CONTINUING EDUCATION PROGRAM: FOCUS...

Diagnosis of hepatocellular carcinoma

V. Cartier\textsuperscript{a,*}, C. Aubé\textsuperscript{a,b}

\textsuperscript{a} UNAM University, Department of Radiology, Angers University, Angers University Hospital, 4, rue Larrey, 49933 Angers cedex 09, France
\textsuperscript{b} UNAM University, Angers University, HIFIH Laboratory, 4, rue Larrey, 49933 Angers cedex, France

Abstract  More than 90\% of cases of hepatocellular carcinoma occur on the background of chronic liver disease. Its diagnosis should therefore be based on six-month ultrasound screening, which should be started in these patients. The positive diagnosis of hepatocellular carcinoma is based on its vascularization examined on dynamic CT or MRI images after contrast enhancement. Arterial hypervascularization followed by a washout from the lesion in the portal and/or late phases on a background of cirrhosis provides a positive diagnosis of HCC without histology for nodules over a centimeter in size (international guidelines). Any other appearances require needle biopsy of the nodule and extra-nodular area to confirm the diagnosis. The local staging assessment predominantly involving portal invasion and the general patient assessment should be combined with assessment of the underlying liver disease to guide the treatment decision. The information obtained should be contained in as a standardized report as possible with all of the information required for patient management.

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Hepatocellular carcinoma has two specific diagnostic features. Firstly, it occurs on a background of chronic underlying liver disease in more than 90\% of cases \cite{1-3} and the existence of a predisposing background has led to the introduction of six-monthly screening in at risk patients in order to identify hepatocellular carcinomas early when it is at a stage which allows curative therapy to be offered \cite{4}. Despite the poor prognosis of HCC, however, screening is not widely used. It is carried out in approximately 25\% of patients in France \cite{5}.

The second specific feature of the diagnosis of hepatocellular carcinoma is that an unequivocal diagnosis can be made on imaging criteria without the need for histology \cite{6}, hence the need for a thorough method and careful analysis of the appearances of lesions which may to represent hepatocellular carcinoma.

* Corresponding author.
E-mail address: victoirecartier@hotmail.com (V. Cartier).

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As applies to any cancer, the diagnosis of hepatocellular carcinoma should be combined with a local, regional and systemic staging assessment. Beyond the staging assessment, however, the underlying liver disease is a fundamental aspect of patient management. Hepatocellular impairment and portal hypertension associated with the liver disease are factors, which are added to the staging assessment in order to choose appropriate treatment. This information is included in the BCLC classification, which is currently the only classification that is currently recognized by international guidelines [3,6].

**Imaging techniques**

**Ultrasound**

Ultrasound is the investigation, which should identify the largest number of hepatocellular carcinomas, as it is the screening method used for six-monthly monitoring of cirrhosis. It should, therefore, look for development of new nodules or changes in the appearance of known nodules. Contrast-enhanced ultrasound is no longer recognized as a noninvasive part of the diagnosis in the recent international guidelines [6]. It is still, however, useful in monitoring cirrhosis in order to distinguish a regenerative nodule from a small hepatocellular carcinoma or in a diagnostic needle biopsy or percutaneous treatment to clearly identify the nodule to be biopsied or treated.

**Computed tomography**

Liver investigations in the diagnosis of hepatocellular carcinoma should include four phases: one phase without and three phases with contrast enhancement: one in the arterial phase (30 to 35 seconds after beginning the injection), one in the portal phase (75 to 90 seconds) and one in the late phase (3 minutes). The portal phase should cover the entire abdominal and pelvic cavities in order to provide a staging assessment and investigate for signs of portal hypertension. A chest investigation should be carried out in the arterial phase. The iodine concentration in the contrast medium should be 350 g/L, with an injection volume of between 1.5 and 2 mL/kg (in practice between 120 and 150 mL). The minimum injection flow rate should be 3 mL/s.

**Magnetic resonance imaging**

MRI is still the best investigation to detect and characterize the different nodules, which develop in cirrhosis [7].

The investigation involves a rapid spin echo T2 weighted image with fat saturation (fat saturation increases the contrast of the lesion), an both in phase and out of phase T1 echo gradient image to investigate for a fatty component in the tumor and a diffusion-weighted image with a b value of approximately 600 mm²/s² to improve detection of small lesions and help in their characterization, unenhanced T1 weighted image with fat saturation without and then after contrast enhancement in the arterial, portal and late phases.

Ideally, if large volume ascites is present, this should be aspirated in advance in order to reduce movement artefacts.

