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MDCT features of hepatocellular carcinoma (HCC) in non-cirrhotic liver

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KEYWORDS
Hepatocellular; MDCT; Non-cirrhotic liver; Hyperenhancement; Washout

Abstract

\textbf{Purpose:} To describe the multidetector row computed tomography (MDCT) imaging features of HCC that develops in patients who are free from underlying liver cirrhosis and to determine if the MDCT presentation of this specific tumor differs from that of the more common HCC that develops in patients with liver cirrhosis using a retrospective case-control study.

\textbf{Patients and methods:} The MDCT examinations of 38 patients with HCC in non-cirrhotic liver (group 1) were quantitatively and qualitatively analyzed and compared to those obtained in 38 patients with HCC in cirrhotic liver (group 2) matched for age and gender. Quantitative and qualitative characteristics of HCC of both groups were compared using univariate analysis.

\textbf{Results:} HCCs were significantly larger in group 1 (81.5 mm ± 55.5) than in group 2 (44.5 mm ± 39.1 SD; \( P = 0.0015 \)). In group 1, HCCs were more frequently single tumors (87\%) than in group 2 (37\%) (\( P < 0.0001 \)), encapsulated (92\% vs. 47\% respectively; \( P < 0.0001 \)), had more frequently fatty component (24\% vs. 8\%, respectively; \( P = 0.0279 \)) and internal hemorrhage (29\% vs. 3\%, respectively; \( P = 0.0033 \)). No significant differences were found between the two groups for location, hyperenhancement of HCC during the arterial phase, washout during the portal phase, endoluminal portal involvement by HCC, endoportal cruric thrombus, invasion of adjacent organs and underlying liver steatosis.

\textbf{Conclusion:} HCC in non-cirrhotic liver are larger than those observed in cirrhotic liver and more frequently present as a single encapsulated tumor. They have the same patterns of enhancement than HCC that develops in cirrhotic liver.

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The imaging features of hepatocellular carcinoma (HCC) in patients with liver cirrhosis have been well described [1]. The main diagnostic criteria consist of hypervascularization during the arterial phase (i.e., the so-called “wash-in”) and a subsequent washout during the portal phase of enhancement on contrast-enhanced imaging [2]. When these criteria are both present, the diagnosis of HCC is made with high degrees of confidence, thus obviating the need for further confirmatory tumor biopsy [3]. However, these criteria have been developed for HCCs occurring in patients with liver cirrhosis, so that they may not apply for HCCs that develop in patients with non-cirrhotic liver [4].

To our knowledge, a few studies have specifically addressed the issue of imaging presentation of HCC in patients without cirrhosis, although this specific tumor has distinctive features by comparison with the more common HCC that develops in liver cirrhosis [5,6]. Three studies have described imaging criteria for the diagnosis of HCC in non-cirrhotic liver [4,6,7]. Of these, two studies have stressed the importance of making the correct diagnosis of HCC occurring in non-cirrhotic liver because myriad other tumors may have similar presentation [4,6]. Indeed, hypervascular tumor arising in an otherwise healthy or non-cirrhotic liver may correspond to metastatic neuroendocrine tumor, angiosarcoma, epithelioid hemangioendothelioma, angiomylipoma, focal nodular hyperplasia or hepatocellular adenoma [4].

The goal of this study was to describe the multidetector row computed tomography (MDCT) imaging features of HCC that develops in patients who are free from underlying liver cirrhosis and to determine if the MDCT presentation of this specific tumor differs from that of the more common HCC that develops in patients with liver cirrhosis using a retrospective case-control study.

Patients and methods

Patients

The database of our institution was queried from January 2003 to December 2014 inclusively to identify all patients with HCC that developed in non-cirrhotic liver who were investigated during this period. Initially retrieved patients were further included in the study when they had MDCT examinations available for review, a histopathologically confirmed HCC, normal liver function test results, no liver dysmorphism on MDCT and a METAVIR score ≤ F3. Exclusion criteria were the absence of MDCT examinations, absence of definite histological diagnosis of HCC and F4 METAVIR score. Our review board approved the retrospective data analysis. The need for informed consent was waived.

