Hepatocellular carcinoma (primary cancer of the liver)

Jean-Claude BARBARE (1), Valérie BOIGE (2), Karim BOUDJEMA (3), Robin LESCESNE (4), Jean-Claude TRINCHET (5)

(1) Institut National du Cancer, Boulogne Billancourt, (2) Institut Gustave Roussy, Villejuif, (3) Hôpital Pontchaillou, Rennes (4) Clinique Saint Etienne, Bayonne, (5) Hôpital Jean Verdier, Bondy

Introduction

Hepatocellular carcinoma (HCC) habitually develops in cirrhosis, more rarely in chronic noncirrhotic liver disease, and exceptionally in a healthy liver. With cirrhosis, there is the cancer, the precancerous state, and disturbed liver function, particularities that condition the prognosis and therapeutic strategy.

In France, the annual incidence is 11/100,000 in men and 1.5/100,000 in women; as in other Western countries, a sharp increase in incidence has been observed over the last 20 years mainly because of the increase in cirrhosis due to the hepatitis C virus [1].

The level of evidence available on treatment efficacy is low; in particular, no randomized prospective study has demonstrated the effectiveness and the respective place of surgical and percutaneous treatments.

Pretherapy explorations

Evaluation of liver without tumor

DIAGNOSIS OF CIRRHOSIS
• Diagnosis can be easy based on clinical, biochemical (prothrombin time, platelets, albuminemia, fibrosis markers), endoscopic (esophageal varices), and morphological (hepatic dysmorphia and signs of portal hypertension on ultrasound or CT).
• If the patient has no symptoms, a nontumoral liver biopsy remains indispensable to confirm cirrhosis. Alternatives noninvasive methods are being tested.
• Etiological workup for cirrhosis.

EVALUATION OF THE SERIOUSNESS OF CIRRHOSIS
• Clinical and biochemical examinations (prothrombin time, albuminemia, bilirubinemia), determination of Child-Pugh score.

Hepatocellular carcinoma diagnosis

After discovery of a hepatic nodular focal lesion on ultrasound or when there are symptoms of advanced tumor, a diagnosis of hepatocellular carcinoma is usually advanced.

Helical CT with arterial and portal acquisition and MRI are the reference examinations; the most suggestive sign of hepatocellular carcinoma is a hypervascularized nodule with early arterial time and late wash-out at the portal time [3]. MRI seems to perform a little better than CT in detecting and describing nodules [4] which can distinguish a regenerative nodule from a cancerous nodule. MRI is useful when CT contributes no useful information for diagnosis. In a patient with cirrhosis, a focal, hypervascularized lesion larger than 2 cm in diameter nearly always means HCC [3].

HEPATOCELLULAR CARCINOMA DIAGNOSTIC CRITERIA (ACCORDING TO THE EASL 2000 BARCELONA CONFERENCE) [5]

• Histological or cytological test using ultrasound- or CT-guided needle biopsy (required if the lesion is <2 cm).
• Noninvasive criteria of HCC diagnosis (limited to patients with cirrhosis):
  — nodule >2 cm with arterial hypervascularization + alpha-fetoprotein (AFP) >400 μg/l
  — nodule >2 cm with arterial hypervascularization demonstrated by two imaging methods in agreement, helical CT and MRI (possibly echo-Doppler or contrast-enhanced ultrasound).

The presence of HCC risk factors (age >55 years, male sex, advanced cirrhosis), an increase in the size of the nodule or AFP (but no substantial rise in transaminases) during short-term follow-up and the presence of portal obstruction with characteristics of tumoral thrombosis (hypervascularization and vein enlargement), are also arguments in favor of the HCC diagnosis.
Certain forms of HCC (infiltrating forms, 10%-15% of cases) are difficult to diagnose when there is no focal lesion visible on imaging and are usually difficult to access in treatment. Similarly, diagnosis can be difficult in cases of nodule diameter ≤1 cm, which can be a HCC, a benign lesion, or even disappear during follow-up; re-evaluation with imaging 3 months later is recommended.