**Imaging appearances of hepatocellular carcinoma**

**Typical appearance**

The most common form of hepatocellular carcinoma is single or a small number (3 to 4) of nodular lesions. A capsule is present in 75% of cases of HCC over 2 centimeters in size [8]. Unenhanced, the nodule has variable echogenicity (small nodules are slightly more often hypoechogenic) but is more likely to be slightly hypodense on CT, hypointense on T1 weighted MRI and hyperintense on T2 weighted MRI [9].

A hyperintensity on diffusion-weighted imaging is highly suggestive of hepatocellular carcinoma, although absence of a diffusion-weighted hyperintensity in no way excludes it [10].

The characteristic appearance is vascularization of the nodule due to arterial neoangiogenesis, which progressively substitutes an arterial vascularization for the portal vascularization of the regenerative nodule. The typical form of hepatocellular carcinoma therefore displays hypervascularisation in the arterial phase followed by a hypodensity in the portal and/or late phase. This hypodensity defines the washout from the lesion (Fig. 1). Washout is defined as a hypodensity compared to the neighboring parenchyma occurring in the portal and/or late phase and following arterial hypervascularisation. This is an important definition, as it is one of the key factors in the noninvasive diagnosis of HCC as they appear in the international guidelines [6,11].

This typical appearance is increasingly common in lesions over 2 centimeters in size.

**Atypical appearances**

**Atypical tumors**

Atypical numbers, shapes and enhancement are seen and the HCC may be multinodular when first found. It may be hypodense in the arterial or portal phases and not therefore display any characteristic enhancement. In addition, infiltrative forms are seen which are often poorly demarcated, in which case they are often poorly hypervascularized in the arterial phase. These atypical tumors account for 15 to 20% of the hepatocellular carcinomas:

- small hepatocellular carcinomas (< 2 cm) do not display the typical appearances in 20 to 60% of cases depending on the technique used [12–14]. Arterial hypervascularization and washout from the lesion are less common when it is small and if it is well differentiated [15]. The histological concept of the early HCC is often a lesion between 10 and 15 mm in diameter with no clearly demarcated outline and very modest arterial vascularization with no arterial washout (Fig. 2) [16];
- HCC occurring in steatotic liver disease has a few specific features. It often appears as a large heterogeneous lesion containing areas of clearly demarcated necrosis with regular outlines. It may be encapsulated and enhance unevenly in the arterial phase [17];
- HCC is rare in a healthy liver (incidence < 10%) and in 20% of cases is associated with hepatitis B virus infection, as the virus has a direct carcinogenic effect. It may, however,
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Figure 1. Typical hepatocellular carcinoma in cirrhosis. Magnetic resonance imaging. T1 weighted images with fat saturation without (a) and then after gadolinium enhancement in the arterial (b), portal (c) and late (d) phases; T2 weighted images (e) and diffusion-weighted images (f).

develop in a patient with no known cause of chronic liver disease and normal liver histology. The diagnosis is made late, often at a very advanced stage of the disease, as a large lesion, which is hypervascularized in the arterial phase in a non-dysmorphic liver [18,19] (Fig. 3).

Invasion and pre-treatment assessment

Apart from the specific features of the tumor, the presence of local or systemic invasion and extent of the underlying liver disease contribute to the treatment decision through the BCLC classification [3].

Local invasion

The most common local invasion is vascular. Vascular micro-invasion is not accessible to imaging and is proportional to the size of the tumor. The presence of satellite nodules around a bulky tumor is a sign of microvascular invasion (Fig. 4).

The most common vascular invasion seen is portal. A tumor thrombus may have the same appearances as the tumor, i.e. hypervascularized in the arterial phase with washout from the lesion in the portal phase. Vascular invasion of the portal trunk may appear as an arterio-portal fistula (Fig. 5) and if appearances of an arterio-portal fistula are seen in a cirrhotic patient even if it may be non-malignant in origin, the patient should be investigated for hepatocellular carcinoma, particularly as the tumor may be mostly endoportal with a very small parenchymal mass and is often infiltrative and therefore more difficult to identify.

Conversely, thrombus associated with a hepatocellular carcinoma is not necessarily tumor and may be made up of
Figure 2. Early hepatocellular carcinoma (HCC). Computed tomography after iodine enhancement in the arterial (a), portal (b) and late (c) phases. Monitoring of severe alcoholic cirrhosis. An 18 mm lesion (arrow) representing a histologically proven hepatocellular carcinoma (early HCC). The outlines are blurred and arterial phase iodine enhancement is very slight. There is no washout in the portal or late phases.

