Imaging features of combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma in patients undergoing liver surgery

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Purpose

The cHCC-CC is a rare variant of primary liver cancers (0.87%-4.7%), comprising elements of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC).

The history of cHCC-CC’s classification started in 1949, with Allen and Lisa that described cHCC-CC and classified it into three subtype. Type A or "double cancer" represents cases in which HCC and CC exist separately; type B, "combined" type, HCC and CC components exist contiguously, but independently; and type C, "mixed" type, occurs when HCC and CC components are admixed within a mass.

More recently, cHCC-CC is considered as a distinct type of primary liver carcinoma, which is morphologically and phenotypically intermediate between HCC and CC and may be derived from hepatic progenitor cells with the bipotential to differentiate into both hepatocytic and cholangiocyctic lineages. (Kim et al. in 2004 and Zhang et al. in 2008)

The actual incidence of cHCC-CC is not known, ranging substantially between studies and geographical region, with greater numbers reported in Asia. Most of the studies suggested that cHCC-CCs are more commonly diagnosed in patients with chronic hepatitis and liver cirrhosis, with a conspicuous male predominance.

On imaging, the diagnosis of cHCC-CC is problematic with the diagnosis established in the great majority of cases in the postsurgical period, when the most important therapeutic decisions have already been made. Cases are very often misdiagnosed as HCC or CC in the initial evaluation. This misinterpretation may have therapeutic implications, since treatment may differ significantly from that of HCC or CC alone.

To clarify the imaging features of combined hepatocellular and cholangiocarcinomas (cHCC-CC) in comparison with hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) imaging, in a retrospective study of patients undergoing hepatectomy, core biosy and liver transplantation (LT).
Methods and Materials

Study Population

The database of the Department of Pathology from December 2004 to January 2012 was cross-referenced with the database of Departement of Radiology to identify all patients with pathology-confirmed diagnosis of cHCC-CC who had undergone MRI and CT.

This retrospective study includes nine patients (eight male, one female, mean age 54.8 years, range 42-70 years) who had either an hepatectomy (n=3) or a core biopsy (n=1) for HCC and CC, either a liver transplantation (LT) (n=5) for HCC.

All the patients were evaluated with presurgical imaging study MRI (n=4) and CT (n=9); 5/9 were treated with presurgical Transarterial Chemoembolization (TACE).

All the patients had a clinical history of chronic liver disease: 8 cirrhosis (5 alcoholic, 1 HCV/HIV, 1 glycogenosis type III, 1 hemochromatosis) and 1 non alcoholic steatohepatitis (NASH).

A serum alphafetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) test was available in 9 and 3 patients, respectively.

The body mass index (BMI) 's mean is 24.6 (range 34-15.4).

Pathological Analysis

Lesions were confirmed histopathologically as hepatic tumors comprising unequivocal elements of both HCC and CC according to the tumor classification of the World Health Organization.

The bidirectional differentiation was further supported by immunohistochemical stain.

For each specimen, biliary differentiation was confirmed with immunohistochemical stains characteristic of bile duct differentiation (cytokeratin 7, cytokeratin 19) whereas hepatocellular differentiation was confirmed with immunohistochemical stains characteristic of hepatocyte differentiation (anti-glypican, anti-hepatocyte and anti-AFP).

MRI Technique

All MRI examinations were performed on a Achieva 1.5T (Philips Healthcare, Best, The Netherlands), MRI system using a phased-array torso coil. In all patients a standard upper abdominal protocol was performed. The parameters are displayed in Table 1 on page 5.
Postcontrast sequences were acquired at 18 seconds, approximately (early phase), 40 seconds (venous phase), 120 seconds (interstitial phase) and 5 minutes (delayed phase) after gadolinium administration.

Gadoteric acid, 0.5 mmol/mL (Dotarem; Guerbet France) was administered intra venous in all patients by a power injector as a bolus of 0.2 mL/kg gadolinium chelate at 2 mL/sec.

**CT Technique**

All CT examinations were performed on a Brilliance 64-slice (Philips Healthcare, Best, The Netherlands). In all patients a standard abdominal protocol was performed. The parameters are displayed in Table 2 on page 5.

The protocol is based on 4 dynamique CT phases: a precontrast phase and three postcontrast phases that were acquired at 20-25 seconds (early phase), 40 seconds (venous phase), 5 minutes (delayed phase) after iodine based contrast administration.

Iomeprol, 350 mgI/mL (Bracco Imaging s.p.a.; Milano, Italy) was administered intra venous in all patients by a power injector as a bolus of 1.5 mL/kg iodine based contrast at 3-5 mL/sec.

**Images Analysis**

MR/CT images were retrospectively reviewed in consensus by two abdominal radiologists, with knowledge of the diagnosis of cHCC-CC.

Images were reviewed on a picture archiving and communication system PACS (Carestream Health, New York, U.S.A.) in all patients.

