Findings in Multidetector Computed Tomography in the diagnosis of hepatocellular carcinoma in patients with cirrhosis and correlation with pathology of liver explants

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Abstract
Objectives: To describe the imaging behavior of hepatocellular carcinoma in cirrhotic patients using a dynamic multidetector computed tomography (MDCT) technique, and to correlate these findings with histological tumor grades.
Materials and methods: A retrospective, descriptive observational study was conducted to evaluate 51 nodules in 32 liver transplant patients diagnosed with liver cirrhosis. The pathology of liver explants was used as reference. Nodules with hepatocellular carcinoma histopathology were retrospectively analyzed by computed tomography scans performed pre-transplant. Using a dynamic multidetector computed tomography technique, we evaluated the most common imaging behavior reported in the literature: arterial phase enhancement, washout, capsule, and intratumoral arterial vessels.
Results: Forty-six of 51 (90%) tumors showed arterial enhancement. Of the 46 tumors with arterial enhancement, 39 (85%) had washout in portal-late phase. Five of 51 (10%) were hypovascular. Twenty-two of 51 (43%) had capsule, and 12 of 51 (24%) showed intratumoral arterial vessels. The most frequent combination of findings was the association between arterial phase enhancement and washout in the portal venous-delayed phase (39 of 51 tumors or 76%). The most frequent histological grade was grade II (35 of 51 tumors or 69%). Statistically significant relationships were found between histological grade tumors and imaging behavior, hypovascular and arterial phase enhancement.
Conclusion: In our population, arterial enhancement with washout in the portal venous and delayed phases was observed in most tumors. Our results are consistent with previous reports, demonstrating the high reliability of this imaging pattern for the diagnosis of hepatocellular carcinoma.

Keywords
Cirrhosis; Hepatocellular Carcinoma; Dynamic Multidetector Computed Tomography

Introduction
Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in men and the seventh in women, with a five-year survival rate of approximately 12%. The main predisposing factor for the development of HCC is cirrhosis1,2. In Argentina, the main etiologies for cirrhosis are alcoholism or hepatitis C virus and, with a lower prevalence, the hepatitis B virus or cryptogenic cirrhosis3. Surgery is the best therapeutic option for HCC because of its lower rate of local recurrence and increased survival time. Surgical therapies include resection and transplantation: while the former is indicated for a small percentage of patients with small single tumors (< 2 cm) with favorable anatomic location and relative preserved liver function (Child-Pugh class A), for all other patients liver transplantation is the surgical therapy of choice4-6. Given the growing demand for liver transplantation, an appropriate allocation of organs to patients on waiting lists is crucial. This choice is based on the Model for End-Stage Liver Disease (MELD) model7,8, which awards additional score to patients who meet the Milan criteria for the diagnosis of HCC. For this reason, the proper identification and staging of a tumor has a considerable impact on organ allocation and...
the whole liver transplantation process. The American Association for the Study of Liver Diseases (AASLD) practice guidelines on the management of hepatocellular carcinoma updated in 2010 propose that HCC can be diagnosed in patients with cirrhosis if typical imaging features are found by a single imaging technique (dynamic computed tomography –CT- or magnetic resonance-MR- scan) without the need for biopsy. Among the dynamic imaging techniques recommended by the practice guidelines, multidetector computed tomography (MDCT) has a high diagnostic efficacy, with sensitivity ranging between 50 and 96% and specificity ranging between 75 and 96%. The groups that studied the efficacy of MDCT in the Argentine population with local etiological factors obtained 87% sensitivity and 83% specificity for the detection and characterization of HCC in patients with a diagnosis of cirrhosis. The main objective of this study is to describe the imaging behavior of hepatocarcinoma in patients with a diagnosis of cirrhosis who underwent transplantation at our institution. In addition, as a secondary objective, we would like to determine if there is a relationship between imaging findings and histological tumor grades.

Materials and methods

We conducted a retrospective, observational and descriptive study in 32 patients with a diagnosis of cirrhosis who underwent liver transplantation and had dynamic MDCT performed at our institution between February 2007 and December 2011. We evaluated 51 tumors of variable size between 10 mm and 55 mm, obtained from 55 men and 7 women (mean age: 62 years). The most common etiologies for cirrhosis were hepatitis C virus and cryptogenic cirrhosis. Table 1 shows absolute and relative frequencies of the various etiologies. We have not included patients who had received local therapy (chemoembolization, radiofrequency ablation or alcoholization) before transplantation because such therapy could have interfered with an appropriate analysis of imaging patterns. In this respect, for images to be representative of findings in explants, we only took into account patients with CT scans performed not more than 6 months before transplantation. The pathology of the explant liver was used as reference and nodules with a histopathological diagnosis of HCC were retrospectively analyzed in computed tomographies performed before transplantation.