Figure 3. Hepatocellular carcinoma in a healthy liver. Computed tomography without (a) and then after iodine enhancement in the arterial (b), portal (c) and late (d) phases. Assessment of abdominal pain. The patient was found to have a 9 cm bulky lesion in the right lobe of the liver with a necrotic center, which was hypervascularized in the arterial phase, with no washout from the lesion.
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Figure 4. Bulky hepatocellular carcinoma with a satellite nodule on magnetic resonance imaging. T1 weighted images with fat saturation without (a) and then after gadolinium enhancement in the arterial (b), portal (c) and late (d) phases. Alcoholic cirrhosis. Bulky hepatocellular carcinoma, 9 cm in size, encapsulated and necrotic, enhancing in the arterial phase with washout in the portal and late phases. Small satellite nodule (arrow) under a centimeter in size with the same enhancement kinetics.

fibrin, in which case it carries a different prognosis. In order to distinguish fibrin from tumor thromboses, an attempt should be made to identify vascularization in the thrombus, which suggests tumor invasion. This may be carried out by contrast-enhanced ultrasound or contrast-enhanced CT or MRI. If any doubt remains, a biopsy of the thrombus may be taken from one of the portal branches in order to establish the type of thrombus.

Figure 5. Hepatocellular carcinoma (HCC) with arterio-portal tumor fistula. Computed tomography in the arterial (a) and portal (b) phases. Viral cirrhosis (c). Hepatocellular carcinoma in the left lobe of the liver with proximal left arterio-portal fistula and portal tumor thrombus. Opacification of the portal trunk and its branches from the arterial phase. Hypodense appearance of the HCC in the late phase (arrow heads).
Invasion of the suprahepatic veins is rarer but must always be looked for. This may extend to the inferior vena cava.

Biliary invasion is also rare, although forms of the disease are found which result in predominantly endobiliary growth. The underlying liver disease and appearances of an endobiliary rather than infiltrative mass should suggest the diagnosis of HCC rather than cholangiocarcinoma. A biopsy is required for an unequivocal diagnosis.

Invasion of the liver capsule and neighboring structures (particularly the abdominal wall) should be looked for, although these are uncommon.

Remote disease

Metastases occur mostly in the lungs, abdominal and lymph nodes and in bone [20]. Caution, however, is required, when assessing whether or not, particularly hilar lymphadenopathy, is metastatic as inflammatory lymphadenopathy is common in viral liver disease.

Non-malignant aspects of the pre-treatment assessment

In addition to clinical and laboratory findings which reflect the underlying liver disease, the radiological features of the liver disease should be reported.

Hepatic dysmorphism, particularly atrophy, influence the potential for excision.

Portal hypertension is a major prognostic indicator in the treatment of HCC. In addition to clinical assessment indicators (porto-suprahepatic gradient, indocyanine green test and Fibroscan), CT and esophagogastroscopy should be carried out to look for portosystemic shunts.

Positive diagnosis

As defined in the recent EASL and EORTC definitions, a positive diagnosis of hepatocellular carcinoma can be made without histology definitions under certain conditions [6] (Fig. 6).

To summarize this figure:
- a lesion under a centimeter in size should be followed up at 3 months;
- a lesion over a centimeter in size may be diagnosed with certainty if underlying cirrhosis is present and imaging appearances are typical (arterial hypervascularization with washout from the lesion in the portal and/or late phase) on CT and/or MRI (if either of these investigations is negative, the second should be performed).

Outside of these situations the diagnosis requires a needle biopsy for histological examination. If this is negative (no histological identification of the nodule), a further biopsy is required.

Standardized report

The different aspects of the diagnosis described above should be included in as standardized a report as possible (Appendix A), which should state the clinical findings (Child-Pugh classification, cause of the lesion), history of any HCC already treated, the signs of liver disease (dysmorphism,
portal hypertension); a description of the lesion(s) suspected to be HCC; local and general extension; whether the diagnosis of HCC can be confirmed on imaging (typical appearance according to the guidelines) or whether needle biopsy is needed.

Conclusion

Hepatocellular carcinoma occurs on a background of chronic liver disease and should therefore be screened for routinely by six-monthly ultrasound. An unequivocal diagnosis can be made on imaging because of the typical appearances as they are defined in the international guidelines, although if these typical appearances are not present, any nodule developing in cirrhosis over a centimeter in size must be biopsied to obtain an unequivocal histological diagnosis. As applies to any cancer, a local and general staging assessment should be performed. In addition and because of the underlying liver disease which influences the treatment decision, information about the liver disease such as hepatic dysmorphism and portal hypertension should be included. The treatment decision is based on the BCLC classification (Table 1).

