Full Length Research Paper

Quantitative analysis of hepatocellular adenomas with triphasic contrast enhanced multislice spiral computed tomography (MSCT)

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The purpose of this study is to evaluate the enhancement characteristics of hepatocellular adenomas with triphasic contrast enhanced computed tomography (CT) by quantitative analysis of 19 lesions in 11 patients. There were significant differences between the attenuation values of hepatocellular adenomas and liver in unenhanced, arterial and delayed phases, but there were no significant differences in portal venous phase. The attenuation values of tumors ≤5 cm were significantly higher than tumors >5 cm in arterial phase, but there were no significant differences in other phases. Triphasic contrast enhanced multislice spiral computed tomography (MSCT) scan combined with quantitative evaluation is valuable in detecting and differentiating hepatocellular adenomas.

Key words: Adenoma, liver cell, tomography, spiral computed, quantitative evaluation, contrast enhancement.

INTRODUCTION

Hepatocellular adenoma is a rare benign hepatic neoplasm with characterized risk for hemorrhage and may undergo malignant transformation (Tao, 1991; Foster and Berman, 1994; Strobel et al., 2008). It is hard to distinguish it from other hepatic neoplasms for lack of image characterization, although some articles have focused on it (Ichikawa et al., 2000; Mathieu et al., 1986; Ruppert-Kohlmayr et al., 2001; Winterer et al., 2006; Kerl in et al., 1983). Diagnosis of hepatocellular adenoma can be based on its enhancement pattern (Mathieu et al., 1986). Quantitative analysis as a method to evaluate enhancement pattern, is an appropriate tool used to diagnose and differentiate hepatocellular adenoma (Ruppert-Kohlmayr et al., 2001).

The purpose of this study is to evaluate enhancement characteristics of hepatocellular adenomas with triphasic contrast enhanced multi-slice spiral CT (MSCT) scans by quantitatively analyzing 19 lesions in 11 patients, and to improve CT diagnostic accuracy.

MATERIALS AND METHODS

Patients

The study group consisted of 11 patients with 19 hepatocellular adenomas (13 confirmed by operation, six confirmed by percutaneous biopsy) from our institutions between September 2004 to May 2009. Eight patients had solitary adenoma and three patients had multiple lesions (one patient with two adenomas, one with four adenomas and one with five adenomas). The mean age was 31.5 years (range, 19 - 62 years). Of the 11 patients, eight were females and three were males. Six cases of hepatocellular adenomas were discovered fortuitously. Two other patients were explored because of acute hemorrhage. Other clinical symptoms prompted discovery of the remaining cases: pain in the right abdomen in three patients (associated with a palpable mass in one). Two female patients had a history of oral contraceptive use. One woman was combined with glycogen-storage disease.

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Abbreviations: CT, Computed tomography; MSCT, multislice spiral computed tomography; HAP, hepatic arterial phase; PVP, portal venous phase; DP, delayed phase; ROI, region-of-interest; UP, unenhanced phase; FNH, focal nodular hyperplasia.
Computed tomography (CT) protocol and contrast material infusion

The CT scanner used was Toshiba Aquilion 16 CT. They were examined by hepatic plain CT firstly, and then were examined on contrast enhanced CT scan. All patients received low osmolarity contrast medium Iopamidol (Bracco S.P.A., Italy) 300 mg I/mL 100mL at a flow rate of 3 – 4 mL/s, by means of a power injector (AD2002-CT, MEDEX, France) through an 18- or 20-gauge plastic intravenous catheter placed in an ulnar vein. Bolus-tracking technique (Sure Start, Toshiba, Tokyo, Japan) was performed in order to optimize scan delays for hepatic arterial phase (HAP) scanning automatically. The mean injection-to-scan delay for HAP was 28 s (range, 25 - 32 s) and the timing of the contrast enhanced CT scans was defined: Portal venous phase (PVP) imaging was initiated 30 - 40 s after the start of HAP. Delayed phase (DP) images were obtained at a fixed delay of 180 s after the start of contrast medium injection. Patients were demanded to hold breath in the scanning. The CT scanner detector configuration was 16×0.5 mm. The tube voltage applied throughout all CT studies was 120 kVp and the tube current was adjusted according to patient characteristics.