The final cohort study (group 1) consisted of 38 patients (35 men and 3 women) with a mean age of 68.5 years ± 11.5 SD (range, 32–83 years). Four patients had a prior history of viral hepatitis B (two chronic and two cured), and two patients had a prior history of viral hepatitis C. The alphafetoprotein level was available for 27/38 patients (71%). HCC was discovered incidentally in 27/38 patients (71%) or because of abdominal symptoms in 4/38 patients (11%), altered general status in 4/38 patients (11%), hemoperitoneum in 2/38 patients (5%) or during yearly follow-up for viral hepatitis in 1/38 patient (2%). Surgical resection was performed in 30/38 patients (79%).

The results of histopathological analysis were available for review in all patients. Tissue samples from HCC were obtained after surgical resection in 30/38 patients (79%) or after percutaneous biopsy in 8/38 patients (21%). All histopathological examinations were performed by a pathologist with a 15-year experience in hepatic tumors who established the Edmonson grade. Tissue samples were also obtained from the liver parenchyma to confirm the absence of cirrhosis. Fibrosis was classified according to METAVIR score. The METAVIR scoring system has been described elsewhere [8]; briefly, the METAVIR fibrosis score ranges from F0 to F4 (absent, minimal, moderate, severe and confirmed cirrhosis) [8].

A control group (group 2) was identified, which consisted of 38 patients who were matched for age and gender and who had undergone MDCT during the same period for HCC that developed in a cirrhotic liver. They were 38 patients (35 men and 3 women) with a mean age of 68.6 years ± 11 (SD) range, 34–83 years). In this group, HCC was histopathologically confirmed in all patients, either after percutaneous biopsy in 36/38 patients (95%) or after surgical resection in 2/38 patients (5%). Cirrhosis was also histopathologically confirmed in all patients.

MDCT protocol

All patients underwent MDCT of the abdomen and pelvis using a VCT Lightspeed® (General Electric Healthcare, Milwaukee, USA) using a standardized multiphasic protocol that consisted of an unenhanced pass followed by three contrast-enhanced passes obtained at 10, 70 and 120 s after the start of intravenous administration of iodinated contrast material. A non-ionic iodinated contrast material (Iodixanol®, GE-Healthcare, Little Chalfont, UK) containing 350 mg of iodine per milliliter was injected at a dose of 1.5 mL/kg of body weight and administered at a rate of 3–4 mL/s using an automated power injector. Images were acquired in cephalocaudal direction, during one breath-hold while the patient was in supine position.

Imaging and reconstruction parameters were as follows: voltage, 120 kVp; tube current, 120–170 effective mA; axial resolution, 0.625 mm; beam collimation, 40 mm; gantry rotation time, 0.6 s; beam pitch, 0.6. After acquisition, CT data were reconstructed twice using a B30 soft tissue reconstruction kernel in the axial plane. A first set of axial images was obtained with a thickness of 2 mm at 2 mm intervals. A second set was obtained at 0.625 mm thickness at 0.5 mm intervals for multiplanar reconstructions and maximum intensity projection (MIP) views. In addition, all patients of both groups had MDCT of the thorax.

Image analysis

For this retrospective study, MDCT images were reviewed in a random manner using the workstation of a picture archiving system (PACS) by two experienced abdominal radiologists working in consensus. The two radiologists were aware of the original goal of the study but did not know if the patients had or not underlying liver cirrhosis. During the reading sessions, axial images, 3-mm thickness multiplanar reconstructions
and 10—15 mm thickness MIP views were analyzed as a single imaging set. To avoid review bias, MDCT images were analyzed without any information relative to the patients. Several variables were evaluated by using a standardized data collection form. For each reading, the two radiologists reached a consensus opinion. In patients with multiple lesions of HCC, only the appearance of the dominant lesion was analyzed.

Quantitative analysis
Quantitative variables included the number of HCC nodules and dimensions of dominant HCC (i.e., largest and shortest axial diameters). Dimensions were calculated with electronic callipers on magnified images by the two observers who agreed on the results for each measurement.

Qualitative analysis
MDCT images obtained before intravenous administration of iodinated contrast material were analyzed for presence of fat content and internal hemorrhage within HCC.