**TAKE-HOME MESSAGES**

- Screening for HCC should be by six-monthly ultrasound.
- Atypical appearances (arterial enhancement and portal and/or late phase washout) allow a noninvasive diagnosis of HCC in cirrhosis to be made.
- In all other situations, a biopsy is required to confirm the diagnosis.
- The staging assessment, including imaging, should incorporate an assessment of the underlying liver disease.

**Clinical case**

A 71-year-old male patient was being followed up for viral cirrhosis. He was found on a six-monthly ultrasound to have a 15 mm hypoechogenic nodule in the right lobe of the liver.

A CT (Fig. 7) performed without and then with iodine enhancement in the arterial, portal and late phases, confirmed a non-liquid, 15 mm hypodense nodule, which did not enhance. MRI (Fig. 8) with T1 weighted images both without (a) and then with gadolinium enhancement in the arterial (b), portal (c) and late (d) phases and T2 weighted image (e) were obtained and confirmed a hypointense nodule in the right lobe of the liver on a T1 weighted image, which did not enhance significantly in the arterial phase and which was hypointense in the portal and late phases.

**Questions**

1. Why can you not make a conclusive diagnosis of HCC?
2. What is your practical approach?
3. Which image allows you to confirm that there is no arterial enhancement?
4. Do you conclude that the diagnosis is HCC?
5. What is your practical approach then?
6. The histologist reported a moderately differentiated HCC. What hypotheses would you offer to explain the appearances of this HCC?

**Answers**

1. Because of the lack of arterial enhancement and washout from the lesion.
2. Another investigation (MRI) would be useful to look for the typical appearances of HCC, allowing a positive noninvasive diagnosis to be made. Simply monitoring a lesion over 1 cm in size in a cirrhotic liver is not acceptable.
3. The subtraction image (arterial — without injection) (Fig. 8f).
4. No. Not typical appearances of HCC.

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<table>
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<th>PS</th>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>0</td>
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</tr>
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HCC: hepatocellular carcinoma.
A and B stages: all the criteria. C and D stages: one of the criteria.
Figure 7. Computed tomography without and then with iodine enhancement in the arterial, portal and late phases confirming the presence of a non-liquid, hypodense 15 mm nodule, not enhancing with contrast.
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Figure 8. Magnetic resonance imaging with T1 weighted images without (a) and then after gadolinium enhancement in the arterial (b), portal (c) and late (d) phases and T2 weighted image (e) confirming a hyperintense T1 weighted nodule in the right lobe of the liver not enhancing significantly in the arterial phase and hypointense in the portal and late phases.

5. Perform a biopsy, simply monitoring the lesion over 1 cm in size in a cirrhotic liver is not acceptable.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
Appendix A.

REPORT:
HEPATOCELLULAR CARCINOMA (HCC)

Clinical details:
- First assessment or follow up
- Chronic liver disease yes/no. If yes, cause and optimally Child-Pugh classification
- Nodules already treated (site, type and date of treatment)

RESULTS:
- Signs of liver disease: dysmorphism, steatosis, fibrosis
- Signs of portal hypertension: porto-systemic shunting
- Identification of lesions previously treated - signs of local recurrence: Yes / No
- (New) characteristic lesions, with, for each lesion:
  - shape: infiltrative/nodular
  - borders: distinct/irregular
  - size: ... cm
  - site (diagram)
  - density/unenhanced signal (T1 and T2)
  - enhancement: typical/atypical vascular profile
  - signs of vascular invasion (portal, suprahepatic) Yes / No
  - if yes, evidence supporting platelet/tumour thrombus.
  - biliary tract invasion
  - extra-capsular invasion

EXAMPLE:
- nodular lesion
- distinct boundaries
- maximum diameter 43 mm
- segment 5
- hypointense on T1 and hyperintense on T2
- typical vascular profile

METASTASES:
- site, number

SUMMARY AND CONCLUSION:
Definite feature of HCC or need for liver needle biopsy.
Type: infiltrative or nodular
Presence or absence of local extension
Presence or absence of metastases
Signs of chronic liver disease

ADDITIONAL INFORMATION FOR LIVER RESECTION:
- Volumetry:
  - total liver volume
  - total tumour volume
  - total liver volume excluding tumour
  - R liver / L liver / L lobe / segment volume
- Vascular analysis: anatomy
  - arterial
  - portal
  - hepatic vein (accessory vein to R liver)
References