Morphology and quantitative analysis

CT findings of the lesions including size, location and the contrast pattern were recorded by two experienced radiologists (with 6 and 15 years experience, respectively as a gastrointestinal radiologist) retrospectively together.

The attenuation values of lesions, liver parenchyma and tumor-to-liver contrast in each phase and the contrast enhancement of lesions and liver parenchyma in each contrast enhanced phase were calculated and analyzed. The attenuation values were measured for the hepatic parenchyma and tumors in all the 11 patients using a circular region-of-interest (ROI) cursor in the unenhanced scans and three phases of the contrast enhanced scans. In the liver, attenuation values were measured in at least three separate areas on the image and all measured attenuation values were averaged in each phase. An attempt was made to maintain a constant ROI area of approximately 2 cm². Visible blood vessels, bile ducts, and artifacts were carefully excluded from the ROI measurements in the hepatic parenchyma. Tumor attenuation values were measured in one to three separate portions of the tumor according to lesion size. The tumor ROI was chosen to be approximately 1 cm² while still avoiding regions of hemorrhage, tumor capsule, necrosis, calcifications, and shunt vessels. Tumor-to-liver contrast as an indicator of the conspicuity of hepatic tumors was defined as the difference in attenuation between the hepatic tumor and hepatic parenchyma. It was calculated with the formula: Tumor-to-liver contrast = attenuation of tumor – attenuation of liver parenchyma

The contrast enhancement of the tumor and liver during each phase was calculated as the absolute difference in the attenuation values of the adenoma and liver in Hounsfield units between the unenhanced scan and each contrast enhanced scan.

All the lesions were divided into two size categories: tumors ≤5 cm and tumors >5 cm. The attenuation values of lesions and tumor-to-liver contrast of two size categories in each phase were recorded and compared.

Statistical analysis

Software statistical package for the social sciences (SPSS) 13.0 was used to analyze the results. The attenuation values of lesions, liver parenchyma and tumor-to-liver contrast and the contrast enhancement of lesions, liver parenchyma in each phase were analyzed by paired t test. The attenuation values of hepatocellular adenomas and tumor-to-liver contrast of two size categories were compared by student’s t test. A p value less than 0.05 was considered statistically significant at the 95% confidence interval.

RESULTS

Morphology

We found 19 hepatocellular adenomas in the 11 patients. Eight patients had solitary adenoma and three patients had multiple lesions (one patient with two adenomas, one with four and one with five adenomas). The tumors were predominantly in the right hepatic lobe (13 of 19). The size of the tumors ranged from 1.2 cm to 12 cm (mean 5.1cm) and there were seven lesions ≤5 cm in size and 12 lesions >5 cm.

In unenhanced CT, the tumors were demonstrated as hypodense (10/19) or slightly hypoattenuating (9/19) masses. The margins of the tumors were well defined in 15 of 19 lesions. Twelve tumors showed homogeneous and seven lesions were heterogeneous. There were two lesions demonstrated as hypoattenuating masses, with an irregular hyperattenuating region (Figure 1a), indicating intralesional hemorrhage which was verified at surgery.

In HAP, seven lesions showed as significant hyperattenuating homogeneous masses (Figure 2a), in which five lesions were ≤5 cm. There were five lesions which showed as hyperattenuating heterogeneous masses and six lesions showed as slightly hyperattenuating heterogeneous masses (Figures 1b and 1c) and one lesion was slightly heterogeneous hypodense.