NEEDLE BIOPSY OF TUMORAL LIVER

Needle biopsy is not systematic in pretherapy tests; it is indicated only when the diagnosis of HCC is not obvious after clinical, biochemical, and morphological evaluation [6], depending on how therapy will be oriented. When transplantation is considered, biopsy can be useful in the pretransplantation workup to avoid false-positives [7] but should not be done before having contacted the referral center because of the risk of seeding along the needle trajectory [3]. The biopsy should be done with a fine needle and through a substantial thickness of nontumoral parenchyma [8] and, especially if transplantation is planned, with protection for the route to the wall [7]. In cases of percutaneous treatment, a biopsy using the same introductory needle can be done during the first session. Finally, if there is a suspicious nodule that is inaccessible to biopsy in a patient with Child-Pugh A cirrhosis, diagnostic and therapeutic resection can be discussed.

Assessment of extension

- Clinical examination
- AFP
- Thoracoabdominal CT (or MRI + thoracic CT) with injection of contrast product to specify i) tumor morphology (lesion size and number), ii) portal and hepatic vascularization, and iii) whether there is lymph node or visceral extension. CT can calculate hepatic volumes. Echocardiography can be useful to define the state of portal or hepatic flow. MRI is useful if CT does not describe the nodule or tumor extension sufficiently. Currently, no imaging exam can detect very small HCC, frequently associated with visible tumors.
- Brain CT and bone scintigraphy: should be done only when there is a relevant clinical sign.
- Preoperative workup in consultation with the anesthesiologist (respiratory function, gasometry, ECG, echocardiography, etc.) if surgery is planned.

Epidemiologically associated cancers

Cancers related to alcohol or tobacco intoxication, in particular if transplantation is planned.

After these tests, it is necessary to:

- have evaluated the condition of the nontumoral liver (cirrhosis? fibrosis? functional problems?)
- be certain that there is at least a strong probability of HCC diagnosis
- have evaluated the extension of the tumor and portal hypertension
- have searched for signs of poor prognosis (tumor aggression), i.e., local vascular tumor extension, whether the tumor is infiltrating or not, AFP >1000 μg/l, or rapid progression as judged by imaging and/or AFP.

Classification

The Okuda classification has been the most frequently used, but other, more recent typings developed from multivariable studies, show better performance [2]. The best validated, in particular by prospective studies, is the CLIP (Cancer of the Liver Italian Program [2]) classification. However, these classifications should be evaluated by independent studies. They are especially useful in trials because they do not show good performance in clinical practice in recognizing patients who may benefit from curative treatment. Consensus is necessary to standardize patient management.

CLIP classification

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh class</td>
<td>A 0, B 1, C 2</td>
</tr>
<tr>
<td>Tumor morphology</td>
<td>Single nodule and extension ≤50% 0, Multinodal and extension ≤50% 1, Diffuse or extension &gt;50% 2</td>
</tr>
<tr>
<td>Alpha-fetoprotein (μg/l)</td>
<td>≤400 0, &gt;400 1</td>
</tr>
<tr>
<td>Portal thrombosis</td>
<td>No 0, Yes 1</td>
</tr>
</tbody>
</table>

SCORE TOTAL (0–6)

Treatment

Methods

CURATIVE TREATMENT

Curative treatment is discussed when a single tumor measures <5 cm in diameter or, when there are several tumors, if there are no more than three nodules no larger than 3 cm in diameter, in absence of thrombosis of the trunk or a lobar branch of the portal system (= Milan criteria = small HCC [5, 6]).

Transplantation: in small HCC, transplantation cures 2/3 of patients with results comparable to those of transplantation cirrhosis without tumor [7], but the frequent contraindications (age, physiological condition) and the shortage of organs limits the indications. Because of the waiting period before transplantation, which runs the risk of tumor progression, the problem of interim treatment, for which the advantages and modalities are not clearly defined. Therapeutic trials are necessary. Live donor transplantation can be planned if the waiting period seems excessive [7].

