ORIGINAL RESEARCH

Small hepatocellular carcinoma keeping hypodense during dual phase helical CT scan and correlative pathology

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Abstract

Rationale and Objectives: To evaluate the dual-phase helical computed tomography (CT) appearance of small hepatocellular carcinoma (SHCC) with hypodense and to evaluate its correlation with pathology.

Materials and Methods: The helical CT dual-phase appearance of 33 lesions with keeping hypodense was retrospectively analyzed, all lesions were confirmed as SHCC by histopathology. CT appearance included border, inner density.

Results: In 33 lesions, which were confirmed as SHCC by pathology, keeping hypodense during hepatic arterial phase and portal venous phase, 19 lesions are ill-defined borders and 14 lesions are well-defined borders, 22 lesions show homogenous hypodense and 11 lesions show heterogeneous hypodense in non-enhancing CT scan; however, only 9 lesions are ill-defined borders and the other 24 lesions are well-defined borders with slightly irregular contours, only 9 lesions show homogenous hypodense and the other 24 lesions show heterogenous hypodense with flecks of more hypodense in enhancing CT scan.

Conclusion: SHCC with hypodense prefers to have a well-defined border with slightly irregular contour, and flecks of more hypodense in the lesion in dual-phase enhancing helical CT scan.

Key words

Carcinoma, Hepatocellular, Tomography, X-ray computed, Diagnostic imaging

1 Introduction

Most of small hepatocellular carcinomas (SHCC, $\leqslant$3.0cm in diameter) are hypervascular and characterized as homogenous or heterogenous hyperdense in hepatic arterial phase and iso- or hypodense in portal venous phase during dual-phase helical CT scan [1, 2]. Compared to this common pattern, SHCC keeping hypodense during arterial and portal-vein phase is an unusual CT appearance so that rare literatures have mentioned of it [3, 4]. There exist some difficulties in making correct diagnosis in routine clinic settings. The purpose of this study is to evaluate dual-phase helical CT appearance of this pattern in detail.

2 Materials and methods

2.1 Ethics

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. This study was approved ethically by Sun Yat-sen University Cancer Center. All patients provided informed written consent.

2.2 Patients

Between January 1997 and January 2007, the dual-phase CT appearance was analyzed retrospectively in 145 patients with 160 SHCCs in our hospital. There were 33 lesions in 31 patients, which kept hypodense in dual-phase helical CT. There were 28 males and 3 female (range, 28-70 years, mean age, 50 years). Among them, 29 patients had single lesion and another 2 patients had 2 lesions each. 27 lesions received surgical operation and the other 6 lesions received radio-frequency ablation by ultrasound. All lesions were confirmed as SHCC by histopathology.

2.3 Histopathologic examinations and analysis

Twenty-seven surgical resected lesions were sampled from their borders and centers respectively. 2-5 specimens were sampled according to the size of the lesions. After fixed in 10% formaldehyde solution, embedded in paraffin wax and hematoxylin and eosin staining, serial sections were observed and evaluated with light microscope by a pathologic professor who specialized in hepatic diseases. Differentiation of tumor cells was graded primarily based on Edmondson and Steiner's grading. In addition, histopathologic parameters included vascular supplication, necrosis, fatty metamor-phosis, and hyaline degeneration of tumor cell in the lesion.

2.4 Imaging examinations and analysis (CT scanning and Image assessment)

Dual-phase helical CT examinations were performed in 31 patients using on a helical CT scanner (Toshiba Xpress/sx, rotation time, 1sec, 120kV, 250mAs, matrix 512×512, 10-mm collimation, pitch, 1). The non-enhancing CT scan of the whole liver was performed; after a bolus injection (3ml s^{-1}) of 300 iopromide (1.5ml kg^{-1}) through the antecubital vein were given, images of arterial (25s after injection) and portal (60s after injection) phase were obtained respectively.

Three experienced radiologists, who were unaware of the clinical findings, evaluated the CT images separately. Any disagreements were resolved by consensus.

The number, distribution and diameter of the lesions, description of their border (well-defined or ill-defined), the inner density(homogenous or heterogenous)were evaluated. The CT values in the lesions during every phase were measured by drawing region of interest (ROI) manually. ROI of the lesion preferred to the central areas, avoiding the more hypodense areas. ROI of hepatic parenchyma prefered to the area no less than 3cm away from the lesions on the same traverse slice, avoiding the vessels in the liver. ROI of every case kept the same location, diameter and shape during various phases.