On PVP and DP images, the adenomas showed all kinds of density. Of the 19 adenomas, one was hyperattenuating and five were slightly hyperattenuating to liver on PVP images, while seven were isoattenuating and six were hypoattenuating to liver on PVP images. The isoattenuating tumors would be invisible on PVP images if a tumor capsule, displaced vessels, or exophytic distortion of the hepatic surface had not been noted (Figure 3b). On DP images, eight lesions demonstrated as isoattenuating tumors and 10 lesions showed as slightly hypoattenuating or hypoattenuating tumors while one lesion was slightly hyperdense.

A tumor capsule was identified in 15.8% (3/19) and surrounded the adenoma partly or completely. Tumor capsules were seen as hyperattenuating (n = 2) (Figure 1b) or hypoattenuating (n = 1) (Figure 3a) relative to both liver and adenoma on HAP images, and as hyperattenuating on PVP and DP.

Central scars were detected in 15.8% (3/19) of all hepatocellular adenomas. Scars were present in all large (>5 cm) hepatocellular adenomas. Central scars were seen as hypoattenuating relative to adenoma on triphasic
Figure 1a. Multiphasic transverse CT sections of hepatic adenoma in a 28-year-old woman. Non enhanced CT stion demonstrates a heterogeneous, predominantly hypoattenuating mass (black arrow), with an irregular hyperattenuating region (white arrows) that proved as hemorrhage.

Figure 1b. Multiphasic transverse CT sections of hepatic adenoma in a 28-year-old woman. HAP image shows heterogeneous enhancement of the tumor with hypoattenuating necrosis (white arrows). The tumor capsule (black arrows) is hyperattenuating relative to both liver and adenoma.
Figure 1c. Multiphasic transverse CT sections of hepatic adenoma in a 28-year-old woman. On delayed phase image the necrosis (arrows) shows more clearly.

Figure 2a. Transverse CT sections and maximum intensity projection (MIP) image shows an adenoma in a 65-year-old man. HAP stions show a well-defined, homogeneous hyperattenuating mass (white arrows), with a feeding vessel (black arrows) originating from the left hepatic artery.
Figure 2b. Transverse CT sections and maximum intensity projection (MIP) image show an adenoma in a 65-year-old man. MIP image shows the feeding artery (black arrow) and the tumor (white arrow).

Figure 3a. Multiphasic transverse CT sections of hepatic adenoma in a 22-year-old woman. On HAP image tumor shows marked enhancement. The central scar (white arrow) and tumor capsule (black arrows) shows hypoattenuating.

contrast enhanced images in two cases. But in the other case central scar showed enhancement in DP (Figure 3c).

Hemorrhage and necrosis were present in the adenomas in 10.5% (2/19) and 21.1% (4/19), respectively. All hemorrhage lesions and most necrosis lesions (3/4) were larger than 5 cm. Large intratumoral vessel (Figure 2b) was found in one case.
Figure 3b. Multiphasic transverse CT sections of hepatic adenoma in a 22-year-old woman. PVP image shows nearly homogeneous enhancement of the adenoma, which is now isoattenuating to liver and would be invisible except for its capsule (arrows) and central scar.

Figure 3c. Multiphasic transverse CT sections of hepatic adenoma in a 22-year-old woman. Delayed image the adenoma shows as a hypoattenuating area. The central scar (white arrow) and tumor capsule (black arrows) show hyperattenuating to the tumor and liver.

Quantitative analysis

Measurement parameter: Attenuation

Attenuation comparison between adenomas and liver in unenhanced phase (UP) and three contrast enhanced phases is shown in Table 1. From the table we can see that there were significant differences between attenuation values of lesions and liver parenchyma in UP, HAP and DP, but there were no significant differences in PVP. The results of attenuation dynamics of hepatocellular adenomas...
Table 1. Attenuation comparison between lesions and liver in unenhanced phase and three contrast enhanced phases.