For histopathological examination of the liver explant, pieces were fixed in 10% formalin and 7-mm to 10-mm thick parallel transverse slices were performed at regular intervals. Histologic grade was assessed in each piece according to the College of American Pathologist (CAP) protocol.

Table 1. Absolute frequency and percent relative frequency of etiologies of cirrhosis present in the studied population

<table>
<thead>
<tr>
<th>Etiology of cirrhosis</th>
<th>AF</th>
<th>%RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis C virus + alcoholism</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hemochromatosis + alcoholism</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

AF: absolute frequency; %RF: percent relative frequency.

Figure 1 Axial slices. (a) Sixty-eight year-old male patient with a diagnosis of cirrhosis due to hepatitis C virus. Arterial phase: hepatocellular carcinoma with hypervascular behavior (arrow). (b) Portal venous phase: washout.
Computed tomographies were performed with a multi-slice, 64-row CT scanner (Aquilion, Toshiba, Tokyo, Japan) with the administration of 1.5 ml/kg of intravenous non-ionic iodinated contrast agent (Iopamiron 370, Schering) by infusion pump (Stellant, Medrad) at a flow of 3 to 4 ml/s. Images were obtained in the arterial phase (at 30-35 seconds), in the portal venous phase (at 65-70 seconds) and in the delayed phase (at 10 minutes). Volumetric images 0.5-mm thick were acquired at 0.3-mm intervals with a pitch factor of 0.828 and tube rotation of 0.5 seconds. Image volume was reconstructed in the axial, coronal and sagittal planes.

All images were evaluated by two observers with 6- and 3-year experience as radiologists at the Liver Transplantation Unit. The level of agreement between the two observers was 100%. The most common features reported in the literature were evaluated: enhancement at arterial phase, washout in the portal venous phase and/or in the delayed phase, the presence or absence of capsule and abnormal intratumoral arterial vessels.

We considered as positive washout only those lesions that were hypodense to liver in the portal venous-delayed phase and did not assume as positive washout those lesions that remained isodense or hyperdense to liver.

For statistical analysis, we used the statistical software SPSS 12.1 to perform inferential and descriptive statistical calculations. The analysis of correlation between variables was performed by estimating the point biserial correlation coefficient. We assumed as statistically significant a correlation between variables with significance below 0.05.

Results

We analyzed 51 tumors with a variable size between 10 mm and 55 mm. Of the total number of tumors, 46 (90%) showed arterial enhancement with 39 of them (85%) showing washout in the portal venous and/or delayed phase (figs. 1 and 2).

The most common combinations of imaging findings were: arterial enhancement with washout in the portal venous and/or delayed phase (39/51 tumors: 76%), arterial enhancement and capsule (20/51: 39%) and then arterial enhancement, washout in the portal venous-delayed phase and capsule (17/51: 33%).

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The combinations that were found are shown in Table 2.

Figure 2 (a) Forty-five year-old male patient with a diagnosis of cryptogenic cirrhosis. Arterial phase: hypervascular lesion with inhomogeneous enhancement (mosaic pattern). (b) Portal venous phase: no categorical washout. The arrowhead points repermeabilization of the umbilical vein, related to redistribution of flow as expression of portal hypertension. (c) Delayed phase: washout becomes evident.

Of all 51 tumors, 5 (10%) were hypervascular with an average size of 18 mm (fig. 3). Twenty-two hepatocarcinomas (43%) had a capsule (fig. 4) and 12 (24%) had intratumoral arterial vessels (figs. 5 and 6).
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In addition, we found statistically significant associates between: 1) tumor size and the presence of capsule (rpb: 0.294; p < 0.05), and 2) tumor size and the existence of intratumoral arterial vessels (rpb: 0.446; p = 0.01). All other associations tested were not found to be statistically significant. All associations are shown in Table 3.

Table 2. Absolute frequency and percent relative frequency of combinations of imaging behaviors identified by computed tomography in relation to the total number of tumors studied

<table>
<thead>
<tr>
<th>IB</th>
<th>AF</th>
<th>%RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE + W</td>
<td>39</td>
<td>76</td>
</tr>
<tr>
<td>AE + C</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>AE + W + C</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>AE + W + IAV</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>IAV + C</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>AE + W + IAV + C</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

C: capsule; IB: imaging behavior; AF: absolute frequency; %RF: percent relative frequency; W: washout in the portal venous-delayed phase; AE: arterial phase enhancement; IAV: intratumoral arterial vessels.