3 Results

3.1 Non-enhancing CT scan appearance

Among 33 lesions, the size of the largest one is 3.0cm×3.0cm and the smallest is 0.8cm×0.7cm. All lesions were spheroidic. 19 lesions had ill-defined borders (see Figure 1a, 2a) and the remaining 14 had well-defined borders (see Figure 3a). 22 lesions showed homogenous hypodense (see Figure 2a, 3a), and the remaining 11 lesions showed heterogenous hypodense (see Figure 1a).

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3.2 Dual-phase enhancing CT scan appearance

All 33 lesions enhanced slightly to various degrees in hepatic arterial phase and portal venous phase. Moreover, the density of the lesions in portal venous phase was higher than on hepatic arterial phase. However, the lesions kept hypodense compared with adjacent normal hepatic parenchyma during the dual-phase enhancing CT scans. The change of the CT value of the lesions and the normal hepatic parenchyma was recorded in the table. The CT value of the normal hepatic parenchyma kept higher than that of the lesions during various phases (P<0.005). The change of the CT value of the lesion was that the value during enhancing CT scan (arterial phase and portal-venous phase scan) was higher than that in non-enhancing CT scan. By analysis of variance (F=546.734, P<0.05),

Table. The change of CT values in the lesion during dual-phase enhancement

CT value	Normal hepatic parenchyma(HU)	Lesion(HU)
Non-enhancing CT scan	60±5	45±6
Hepatic arterial phase	75±6	56±7
Portal venous phase	112±7	74±7

After enhancement, 24 lesions had well-defined borders (see Figure 1b, 1c, 2b,3b,3c) and the contour of the lesions was slightly irregular (see Figure 1c,2c,3c), the remaining 9 lesions had ill-defined borders (see Figure 2b). 9 lesions showed homogenous hypodense (see Figure 2b, 2c) and the remaining 24 lesions showed heterogenous hypodense with multiple flecks of more hypodense (see Figure 1b,1c,3b,3c).

Histopathologic appearances

(1) According to Edmonton grading system, the differentiation of the tumor cell: grade Ⅱ in 21 lesions, gradeⅢ in 5 and gradeⅣ in 1, respectively.

(2) 10 lesions were hypovascular and 17 were relatively hypervascular.

(3) Others: flecks of necrosis were seen in 13 lesions and no necrosis in the remaining 14 lesions. Fatty metamorphosis of the tumor cell was found in 8 lesions. To various degrees, Hyaline degeneration of tumor cell was found in 12 lesions. Fibrous septum was found in the borders of 6 lesions. One of the pathologic specimens sampled from the resected lesion were shown as Figure 4a~c.

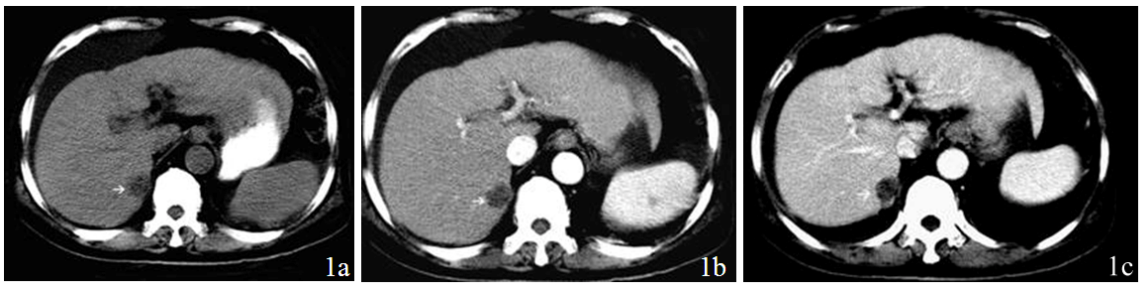

Fig 1a~c. Case 1(SHCC): 1a. Non-enhancing helical CT shows a hypodense lesion with ill-defined border in segment Ⅶ of the right hepatic lobe, the density of the lesion is homogenous. 1b. Hepatic arterial phase of enhancing helical CT shows the density of the lesion is heterogenous with multiple flecks of more hypodense, the border of the lesion is well-defined and slightly irregular. 1c. The portal venous phase of enhancing helical CT shows the density of the lesion is heterogenous with multiple flecks of more hypodense, the border of the lesion is well-defined and slightly irregular.