<table>
<thead>
<tr>
<th>Phases</th>
<th>Hepatocellular adenoma</th>
<th>Liver parenchyma</th>
<th>Tumor-to-liver contrast</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UP</td>
<td>48.3±7.8</td>
<td>61.2±4.7</td>
<td>-12.9±6.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HAP</td>
<td>107.5±10.7</td>
<td>74.2±3.3</td>
<td>33.3±5.9</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PVP</td>
<td>98.8±6.3</td>
<td>101.3±5.1</td>
<td>-2.5±7.1</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>DP</td>
<td>83.2±7.2</td>
<td>94.2±4.4</td>
<td>-11.0±5.6</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Attenuation values and tumor-to-liver contrast (HU, x ±s). UP = Unenhanced phase, HAP = hepatic arterial phase, PVP = portal venous phase, DP = delayed phase.

Figure 4. Graphs show time–attenuation curves of hepatocellular adenoma (solid line) and hepatic parenchyma (dotted line) during unenhanced phase (UP), hepatic arterial phase (HAP), portal venous phase (PVP) and delayed phase (DP) MSCT. Attenuation values of hepatocellular adenoma were significantly higher than hepatic parenchyma in HAP, but lower in UP and DP.

Table 2. Contrast enhancement comparison between lesions and liver in three contrast enhanced phases.

<table>
<thead>
<tr>
<th>Phases</th>
<th>Hepatocellular adenoma</th>
<th>Liver parenchyma</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP</td>
<td>59.2±8.2</td>
<td>13.0±4.3</td>
<td>46.2±7.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PVP</td>
<td>50.5±6.3</td>
<td>40.1±5.7</td>
<td>10.4±6.1</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>DP</td>
<td>34.9±5.2</td>
<td>33.0±4.9</td>
<td>1.9±5.6</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Enhancement values and difference (HU, x ±s). HAP = hepatic arterial phase, PVP = portal venous phase, DP = delayed phase.

and liver parenchyma were visible on graphs of the time–attenuation curves in Figure 4.

**Calculated parameter: Enhancement**

Contrast enhancement comparison between adenomas and liver parenchyma in three contrast enhanced phases is shown in Table 2. In HAP, the enhancement of hepatocellular adenoma was highest, while the enhancement of hepatic parenchyma was lowest. The differences of contrast enhancement between lesions and liver were statistically significant in HAP and PVP, but there were no significant differences in DP. The results of contrast enhancement dynamics of hepatocellular adenomas and liver were visible on graphs of the time-enhancement curves in Figure 5.

**Attenuation comparison between two size categories**

In HAP, the attenuation values and tumor-to-liver contrast of tumors ≤5 cm were significantly higher than tumors >5 cm, but there were no significant differences between two
size categories in the other phases. Comparison of attenuation of adenoma and tumor-to-liver contrast between two size categories is shown in Table 3.

**DISCUSSION**

Hepatocellular adenoma is a benign, mostly incidentally discovered hepatic neoplasm which occurs predominantly in young and middle-aged women (Winterer et al., 2006). It is hard to distinguish it from other hepatic neoplasms for lack of image characterization, although some articles have focused on it (Ichikawa et al., 2000; Mathieu et al., 1986; Ruppert-Kohlmayr et al., 2001; Winterer et al., 2006; Kerlin et al., 1983).

Diagnosis of hepatocellular adenoma can be based on its enhancement pattern (Mathieu et al., 1986). Quantitative analysis as a method to evaluate enhancement pattern, is an appropriate tool to be used to diagnose and differentiate hepatocellular adenoma (Ruppert-Kohlmayr et al., 2001). However, there were few researchers who used the quantitative method to evaluate hepatocellular adenoma. Andrea et al. (2001) used the single detector row helical CT combined with quantitative evaluation to analyze hepatocellular adenoma in order to differentiate it from other tumors. But their analysis had some limitations. First, the patients of hepatocellular adenoma in their evaluation were only five. Second, the attenuation values in DP could not be calculated, so the entire enhancement characteristics of hepatocellular adenomas did not show well. Mathieu et al. (1986) had also evaluated it, but the CT scanner and scan protocol they used have become outdated. MSCT which is now being widely used has dramatically accelerated scan acquisition in liver and could easily catch the exact time of each contrast enhanced phase with the bolus-tracking technique. In order to better understand the enhancement patterns of hepatocellular adenoma, 11 cases with MSCT to characterize it was reviewed.