The following characteristics were evaluated: tumor location; the number and size of lesions; margins (well-defined or ill-defined); MR signal intensity of tumor on non contrast-enhanced T1-weighted and T2-weighted (hypointense/hyperintense) and characteristic of tumor signal (homogeneous/heterogeneous); enhancement pattern was analyzed on gadolinium-enhanced T1-weighted images and iodine contrast-enhanced CT images on arterial, portal and delayed phase; the presence of necrosis; the presence of a tumoral capsule, biliary dilatation directly related to the mass, vascular invasion and satellite tumors; imaging findings consistent with cirrhosis (lobulated liver contours and hypertrophy of the left lobe and/or caudate lobe and/or hypotrophy of the quadrate lobe and/or right liver) and signs of portal hypertension (ascites, splenomegaly and porto-systemique shunts); lymph node involvement (short axis more than 1.0 cm) and metastasis.
### Table 1: Parameters of Precontrast and Postcontrast Sequences

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Precontrast sequences</th>
<th>Postcontrast sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1w in/out phase</td>
<td>T2w</td>
</tr>
<tr>
<td>Plane</td>
<td>Axial</td>
<td>Axial</td>
</tr>
<tr>
<td>TR (msec)</td>
<td>185</td>
<td>496</td>
</tr>
<tr>
<td>TE (msec)</td>
<td>2,3/4,6</td>
<td>80</td>
</tr>
<tr>
<td>FLIP (*)</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>Matrix (phase x frequency)</td>
<td>256 x 133</td>
<td>296 x 183</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>380 x 285</td>
<td>380 x 285</td>
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<tr>
<td>Scan Percent (%)</td>
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<td>81</td>
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<tr>
<td>No. of section</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
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<td>6,12</td>
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<tr>
<td>Intersectional Gap (mm)</td>
<td>1</td>
<td>0,88</td>
</tr>
<tr>
<td>No. of signal acquisition</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

TR, repetition time; TE, effective echo time; 3D FS, three-dimensional Fat Supression sequence.

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**Table 2:** Parameters Pre-contrast and Post-contrast Phases BCT: bolus chase technique

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-contrast</th>
<th>Early</th>
<th>Venous</th>
<th>Delayed</th>
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<tbody>
<tr>
<td>Thickness (mm)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Reconstruction interval (mm)</td>
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<td>0,5</td>
<td>0,5</td>
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<tr>
<td>KV</td>
<td>120-180</td>
<td>120-180</td>
<td>120-180</td>
<td>120-180</td>
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<tr>
<td>mAs</td>
<td>200-280</td>
<td>200-280</td>
<td>200-280</td>
<td>200-280</td>
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<tr>
<td>Collimation</td>
<td>32x1,25</td>
<td>64x0,625</td>
<td>32x1,25</td>
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<tr>
<td>Pitch</td>
<td>0,906</td>
<td>0,734</td>
<td>0,906</td>
<td>0,0906</td>
</tr>
<tr>
<td>Rotation's time (sec.)</td>
<td>0,5</td>
<td>0,5</td>
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<td>0,5</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>320-440</td>
<td>320-440</td>
<td>320-440</td>
<td>320-440</td>
</tr>
<tr>
<td>Matrix</td>
<td>512x512</td>
<td>512x512</td>
<td>512x512</td>
<td>512x512</td>
</tr>
</tbody>
</table>
Results

Histopathology
The cHCC-CC is a "mixed" type in 6/9 patients and "combined" type in 3/9 patients.

Serum markers
The AFP serum level was elevated in 5/9 but only one up to 200 ng/mL and the CA19-9 serum level was elevated in 2/3 patient. These 2 patients have also an AFP serum level elevated.

Morphologic imaging findings
The cHCC-CC tumor presented as a single mass in all patients, measuring from 1.5 to 10 cm on the axial plane (mean size 41 mm).

All the cHCC-CC were 6/9 localized in right liver and 3/9 in the left one.

The cHCC-CC margins were well-defined in 6/9 patients.

The tumor's structure (MRI/CT imaging) was heterogeneous in 6/9 and homogeneous in 3/9 cases.

All the cHCC-CC demonstrated on T1-w hypointensity and on T2-w hyperintensity. (Fig. 1 on page 9)

The cHCC-CC in CT pre-contrast phase was hypodenses in 8/9 patients and 1/9 patients isodense.

Dynamic imaging findings
On dynamic postcontrast imaging, three patterns were observed in:

- 4/9 cases heterogeneous and central early enhancement at arterial phase followed by wash-out contrast on later phases and in one of these we observed a tumoral capsule in delayed phase contrast (HCC-like).