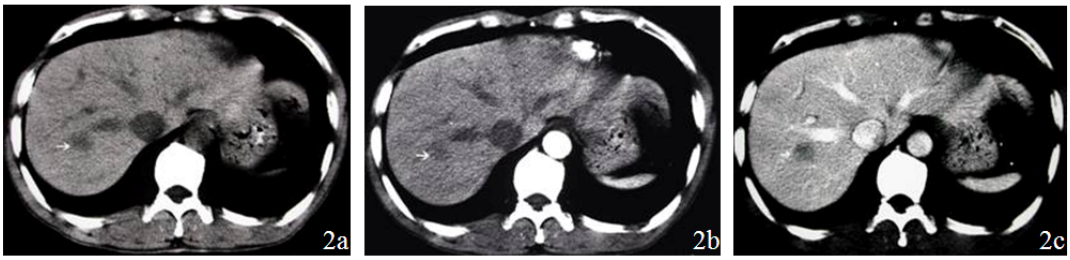

Fig 2a~c. Case 2(SHCC): 2a. Non-enhancing helical CT shows a slightly hypodense lesion with ill-defined border in segment Ⅶ of the right hepatic lobe, the density of the lesion is homogenous. 2b. Hepatic arterial phase of enhancing helical CT shows the lesion is slightly homogenous hypodense with ill-defined border. 2c. The portal venous phase of enhancing helical CT shows the lesion keeps homogenous hypodense with well-defined and slightly irregular border.

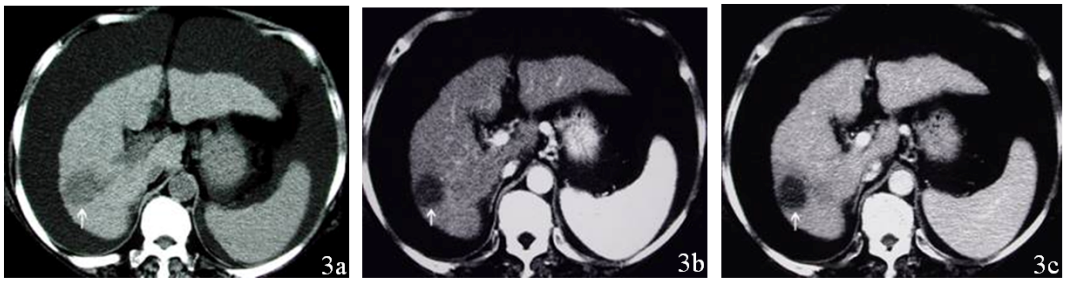

Fig 3a~c. Case 3(SHCC): 3a. Non-enhancing helical CT shows a slightly hypodense lesion with ill-defined border in segment Ⅶ of the right hepatic lobe, the density of the lesion is homogenous. 3b. Hepatic arterial phase of enhancing helical CT shows the lesion is slightly homogenous hypodense with ill-defined border. 3c. The portal venous phase of enhancing helical CT shows the lesion keeps homogenous hypodense with well-defined and slightly irregular border.

Note: The figures are indicated by the CT value average±standard error.

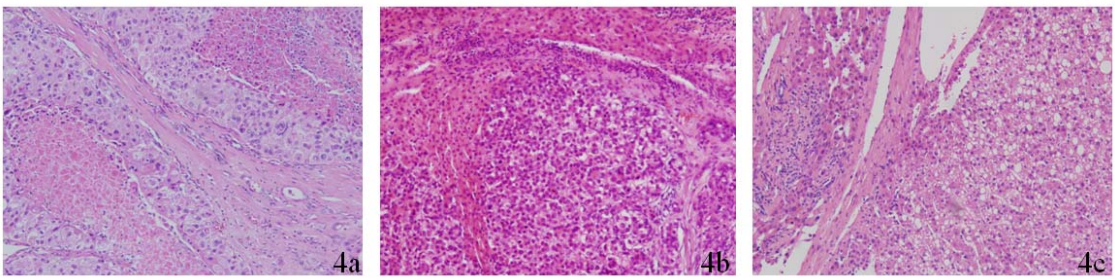

Fig 4a~c. The pathologic specimen sampled from the resected lesion. 4a. The pathologic specimen sampled from the center of resected lesion. Histologic examination shows flecks of necrosis, rare blood capillaries, and the fibrous spetum between tumor cell nests. (HE×100). 4b. The pathologic specimen sampled from the border of the resected lesion. Histologic examination showed hyaline degeneration of tumor cell, rare blood capillaries, fibrous pseudo-capsule at the borderline, the normal hepatic cell and the tumor cell interlaced with each other at the borderline. (HE×100). 4c. The pathologic specimen sampled from the border of the resected lesion. Histologic examination showed fatty metamorphosis of tumor cell, abundant blood capillaries, fibrous pseudo-capsule at the boundary between the tumor and hepatic parenchyma (HE×100).