Resection: resection is discussed if transplantation is not possible, if liver function does not allow it, and if it does not involve more than four liver segments. It is currently believed that the best candidate for resection has a single tumoral nodule, normal bilirubinemia, ALT <2 N, and no sign of portal hypertension [6]. Several specialized centers have published good results in terms of survival after resection of larger tumors [9].

Percutaneous destruction: this is an alternative to surgery [10]. A simple and usually well-tolerated method, it has the advantage of preserving the nontumoral parenchyma. Alcoholization is the best-evaluated method [11], but it is increasingly replaced with radiofrequency, which requires fewer
sessions and, more importantly, is associated with longer local [12,13] and global [13] recurrence-free survival than after alcoholization. Radiofrequency treatment can be envisaged only if the tumor is less than 5 cm in diameter, is accessible to needle biopsy, and is located distant from the hilum and the bile ducts. The longest survival times are observed in patients with HCC ≤3 cm in diameter and complete remission after treatment [14].

It is commonly admitted that treatment using percutaneous destruction should be proposed to patients who have not had resection [6]. Actually, this hierarchy between the two methods has no scientific foundation [15]. Criteria other than survival must therefore be used and multidisciplinary discussion is desirable [16] (see Recommendations).

After treatment with curative intent by resection or percutaneous destruction, there is a very high risk of local recurrence (treatment failure) or distant recurrence (new HCC). This brings up the problem of a possible adjuvant treatment. A preliminary trial has suggested the advantage of injecting radioactive lipiodol (Lipiocis®) [17] via the hepatic artery. Interferon in cases of HCV cirrhosis HCC seems beneficial in terms of survival and/or recurrence [18, 19]; however, the modalities of its administration have yet to be determined.

**Palliative treatment**

**LIPIODOL CHEMOEMBOLIZATION**

Two recent phase III trials and two meta-analyses have observed longer survival in treated patients (20-23). The difference with earlier negative trials is that only patients with preserved liver function were included. In addition, patients for the most part had HCC from chronic liver disease of viral origin. The advantage of lipiodol chemoembolization in patients with HCC from alcoholic cirrhosis remains controversial: the results of the FFCD 9402 trial (no gain in survival in treated patients) confirm the results of earlier studies on the same patient populations [24]. Lipiodol chemoembolization modalities and monitoring after treatment have not yet reached consensus.

Randomized studies favor the efficacy of Lipiocis® for portal thrombosis [25, 26], but this technique is only possible in specialized units because it requires hospitalization in a lead-shielded room.

**SYSTEMIC CHEMOTHERAPIES**

Systemic chemotherapies are toxic and have not proven their efficacy in phase III studies [6]. Phase II studies have observed maximum response rates of 20%-30%. They should only be prescribed in a trial context.

**TAMOXIFEN**

[27-29], anti-androgens [30, 31], interferon [32] and octreotide [33, 34] are not effective.

**Recommendations**

**CIRRHOSIS HCC**

Two main criteria are discussed: tumor characteristics (number, size, vascular extension) and the severity of cirrhosis, evaluated on symptoms (ascites, digestive hemorrhage caused by portal hypertension, encephalopathy, jaundice, etc.) and whether there are signs of liver insufficiency (bilirubinemia, prothrombin time) and/or portal hypertension. Based on these criteria, four situations are defined.

**Symptomatic cirrhosis (Child-Pugh class B or C)**

— large HCC

Histological proof of HCC diagnosis is not indispensable

**Reference**

Reference: symptomatic treatment (level B)

— small HCC

The therapeutic problem is the severity of cirrhosis and not the HCC.

**Reference**

Reference: liver transplantation for severe cirrhosis should be discussed with a reference center (level B).