As regards with the histological grade of tumors, 35 (69%) were grade II (fig. 7), 14 (27%) were grade III (fig. 8) and 2 (4%) were grade I (fig. 9). In our sample, there were no grade IV tumors. Table 4 shows tumor features according to histologic grade.

Table 3. Results of statistical correlations between tumor size and the various imaging behaviors observed.

| S and IAV | 0.446 | 0.01 |
| S and C   | 0.294 | 0.036|
| S and AE  | 0.140 | 0.326|
| S and W   | 0.217 | 0.126|
| S and H   | 0.140 | 0.326|
| S and (AE + W) | 0.217 | 0.126|

S: size; C: capsule; H: hypovascular; W: washout in the portal venous-delayed phase; AE: arterial phase enhancement; rpb: point biserial correlation coefficient; IAV: intratumoral arterial vessels.

![Figure 3](https://via.placeholder.com/150)

Figure 3 (a) Forty-six year-old male patient with a diagnosis of cirrhosis due to hepatitis B virus. Arterial phase: hypovascular lesion. (b) Enhancement of the liver in the portal venous phase, except for the 20-mm hypovascular hepatocarcinoma in segment V (arrow).
Table 4. Characteristics of tumors according to histologic grade, expressed in absolute frequency.

<table>
<thead>
<tr>
<th>HG</th>
<th>N.°</th>
<th>T</th>
<th>AE</th>
<th>AE + W</th>
<th>H</th>
<th>IAV</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2</td>
<td>27</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>35</td>
<td>24</td>
<td>31</td>
<td>27</td>
<td>4</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>III</td>
<td>14</td>
<td>25</td>
<td>14</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

C: capsule; HG: histologic grade; H: hypovascular; W: washout in the portal venous-delayed phase; N.°: number of tumors; AE: arterial phase enhancement; S: average size (mm); IAV: intratumoral arterial vessels.

Table 5. Results of statistical correlations between histologic grade and the various imaging behaviors observed.

<table>
<thead>
<tr>
<th></th>
<th>Rpb</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>HG and AE</td>
<td>0.282</td>
<td>0.045</td>
</tr>
<tr>
<td>HG and H</td>
<td>-0.282</td>
<td>0.045</td>
</tr>
<tr>
<td>HG and W</td>
<td>0.075</td>
<td>0.601</td>
</tr>
<tr>
<td>HG and C</td>
<td>-0.014</td>
<td>0.924</td>
</tr>
<tr>
<td>HG and IAV</td>
<td>0.016</td>
<td>0.911</td>
</tr>
<tr>
<td>HG and AE + W</td>
<td>0.075</td>
<td>0.601</td>
</tr>
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</table>

C: capsule; HG: histologic grade; H: hypovascular; W: washout in the portal venous-delayed phase; AE: arterial phase enhancement; rpb: point biserial correlation coefficient; IAV: intratumoral arterial vessels.

Based on the tests for determining statistical correlations between the variables whose data were obtained from histological examination and the variables whose data were obtained from imaging studies, we found statistically significant associations between: 1) histologic grade and arterial phase enhancement (rpb: 0.282; p <0.05) and 2) histologic grade and hypovascular tumor (rpb: -0.282; p <0.05). All other associations tested were not statistically significant. All associations are shown in table 5.

Discussion

In our population HCC occurred most frequently in men in the seventh decade of life. Thus, our study demographics were similar to those reported in the multicenter study published...
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by Fassio et al.3 for current epidemiology of HCC in Argentina. However, unlike the aforementioned study, where the main causes of cirrhosis were alcoholism and hepatitis C, in our population the first etiology was cryptogenic and the second cause of cirrhosis was the hepatitis C virus.

In patients with cirrhosis, hepatocellular carcinoma is a condition of heterogeneous etiology and presentation, both as regards histologic and imaging features, as evidenced in our study results.

It is important to highlight that in this study the imaging criteria evaluated were directly correlated with the explanted liver. This is a novel approach if we consider that in other publications they were compared with a second imaging method, alpha-fetoprotein or biopsy12.

The high percentages of lesions with arterial phase enhancement and arterial phase enhancement with washout in the portal venous and delayed phases identified in the tumors studied are consistent with previous literature reports (the literature describes this vascular pattern as typical of HCC)10, 16, 18, 20, 23.