Our study showed that there were significant differences in UP, HAP and DP between the attenuation values of hepatocellular adenomas and hepatic parenchyma, but there were no significant differences in PVP (Table 1). In the enhanced CT, the tumor-to-liver contrast in HAP was maximal and showed that the tumor was highly conspicuous in the phase. This is in accord with the contrast...
enhancement shown in Table 2, in which the enhancement of hepatocellular adenoma was highest in HAP, while the enhancement of hepatic parenchyma was lowest in this phase. We thought that tumors showed arterial enhancement because most hepatocellular adenomas are hypervascular, just as previously reported (Kerlin et al., 1983; Welch et al., 1985); but this hypervascularity is extremely transient. On PVP and DP, the tumors showed all kinds of density, especially isodense or ovoid. The reason is that adenomas consist almost entirely of uniform hepatocytes and a variable number of kupffer cells which is similar to the liver (Tao, 1991; Foster et al., 1994; Strobel et al., 2008).

Hepatocellular adenomas are frequent candidates for surgical intervention because of their potential for malignant transformation and their propensity for spontaneous rupture and hemorrhage, in the case of larger (>5 cm) lesions in particular (Nagorney, 1995; Libbrecht et al., 2001; Terkivatan et al., 2001). Dokmak et al. (2009) also reported that the risk of complications of hepatocellular adenoma was associated with tumor size (>5 cm). From our cases, we found that the bigger the tumor shows more likely as a heterogeneous mass and hemorrhage, the more necrosis and central scar are likely happened; the smaller the tumor, more likely it is a homogeneous mass. In our experience all the lesions with hemorrhage and central scar and most necrosis lesions (3/4) were larger than 5 cm. Quantitative analysis also showed that the attenuation values of tumors ≤5 cm were significantly higher than tumors >5 cm in HAP, though the regions of hemorrhage, tumor capsule, necrosis, calcifications, and shunt vessels were avoided in measurement. We infer the reason to be that the large hepatocellular adenomas are easier to be short of blood supply.

The difficulty in characterizing hepatocellular adenomas with radiologic techniques is partially due to the wide range of histopathologic characteristics, including hemorrhage, fatty change, peliotic change, capsules, central scars, and large intratumoral vessels (Kerlin et al., 1983). Most of these characteristics such as hemorrhage, capsules, central scars, and large intratumoral vessels were seen in our cases. We analyzed the frequency of them, but we could not compare all these findings with pathological results because six lesions in this study were confirmed by percutaneous biopsy which was an important limitation to our study.

A central area of scarring can be seen in most liver tumors and the scar characteristic can be a statistically significant differentiating feature (Blachar et al., 2002). In this study central scars were detected in 15.8% (3/19) of all hepatocellular adenomas. Central scars were seen as hypoattenuating on triphasic contrast-enhanced images in two cases. But in the other case, central scar showed hyperattenuating in DP (Figure 3c). From that, we believe that the delayed scar enhancement is not a specific feature and cannot be used to differentiate other tumors from adenoma, such as focal nodular hyperplasia (FNH) and fibrolamellar hepatocellular carcinoma.

Quantitative analysis with triphasic contrast enhanced CT is not only a method to help us understand the contrast pattern of hepatocellular adenoma, but also an appropriate diagnostic tool to be used to differentiate hepatocellular adenoma from FNH (Ruppert-Kohlmayr et al., 2001). Whether it can also be used to differentiate hepatocellular adenomas from malignant tumors is an interesting and challenging question. We would want to compare the quantitative parameters of hepatocellular carcinoma with our results presented here in a future study.

In summary, quantitative evaluation is a useful method to help understand the contrast enhanced pattern of hepatocellular adenoma. Its combination with morphology features on triphasic contrast enhanced MSCT images can help us diagnose and differentiate hepatocellular adenomas from other hepatic tumors.

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