4 Discussion

4.1 The CT appearance of the border of lesions

A conclusion could be drawn from above-mentioned results that SHCC with hypodense commonly had an ill-defined border of in non-enhancing CT scans, however, well-defined border became a common appearance after enhancement. Ill-defined border in non-enhancing CT scan may be due to follows: firstly, most of SHCC lacked pseudo-capsule [4]. Winter et al [5] found that there were only 4 (17%) with fibrous pseudo-capsule among 23 early hepatocellular carcinomas, which was similar to our findings, only 6 (22%) had fibrous pseudo-capsule among 27 lesions. Secondly, the tumor grew invasively, so that the normal hepatic cell and the tumor cell interlaced with each other at the borderline. Grazioli et al [6] reported that the tumor without fibrous pseudo-capsule lacked fibrous connective septum between carcinomatous tissue and normal hepatic parenchyma histologically, carcinomatous tissue and normal hepatic parenchyma interlaced each other without obvious borderline. After enhancement, especially in the portal venous phase, the adjacent hepatic parenchyma was enhanced obviously, in contrast, the lesion were enhanced slightly. Therefore, the density difference between the normal hepatic parenchyma and the lesion increased. Finally, the border of the lesion became well-defined and the contour of the lesion was slightly irregular. In a word, SHCC with hypodense has a character that the border is ill-defined in non-enhancing CT scan, however, it becomes well-defined and the contour of the lesion is slightly irregular after enhancement.

4.2 The CT appearance inside the lesions

According to the results above mentioned, another conclusion could be made that heterogenous hypodense with multiple flecks of more hypodense areas is the common appearance of SHCC with hypodense after enhancement, which is the other character of SHCC with hypodense. Such change may lie in the facts that the lesion and the normal hepatic parenchyma had mild density difference in non-enhancing CT scan, and partial volume effect in the lesion covered up flecks of more hypodense areas, so the lesion had a homogenous hypodense in non-enhancing CT scan. After enhancement, the carcinomatous tissue in the lesion were enhanced to various degrees (see Table), however, due to necrosis, fibrosis, fatty metamorphosis and cystic degeneration histopathologically, flecks of more hypodense areas were not or minimally enhanced [4, 7, 8]. Consequently, the density difference between flecks of more hypodense areas and the carcinomatous tissue in the lesion increased. In enhancing CT scan, flecks of more hypodense areas became more obvious, and the number increased too. Among these 33 lesions, the carcinomatous tissue was enhanced to various degrees after enhancement.

According to Table 1, the change of the CT value of the lesion was that the CT value in enhancing CT scan was higher than that in non-enhancing CT scan. The result showed that the lesion had vascular supply, the lesion was enhanced; however, since the density of the lesion were obviously lower than that of the adjacent normal hepatic parenchyma in the same slice after enhancement, the lesion kept hypodense during various phases. This appearance may be due to the following reasons: firstly, the lesions had necrosis, fatty metamorphosis or hyaline degeneration of tumor cell [4, 5, 7, 8]. In our study, 13 lesions had spots of necrosis and 8 had fatty metamorphosis. Early hepatocellular carcinoma with hypodense in non-enhancing CT scan was caused by the fat infiltration [4]. Stevens et al [7] reported that areas of necrosis in the hepatocellular carcinoma always corresponded to non-enhancing areas after enhancement. Monzawa et al [8] reported that the Hyaline degeneration of tumor cell in the lesion was a reason for keeping hypodense after enhancement. Among these 27 resceted lesions, the tumor cell in 12 lesions Hyaline degeneration. Secondly, the vascular supply was deficient in the lesions. Takaysu et al [4] reported that many well-differentiated or early hepatocellular carcinomas were hypovascular. Among these 27 resected lesions, the differentiation of the tumor cell was grade Ⅱ in 21 lesions. However, only 10 of 27 were hypovascular and the other 17 were hypervascular histopathologically. It could be concluded that the SHCC with hypodense were not necessarily hypovascular; the decrease of vessel was just one of the reasons that the tumors showed hypodense. The reason why the vascular supply to the tumor was plentiful while the lesion kept hypodense during dual-phase helical CT might be follows: 1) the blood sinus in the lesion were compressed by the tumor tissue and became so circuitous that the blood flew