**IF CONTRAINDICATION TO TRANSPLANTATION: percutaneous destruction for Child-Pugh class B patients who do not have ascites (level B).**

When etiological treatment is possible (alcohol weaning, HBV eradication, etc.), cirrhosis can be improved and the therapeutic discussion on the HCC can be re-evaluated (expert agreement).

**Asymptomatic cirrhosis (Child-Pugh class A)**

— small HCC

The main problem is to discuss the indication for transplantation; the opinion of a reference center should be systematically requested except in cases of contraindication (age, severe extrhepatic disease, uncontrolled HIV infection, neoplastic portal trunk obstruction).

• Transplantable disease

**Reference**

Reference: transplantation (level B)

**Alternative**

Alternative: transplantation preceded by local treatment, (percutaneous destruction, lipiodol chemoembolization, Lipiocis® or liver resection) (level C)

Depending on the team, three strategies can be considered: a) put the patient on the waiting list without neoadjuvant treatment if the waiting period is estimated to be short; b) local treatment and putting the patient on the waiting list; c) local treatment with curative intent, rescue transplantation considered in cases of recurrence, the option to favor in cases of HCC less than 2–3 cm in diameter. (7)

• Transplantation not possible

**Alternatives**

**Alternatives** (level B)

— Resection (when there is no biological sign of hepatic insufficiency)

— Percutaneous destruction

Discussion on a case by case basis in multidisciplinary consultation meeting; the criteria to take into account are the morphology and location of the tumor (providing evaluation of resectability and its accessibility for percutaneous treatments), the patient’s operability (physiological age, cardiac
and respiratory workup), aggressivity of the tumor as defined above, liver insufficiency (resection is only appropriate for patients with no biological sign of liver insufficiency) and/or portal hypertension (factor or poor prognosis after resection).

**Adjuvant treatment trials**
- ANRS HC06 LIPIOCIS: Randomized therapeutic trial for adjuvant treatment of hepatocellular carcinoma
- Randomized therapeutic trial for adjuvant treatment of hepatocellular carcinoma with Iressa™ (Gefitinib) (Trial financed by the national PHRC, beginning 2006). Coordinator: Olivier Rosmorduc

**Alternatives**

**ALTERNATIVES** (level C)
- Lipiodol chemoembolization, especially with hypervascularized and well-differentiated tumor.
- Lipiocis® in cases of portal thrombosis.
- Large HCC

Transplantation is not possible; the recurrence rate is high no matter which therapeutic method is used.

**Reference**

**Reference: abstention** (level B)

**Alternatives**

**Alternatives** (level C)
- If there is no biological sign of liver insufficiency:
  - Resection
  - Lipiodol chemoembolization
  - Lipiocis® in cases of portal thrombosis

**HCC WITH NONCIRRHOTIC LIVER**

**Reference**

**Reference: resection** (level B)

The indications are broader than when there is cirrhosis. Histological examination of the nontumoral liver is indispensable. In addition, because of the absence of cirrhosis, there are many problems of differential diagnosis and therefore the tumor must be biopsied. Resection provides good results when there is no portal invasion.

**Alternatives**

Alternatives: If resection is not retained, other therapeutic methods are considered according to the same criteria as when there is cirrhosis. (level B)

**Monitoring (expert agreement)**

**After resection or percutaneous destruction**
- Clinical + biochemical (liver tests and AFP) every 3 months the first year, then every 6 months.
- Preoperative reference examination (MRI or liver CT) at M1, M3, M6, M12, M18, M24, then annually.
- Lung x-ray every 6 months when liver monitoring with MRI.
- Bone scintigraphy and brain CT only if clinical sign.
- Ultrasound every 6 months beginning the second year.

**Screening for other cancers**

Screening related to alcohol and tobacco intoxication if relevant.

**Acknowledgments to readers:** Thierry de Baere (Institut Gustave Roussy, Villejuif), Bernard Denis (Hôpital Pasteur, Colmar), Olivier Rosmorduc (Hôpital St Antoine, Paris)

**REFERENCES**