(Fig. 2 on page 9, Fig. 3 on page 10 and Fig. 4 on page 11)

- 4/9 cases peripheric and thin enhancement at arterial phase followed by a centripetal progressive enhancement on later phases (CC-like).
- 1/9 of our cHCC-CC showed permanent hypodensity on pre- and post-contrast phases due to an important lesion's necrosis (hypovascular pattern). (Fig. 9 on page 16)

Necrosis was present in 4/9 patients, in one of these was 90% of lesion.

**Other imaging features**

Cirrhosis signs were present in 7/9: liver morphological changes in 7/9 patients and a lobulated liver contours in 5/9 patients.

Hypertension signs: ascites was observed in 2/9 patients, splenomegaly in 5/9 and porto-systemique shunts in 3/9.

Lymph node involvement was present in 2/9 patients and one of these was a metastasis.

Biliary dilatation directly related to the mass was present in 1/9 patient.

No vascular invasion or satellite tumors were detected.
Images for this section:

**Fig. 1:** a,b,c,d The same patient displayed in Fig.1. T1w in phase (a), T1w out phase (b), T2w (c) and T2w fat-suppressed (d). The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver with a heterogeneous signal, hypointense on T1w and hyperintense on T2w.

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**Fig. 2:** a,b,c T1w fat-suppressed in the hepatic arterial dominant phase(a), and venous phase(b) and in the equilibrium phase(c) after administration of gadoteric acid. The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver classified as "mixed type", occurs when HCC and CC components are admixed within a mass. We observe a great nodule that shows a heterogeneous early enhancement followed by wash-out contrast on later phases, inside the mass we note a small, posterior nodule that exhibit a contrast retention on later phases.

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Fig. 3: a,b,c Dynamique CT image: pre-contrast phase (a), early post-contrast phase (b), venous post-contrast phase (c) after iodine based contrast administration. The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver that shows a hypodensity on pre-contrast imaging, heterogeneous central early enhancement followed by wash-out contrast on later phases, a typical "HCC-like" enhancement pattern.

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**Fig. 4:** a,b,c T1w fat-suppressed in the hepatic arterial dominant phase(a), venous phase(b) and in the equilibrium phase(c) after administration of gadoteric acid. A well-defined mass in the right liver that shows heterogeneous and central early enhancement followed by wash-out contrast on later phases, a typical "HCC-like" enhancement pattern.

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Fig. 5: a,b,c T1w fat-suppressed in the hepatic arterial dominant phase(a), and venous phase(b) and in the equilibrium phase(c) after administration of gadoteric acid. The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver classified as "mixed type", occurs when HCC and CC components are admixed within a mass. The component HCC-like shows early enhancement in the arterial phase and a mild contrast wash-out in delayed phase.

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**Fig. 6:** a, b, c, d The same patient displayed in Fig.3. T1w fat-suppressed in the hepatic arterial dominant phase(a), and venous phase(b) and in the equilibrium phase(c) after administration of gadoteric acid. The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver classified as "mixed type", occurs when HCC and CC components are admixed within a mass. This image shows the same tumor of previous case but in another position, which exhibit a component CC-like that shows early ring-enhancement, in the arterial phase and a progressive central enhancement in delayed phase.

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Fig. 7: a,b,c,d Dynamique CT image: pre-contrast phase (a), early post-contrast phase (b), venous post-contrast phase (c) and delayed post-contrast phase (d) after iodine based contrast administration. The cHCC-CC tumor appears as a nodular, well-defined mass in the left liver that shows a hypodensity on pre-contrast imaging, a peripheral and thin enhancement in the early phase followed by a centripetal progressive enhancement on later phases, a typical "CC-like" enhancement pattern.

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Fig. 8: a,b,c T1w fat-suppressed in the hepatic arterial dominant phase(a), venous phase(b) and in the equilibrium phase(c) after administration of gadoteric acid. A well-defined mass in the left liver that shows a peripheric and thin enhancement followed by a centripetal progressive enhancement on later phases, a typical "CC-like" enhancement pattern.

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Fig. 9: a,b,c Dynamique CT image: pre-contrast phase (a), early post-contrast phase (b), venous post-contrast phase (c) after iodine based contrast administration. The cHCC-CC tumor appears as a nodular, well-defined mass in the right liver that shows a permanent hypodensity on pre-contrast and post-contrast phases(hypovascular pattern).

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Conclusion

In conclusion, the imaging appearance of cHCC-CC is commonly a solitary mass, heterogeneous, hyperintense on T2-w in cirrhotic patients. In half of the case, after dynamic injection, cHCC-CC look likes HCC and the other half look like CC. This diagnosis could not be based on imaging alone. The combination of both elevated serum tumor markers may help in the diagnosis. The definitive diagnosis of cHCC-CC requires demonstration of both hepatocellular and cholangiocellular differentiation at histopathology analysis, which is usually facilitated by immunohistochemical and special stains to demonstrate both hepatocytic and biliary phenotypes.


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Fig. 10: http://www.lasiad.org/

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