slowly. 2) the vessels in the lesion or around the lesion had tumor embolus which blocked the supplying blood. Lim et al [3] found that the enhancing degree of the tumor was dependent on the degree of the hepatic arterial vascular supply, while the surrounding parenchyma was dependent on the portal venous blood supply. When the arterial blood supply to tumor was not sufficient enough to enhance the tumor higher than the surrounding hepatic parenchyma, the tumor will be hypodense. Moderately or poorly differentiated hepatocellular carcinoma was almost solely blood supplied by the hepatic arteries [9]. Hwang et al [10] reported that moderately or poorly differentiated hepatocellular carcinoma would present hypodense persistently during the arterial-, portal- and delayed-phase of helical CT when the arterial blood supply to a tumor was not sufficient enough. In general, the histopathologic basis of the hypodense SHCC during dual-phase helical CT scan was various.

4.3 Differential diagnosis

In this study, 24 of 33 lesions were diagnosed as SHCC based on the above-mentioned characteristic CT appearance. Therefore, there are some difficulties in diagnosing hypodense SHCC during dual-phase helical CT scan. Obviously, it should be differentiated from other hypodense hepatic disease. The common hypodense hepatic diseases are as follows:

Hepatic metastases: Hypovascular hepatic metastases also manifested hypodense during helical CT dual-phase enhancement, thus it should be differentiated from hypodense SHCC. Metastases are usually numerous foci; due to ischemia and necrosis in the center of the tumor, the lesion will show the more hypodense areas in the lesion. On the other hand, due to incomplete necrosis at the periphery of the lesion, there usually remains a rim with irregular contour. The density of rim is lower than the adjacent hepatic parenchyma but higher than the necrotic tumor center, and it is called "halo sign" [11]. This feature is useful to differentiate metastases from the hypodense SHCC.

Hepatic inflammatory pseudotumor: Histopathologically, a common type of hepatic inflammtory pseudotumor is composed of focal tissue of inflammatory necrosis so that it keeps hypodense during helical CT dual-phase enhancement. However, the lesion is characteristically demonstrated as homogenous hypodense. Spots of more hypodense areas could not be found in the lesion. Simultaneously, the surrounding hepatic parenchyma may present small wedge shape or patchy of enhancing zone during the hepatic arterial phase [12], which is caused by the inflammatory hyperemia involving the tissue near the inflammtory lesion. In contrast, SHCC lacks this feature.

Liver tuberculosis: In the nodular-type lesion, caseous necrosis may present as focal hypodense and should be differentiated from SHCC with hypodense. When spot-like or sandy calcium sediments were found in the lesion, the diagnosis was inclined to the tuberculosis [13]; if the lesion lacks calcified foci, the feature is similar to the inflammatory pseudotumor, which is dominantly composed of inflammatory tissue, thus it is difficult to differentiate them. However, it is relatively easy to differentiate hepatic tuberculosis from SHCC with hypodense after enhancement because the latter always has spots of more hypodense areas in the lesion, but the former usually manifests as homogenous hypodense.

Hepatic malignant lymphoma: The lesion may present as nodular hypodense in the liver. In spite of the fact that the lesion may enhance slightly during dual-phase CT scan, the density is still lower than the hepatic parenchyma after enhancement [14]. So it should been differentiated from SHCC with hypodense. The differences include followings: the malignant lymphoma commonly manifests multiple lesions; moreover, the border of the lesion is fairly clear and smooth, the density in the lesion is homogenously low due to no necrosis. Conversely, SHCC commonly manifests solitary lesion. On the other hand, the border of the lesion is commonly unclear in non-enhancing CT scan and becomes slightly irregular after enhancement. There are flecks of more hypodense areas in the lesion. Therefore, they can be distinguished.

Infracted Regenerative nodules: it is a rare abnormality in cirrhotic liver. Kim T et al [15] reported that such lesions were depicted as different-appearing nodular lesions of hypodense in non-enhancing CT scan and as heterogenous enhancement with regions of iso- and hypodense compared with hepatic parenchyma in enhancing CT scan. Regions that kept isodense as surrounding hepatic parenchyma were histologically consistent with retained viable tissues or the fibous revasculari-

zation. Conversely, the regions that kept hypodense in CT were necrotic tissues, hemorrhage, or fibrous tissues with no or minimal revascularization on histologic analysis.

Funding

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