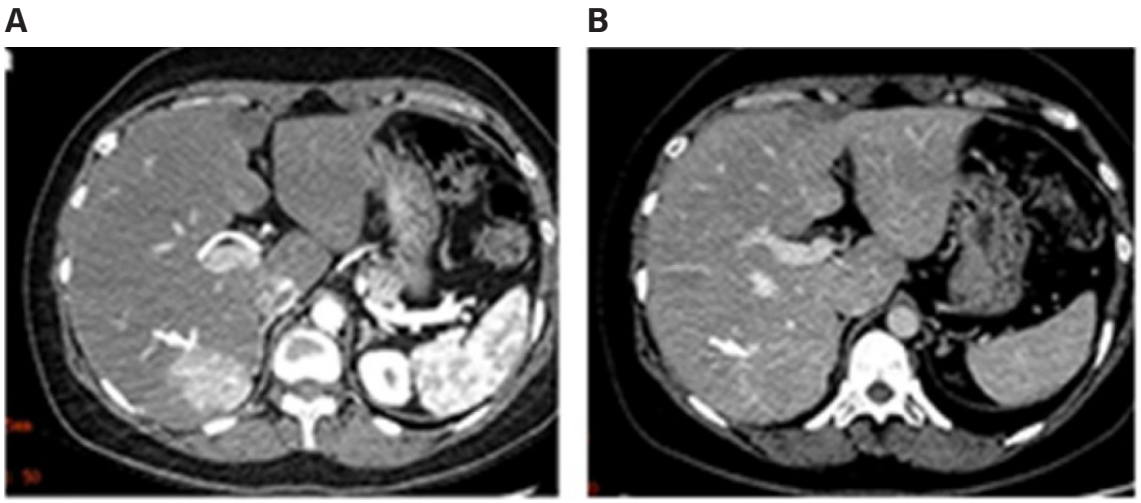

Figure 2. A female patient aged 49 years, with an FNH of 3.4 cm in the right-posterior lobe of the liver. **A:** Feeding arteries at the edge of injury are shown in the monochrome image at 50 keV in AP (arrow). **B:** Visible pseudo-capsule lesions are shown in the monochrome image at 70 keV in PP (arrow).

ence in the CNR between the two kinds of lesions was detected at 70-100 keV in PP (Table 4; Figures 1 and 2).

Detection of liver cancer and hepatic FNH via AFP

The detection rate of AFP was 86.8% for liver cancer, which was significantly higher than that of FNA (3.1%, p<0.0001; Table 5).

Diagnostic efficiency of spectral CT imaging and AFP

The comparison of diagnostic efficiency among the three diagnostic methods indicated that AFP had the highest specificity (73.2%) in identifying liver cancer and hepatic FNH. The spectral CT imaging possessed the highest sensitivity (91.7%) in identifying liver cancer and hepatic FNH. Moreover, both the sensitivity (98.1%) and accuracy (89.1%) of spectral CT imaging combined with AFP were the highest in identifying liver cancer and hepatic FNH (p=0.05) (Table 6 & Figure 3).

Discussion

According to the results in this research, the CNR of liver lesions at low-energy level (40-70 keV) was higher than that at high-energy level (80-140 keV). The explanation may be that the contrast of tissue in high-energy images is generally lower than that in low-energy images [11]. The optimum CNR of liver lesions could be obtained from the best monochrome image that is conducive to lesion detection. In AP and PP, the CNR of FNH was increased compared with that of HCC, and the difference was statistically significant. The evident enhancement of FNHs seemed to be totally caused

Table 5. Detection of liver cancer and hepatic FNH via AFP

Clinical diagnosis	*AFP diagnosis*		x^2	*p*
	Positive n (%)	*Negative n (%)*		
Liver cancer	59 (86.8)	9 (13.2)		
Hepatic FNH	2 (3.1)	62 (96.9)	92.79	<0.001

Table 6. Comparison of diagnostic efficiency among groups

Group	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*	*Positive predictive value (%)*	*Negative predictive value (%)*
AFP	62.2	73.2*	64.1	67.2	49.3
Spectral CT imaging	91.7*	57.9	81.2	82.1	56.4
Combined detection group	98.1*	64.3	89.1*	89.4	79.9*

* p<0.05

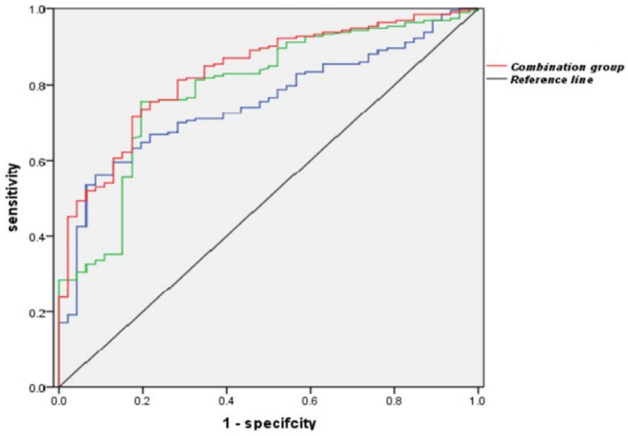

Figure 3. Comparison of diagnostic efficiency among groups via ROC curve.

by arteriogenesis in feeding artery injury in the central scar.

According to previous studies, however, the type of blood supply of HCC is correlated with the pathologic grade [12,13]. As the histological grade of HCC rises from well-differentiated to moderately-differentiated, the number of unpaired arteries is increased, while the number of paired arteries is decreased when the moderately-differentiated HCC progresses into poorly-differentiated HCC.

The serum AFP level is the most frequently used indicator for the assessment of HCC diagnosis and prognosis, but its benefits still remain controversial [14]. Currently, it is not recommended to utilize serum AFP to monitor HCC in the guidelines of AASLD (USA) and EASL-EORTC (Europe) due to cost and benefit issues [15]. Nonetheless, the application of serum AFP to monitor HCC is still recommended in the guidelines of JSH and APASL [16,17]. To our knowledge, there have been no reports about the relationship between FNH and elevated serum AFP level. It is worth noting that there were two FNH patients with positive AFP in this research, and those areas might be regarded as potential sources of the production of AFP and increase of serum AFP level [18,19]. The significance of such regenerated lesions was not clarified at first, but the possible reason of AFP increase may be related to hereditary persistence of AFP (HPAFP). HPAFP, a rare benign autosomal dominant inherited disease, is characterized by continuous expression of AFP in adulthood and is suggested to take it into account in patients with unexplained elevated AFP levels [20]. It is often associated with mutation of the binding sites of hepatocyte nuclear factor-1 (HNF-1), the promoter of AFP gene, and it increases its affinity to HNF-1, thereby enhancing AFP transcription.

Conclusion

In this research, the efficacy and accuracy of spectral CT imaging combined with AFP in differentially diagnosing liver cancer and hepatic FNH were investigated, providing new ideas and bases for differential diagnosis of these two diseases in clinic in the future.

There are certainly some limitations in this research. Firstly, the findings had only preliminary clinical verification, which needs to be verified by other studies involving large numbers of lesions. Secondly, this research only focused on distinguishing HCC from FNH, and more studies on various types of vascular neoplasms are necessary, so as to

reach more accurate conclusions. Thirdly, HCC was not classified according to the pathological grades in this research because there were too few cases of well-differentiated HCC. Finally, the correlation of histopathological features with CT characteristics was not considered in this research, which needs to be perfected and clarified through more subsequent experiments.

Conflict of interests

The authors declare no conflict of interests.

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