MDCT images obtained after intravenous administration of iodinated contrast material were analyzed with respect to the presence of a complete enhancing peripheral capsule [1,5], hyperenhancement of HCC during the arterial phase (i.e., wash-in) (Fig. 1) [3], washout of HCC during the portal or late phase [3], portal or venous invovlement by HCC [1], intraportal curvilinear thrombus [9] and presence of invasion of adjacent organs.

On MDCT, the tumor capsule was defined as a thin curvilinear border that surrounded at least half of the tumor and had attenuation values different from those of the liver [10]. No attempt was made to differentiate between true and pseudocapsule. Venous and/or portal obstruction by HCC was defined as distention of the hepatic and/or portal vein lumen by an enhancing, endovenuous bud originating from the tumor [10]. Intraportal curvilinear thrombus was defined by the presence of spontaneously hyperattenuating intraportal area on unenhanced MDCT images or by the presence of non-enhancing intraluminal portal defect on enhanced MDCT images [9].

Fat content within HCC was considered to be present when areas with attenuation values < −10 Hounsfield units (HU) were observed on unenhanced MDCT images [1,2]. Internal hemorrhage within HCC was considered to be present when spontaneously hyperattenuating areas were identified on unenhanced MDCT images [1]. The diagnosis of hepatic steatosis was evidenced by measurement of hepatic attenuation values in all patients, using region-of-interest (ROI) measurement and compared with that of the spleen on unenhanced MDCT images. The hepatic parenchyma was considered steatotic when splenic attenuation value was at least 10 HU greater than that of the liver [11].

Data collection
For all patients, the results of MDCT examinations and results of histopathological analyses were collected retrospectively by the study coordinator. For all patients qualitative and quantitative variables were tabulated using a standardized data collection form.

Statistical analysis
Statistical analyses were performed by using software (R, version 3.1.2, R Foundation, http://www.r-project.org/).

Descriptive statistics were calculated for all variables evaluated at MDCT (Table 1). Quantitative (continuous) data included means, 95% confidence intervals (CIs), medians and ranges. Qualitative (binary) data included frequencies and 95% CIs (Table 2). To identify variables associated with the diagnosis of HCC in healthy at MDCT, we compared patients in group 1 and patients in group 2. Due to small cell sizes for qualitative data, those variables were compared with the Fisher exact test. As, the number of cases was sufficiently high to assume a normal distribution, a parametric test was used for quantitative comparisons. The unpaired Student’s t-test was used to determine the significance of the differences in size between cirrhotic and non-cirrhotic liver. All statistical tests were two-tailed and a P value of less than .05 was considered to indicate a significant difference.
Table 1 Comparison of MDCT findings for quantitative criteria between 38 patients with HCC in non-cirrhotic liver (group 1) and 38 patients with HCC in cirrhotic liver (group 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (HCC in non-cirrhotic liver; n = 38)</th>
<th>Group 2 (HCC in cirrhotic liver; n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.5 ± 11.5 62.5 [32–83]</td>
<td>68.6 ± 11 62 [34–83]</td>
<td>0.9676</td>
</tr>
<tr>
<td>Short axis of HCC (mm)</td>
<td>64.7 ± 38.4 54 [12–168]</td>
<td>34.8 ± 31.2 22.5 [9–150]</td>
<td>0.0004</td>
</tr>
<tr>
<td>Large axis of HCC (mm)</td>
<td>81.5 ± 55.5 60 [12–200]</td>
<td>44.5 ± 39.1 28 [14–190]</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

SD: standard deviation; significance was searched for using the Student t-test.