HCC usually displays a heterogeneous and global mosaic pattern of enhancement. It is different from the enhancement pattern of hemangioma (which has a peripheral nodular pattern) and from that of metastasis (usually displaying a complete ring pattern of enhancement). A loss of the contrast enhancement obtained in the arterial phase is observed in the portal venous and/or delayed phases (referred to as washout) and the lesion appears hypodense relative to the adjacent liver16, 20, 23.

Hypovascular tumors identified at portal venous phase (which constitute tumors with “unusual” behavior) could be responsible for most false negatives in the diagnosis of HCC by computed tomography.

As regards with the capsule variable, in the total sample the absence of this finding was more common; however, its presence was observed in larger tumors. In this respect, we highlight the importance of image acquisition in the delayed phase, as it favors visualization of the capsule formed by fibrous tissue, apart from contributing to confirm washout of tumor enhancement in those patients with no washout observed in the portal venous phase.

The variable of abnormal intratumoral arterial vessels also showed statistical significance in relation to tumor size. This correlation was positive and moderate. The larger the size of the tumor, the higher the likelihood of observing a capsule and intratumoral arterial vessels.

Figure 6 (a) Arterial phase: enhancement and presence of abnormal intratumoral arterial vessels (arrows). (b) Delayed phase: washout and presence of a capsule (arrows).
In addition, statistically significant but weak associations were found between the histologic grade of tumors and the imaging behaviors of hypovascular and arterial phase enhancement. Histologic grade and arterial enhancement showed a positive correlation. Tumors of more advanced histologic grade more frequently showed arterial phase enhancement (as compared to those of lower histologic grade), while for hypovascular tumors, the relationship with histologic grade was the opposite. That is to say, these less vascular tumors tended to have a lower histologic grade, with a statistically significant but weak association.

Hepatocarcinogenesis is a stepwise process: from regenerative nodule, via low-, medium- and high-grade dysplastic nodules to hepatocarcinoma, where tumors acquire arterial vascularity. During this process, angiogenesis plays an essential role in tumor development. Results obtained from the evaluation of our sample suggest that well-differentiated tumors of low histologic grade would have lower angiogenesis than tumors of higher histologic grade. We think sample size is a conditioning factor for the weak correlation between variables; therefore a larger number of cases would be needed to power the study to disclose possible associations of greater strengths.

In patients with cirrhosis and a diagnosis of HCC, surgery is the therapy of choice. Local resection is limited to a small percentage of patients with relatively preserved liver function (Child-Pugh class A) with small tumors, while in all other cases liver transplantation is the treatment of choice. Transplantation eradicates both the tumor and liver cirrhosis, has a low rate of local recurrence with a high rate of actuarial survival and disease free survival. Transplantation offers benefits and is indicated in patients with tumors that meet the Milan criteria (a single nodule less than 5 cm in size or as many as three nodules not exceeding 3 cm each)5,6. For patients on the waiting list for transplantation, organ allocation is based on MELD system. Patients with a diagnosis of HCC who meet the Milan criteria are given an extra MELD score (a score of 22 plus an additional score for every 3 months on the waiting list)8,9,25.

Accurately diagnosing hepatocarcinoma implies a huge responsibility, with substantial impact at the time of performing a fair allocation of organs to patients on the waiting list.
In 2001, the Barcelona Consensus recommended as diagnostic criterion for hepatocarcinoma in patients with cirrhosis the presence of two imaging techniques showing characteristic features or one imaging technique showing characteristic features and alpha-fetoprotein equal to or above 400 ng/mL, with no need for confirmation by biopsy.26 Nevertheless, in 2010, the American Association for the Study of Liver Disease (AASLD) revised these recommendations and concluded that for tumors larger than 1 cm one diagnostic technique (four-phase dynamic resonance imaging or computed tomography) with nodules showing arterial phase enhancement and washout in the portal venous-delayed phase was enough for diagnosing HCC, independently of other findings.10 Two years later, in April 2012, the European Association for the Study of the Liver and the European Organization for Research and Treatment of Cancer (EASL-EORTC) supported the recommendations of AASLD27.

Based on the above, it is evident how important imaging methods are at present for a comprehensive management of patients with cirrhosis and hepatocellular carcinoma. For this reason, we consider it is essential to know the appearance and frequency of occurrence of the various imaging criteria for the diagnosis of hepatocarcinoma in patients with cirrhosis.

Conclusion

In our population, arterial phase enhancement with washout in the portal venous-delayed phases was found in most tumors. Our results are consistent with previous reports and contribute to strengthen the value of these findings as diagnostic criteria for hepatocellular carcinoma in patients with cirrhosis. Statistically significant (though weak) associations were found between histologic grades of tumors and the hypoattenuating vascular and arterial phase enhancement imaging behaviors.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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References