Table 2 Comparison of MDCT findings for qualitative criteria between 38 patients with HCC in non-cirrhotic liver (group 1) and 38 with HCC in cirrhotic liver (group 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single tumor</td>
<td>33 (87)</td>
<td>14 (37)</td>
<td>&lt;0.0001</td>
<td>0.091</td>
</tr>
<tr>
<td>Location in the right liver</td>
<td>23 (60)</td>
<td>19 (50)</td>
<td>0.4892</td>
<td>0</td>
</tr>
<tr>
<td>Wash-in</td>
<td>33 (87)</td>
<td>38 (100)</td>
<td>0.0543</td>
<td>0</td>
</tr>
<tr>
<td>Washout</td>
<td>33 (87)</td>
<td>36 (95)</td>
<td>0.2619</td>
<td>0.36</td>
</tr>
<tr>
<td>Fat content</td>
<td>9 (24)</td>
<td>3 (8)</td>
<td>0.0279</td>
<td>4.681</td>
</tr>
<tr>
<td>Internal hemorrhage</td>
<td>11 (29)</td>
<td>1 (3)</td>
<td>0.0033</td>
<td>13.45</td>
</tr>
<tr>
<td>Peripheral capsule</td>
<td>35 (92)</td>
<td>18 (47)</td>
<td>&lt;0.0001</td>
<td>18.12</td>
</tr>
<tr>
<td>Portal involvement by HCC</td>
<td>3 (8)</td>
<td>6 (16)</td>
<td>0.4799</td>
<td>0.475</td>
</tr>
<tr>
<td>Venous involvement by HCC</td>
<td>1 (3)</td>
<td>0</td>
<td>&gt;0.99</td>
<td>+∞</td>
</tr>
<tr>
<td>Invasion of adjacent organs</td>
<td>0</td>
<td>1 (3)</td>
<td>&gt;0.99</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>6 (16)</td>
<td>3 (3)</td>
<td>0.4799</td>
<td>1.917</td>
</tr>
</tbody>
</table>

Data are raw numbers; numbers in parentheses are percentages; significance was searched for using the Fisher exact test; all percentages were rounded to the nearest first digit.

Results

MDCT features

The results of descriptive analysis for quantitative and categorical data are reported in Tables 1 and 2, respectively.

In group 1, HCCs were significantly larger for both largest (82.5 mm ± 55.2 SD) and shortest (64.7 mm ± 38.4 SD) axial diameters (P = 0.0015 and P = 0.0004 respectively).

HCC presenting as a single tumor was more frequently observed in group 1 (33/38 patients; 87%) than in group 2, (14/38 patients; 37%) (P < 0.0001).

HCCs containing internal fat were more frequently observed in group 1 (9/38; 24%) than in group 2 (3/38; 8%) (P = 0.0279). Similarly, HCCs containing internal hemorrhage were more frequently observed in group 1 (11/38; 29%) than in group 2 (11/38; 3%) (P = 0.0033).

HCCs were more frequently encapsulated in group 1 (35/38; 92%) than in group 2 (Fig. 2), (18/38; 47%) (P < 0.0001).

No significant differences were found between the two groups of patients for tumor location (P = 0.4892), hyper-enhancement of HCC during the arterial phase (P = 0.0543), washout during the portal phase (P = 0.2619), endoluminal portal involvement by HCC (P = 0.4799), endoportal cruciform thrombus (P > 0.99), invasion of adjacent organs (P > 0.99) and underlying liver steatosis (P = 0.4799).

In group 1, 3/38 patients (8%) had distant synchronous metastases incidentally discovered and asymptomatic at the time of diagnosis. Distant synchronous metastases involved the sacrum in two patients and the lung in one patient. In group 2, 0/38 patients (0%) had synchronous metastases.

Discussion

Our study shows that HCC that develops in non-cirrhotic liver is predominantly a single, large, and encapsulated tumor that shows similar patterns of enhancement than the more common HCC that develops in cirrhotic liver.

In our study, we found that HCC in cirrhotic and non-cirrhotic patients have the same patterns of enhancement. This result is consistent with those reported by Di Martino et al. [4]. We found that 87% of HCCs that developed in non-cirrhotic liver were hypervascular during the arterial phase of enhancement and exhibited washout during the portal phase. These features correspond to the Barcelona criteria for HCC [3]. Therefore, diagnostic imaging criteria that have been developed for HCC that develops in cirrhotic liver can be applied to HCC in non-cirrhotic patients.

Beyond enhancement patterns, other MDCT features are of importance to characterize HCC in non-cirrhotic liver. Indeed, HCC in non-cirrhotic liver differs from HCC cirrhotic liver...
liver in terms of number, dimension, location, fat content, intratumoral hemorrhage and encapsulation.

In our study, 33/38 (87%) HCC in non-cirrhotic liver presented as a single lesion. Our results slightly differ from those of other researchers who found HCC in non-cirrhotic liver presenting as a single focal liver lesion in 57% of patients [7]. Conversely, in patients with cirrhotic liver, 63% of HCCs were multifocal as observed in another study [5].

We found a mean largest axial dimension of 81 mm for HCC in non-cirrhotic patients, which is greater than that of HCC in cirrhotic patients. In non-cirrhotic patient, HCC are usually larger than 4 cm at the time of diagnosis because of their asymptomatic development and also because the patients do not have the screening program offered to patients with cirrhosis [7,12,13]. In patients with cirrhosis, HCCs are usually discovered at an early stage [7]. In patients with HCC that develops in non-cirrhotic liver, HCC is predominantly incidentally discovered during the assessment of other diseases.

In our study, a fatty component was more frequently observed in HCC in patients with non-cirrhotic liver (24%) than in HCC in patients with cirrhotic liver (8%). A fatty component is individualized at imaging in approximately 10–17% of HCCs that develop in non-cirrhotic liver [6] and is an indicator of a better prognosis. Interestingly, intracellular fat accumulation is observed in 36% of well-differentiated HCCs in cirrhotic liver [6]. HCCs often contain various degrees of fatty infiltration. Kutami et al. found fat content in 19.6% of nodules of HCC at pathologic examination and reported that fat content is more frequent in small (<1.5 cm) HCC nodules [14]. Large amounts of fat in HCC are usually easily identified at imaging and this finding is often helpful for diagnostic purpose. In this regard, the presence of fat in a liver lesion helps suggest the diagnosis of hepatocellular tumor including focal nodular hyperplasia, adenoma and HCC although, it can also be present in rare lipomatous tumors [15].

We observed foci of hemorrhage in 29% of HCC in non-cirrhotic patients, consistent with the results of other studies [4,10]. It may be assumed that HCC in non-cirrhotic liver is rather a large tumor that is more prone to internal hemorrhage by comparison with HCC in cirrhotic liver.

We found that the majority (92%) of HCCs in non-cirrhotic liver were well-circumscribed and encapsulated and that none of these tumors were infiltrative. In the study of Smalley et al., involving 61 patients, 3% of HCCs in non-cirrhotic liver were infiltrative [16]. We observed tumor encapsulation in 92% of HCCs in non-cirrhotic liver, which is a higher rate than the 50% reported in the literature [12]. Conversely, we observed encapsulation in 47% of HCCs in cirrhotic liver, which is within the range of prior studies [12].

Despite a large tumor size at the time of diagnosis, HCC in non-cirrhotic liver was associated with portal involvement in 8% of patients and synchronous metastases in 8%. By contrast, we found portal involvement by tumor in 6 patients with HCC in cirrhotic liver, although the difference was not significant. However, it has been shown that venous involvement by HCC is significantly more frequent in patients with cirrhosis [7].

In our study population we had 30/38 patients (79%) with HCC in non-cirrhotic liver who could be cured by surgical resection. By contrast, only 5% of patients with HCC in cirrhotic liver had a resectable tumor. It may be assumed that patients with non-cirrhotic liver have greater hepatic functional capabilities so that hepatic function immediately after partial hepatectomy is less compromised by the liver volume reduction [17–19].

Our study has some limitations. First, it is a retrospective case-control study with potential inclusion bias. Second, our results were obtained from a limited cohort study, so that it may be argued that a complete overview of the possible MDCT presentations of HCC in non-cirrhotic liver was not obtained. So, further studies with more case material are needed to confirm our findings.

In conclusion, HCCs that develop in non-cirrhotic liver are larger than those observed in cirrhotic liver and more frequently present as a single encapsulated tumor. One important result of our study is that the same patterns of enhancement of HCC were observed in the two groups of patients. This suggests that the imaging criteria that are
used for the diagnosis of HCC that develops in cirrhotic liver can be extended to the diagnosis of HCC in non-cirrhotic patients. However, further comparative studies with more case material are needed to confirm this assumption.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**


