Diagnosis, staging and treatment of hepatocellular carcinoma

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Abstract

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Hepatocellular carcinomas are aggressive tumors with a high dissemination power. An early diagnosis of these tumors is of great importance in order to offer the possibility of curative treatment. For an early diagnosis, abdominal ultrasound and serum alpha-fetoprotein determinations at 6-month intervals are suggested for all patients with cirrhosis of the liver, since this disease is considered to be the main risk factor for the development of the neoplasia. Helicoidal computed tomography, magnetic resonance and/or hepatic arteriography are suggested for diagnostic confirmation and tumor staging. The need to obtain a fragment of the focal lesion for cytology and/or histology for a diagnosis of hepatocellular carcinoma depends on the inability of imaging methods to diagnose the lesion. Several classifications are currently available for tumor staging in order to determine patient prognosis. All take into consideration not only the stage of the tumor but also the degree of hepatocellular dysfunction, which is known to be the main factor related to patient survival. Classifications, however, fail to correlate treatment with prognosis and cannot suggest the ideal treatment for each tumor stage. The Barcelona Classification (BCLC) attempts to correlate tumor stage with treatment but requires prospective studies for validation. For single tumors smaller than 5 cm or up to three nodules smaller than 3 cm, surgical resection, liver transplantation and percutaneous treatment may offer good anti-tumoral results, as well as improved patient survival. Embolization or chemoembolization are therapeutic alternatives for patients who do not benefit from curative therapies.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary solid tumor of the liver. Its aggressiveness and extensive dissemination lead to a poor patient prognosis. HCC is estimated to account for 5% of all malignant neoplasias (1). Its prevalence is considered to be high (>20 cases/100,000 inhabitants/year) in the far East and Africa, medium (5 to 20 cases/100,000 inhabitants/year) in Europe, and low (<5 cases/100,000 inhabitants/year) in South America. In Brazil, its prevalence is considered to be low, despite geographic variations (2).

Cirrhosis of the liver, regardless of etiology, is considered to be the main risk factor for the onset of HCC. In Africa and in South Asia,

hepatitis B is the main cause of hepatic disease. In these regions, HCC may develop among young patients, even when they do not have cirrhosis of the liver because infection with the hepatitis B virus occurs during delivery or soon after birth, with the prolonged period of infection being the major determinant of the onset of HCC in these patients. In the Western World and in Japan, hepatitis C virus is the main factor related to the presence of cirrhosis of the liver in patients with HCC. In a survey conducted by the Brazilian Society of Hepatology in Brazil in 1995 cirrhosis of the liver was present in 71% of patients with HCC, with the cause of liver disease being hepatitis B in 39% of cases, hepatitis C in 27% and alcoholism in 37%. In our patient series, hepatitis C virus (43%) and alcoholism (38%) are the major causes of liver cirrhosis in patients with HCC (3).

Cirrhosis of the liver is present in 60 to 100% of patients with HCC (4,5) depending on regional variations. Among our patients with HCC, 90% have cirrhosis of the liver (3).

With the identification of cirrhosis of the liver as the main risk factor for the development of HCC, and in view of the high aggressiveness of this type of neoplasia when diagnosed in advanced stages, periodic follow-up is necessary for an early diagnosis of the tumor.

HCC is a tumor that satisfies the requirements of neoplasias for which screening is justified. There is a well-defined risk group (cirrhosis of the liver), there are effective, noninvasive and low cost diagnostic techniques (ultrasound, US, and alpha-1 fetoprotein, AFP), and curative therapeutic techniques are available which can increase patient survival (resection, liver transplantation and percutaneous treatment).

Diagnosis

An early diagnosis of HCC is required for the institution of treatments considered to be curative. On this basis, screening of each patient with cirrhosis of the liver regardless of etiology is of primordial importance for the detection of tumors in the initial stages of development. It has been suggested that monitoring should be performed by US and by measurements of serum AFP at 6-month interval. The option for a 6-month interval is based on the mean time for tumor duplication, which is about 6.5 months and may range from 1 to 20 months (6,7). Shorter intervals (3 to 4 months) or the use of other imaging methods such as helicoidal computed tomography have been suggested for HCC screening in patients considered to be at high risk. However, the definition of what should be considered a high risk varies among investigators and also among the populations studied. A comparison of the different schedules (reduced intervals between exams) or the use of other imaging techniques is lacking in the literature.

However, only patients who would benefit from curative treatment should be submitted to screening. On this basis, in patients with cirrhosis of the liver classified as Child-Pugh C with no indication for liver transplantation, monitoring with US and AFP will be of no benefit in terms of patient survival.

Ultrasound

US is considered to be the technique of choice for the diagnosis of focal hepatic lesions (8), permitting the detection of tumors of small size (1 cm) still in the early phase of development and thus being justified for the screening of HCC in patients with cirrhosis of the liver (8,9). The ultrasonographic characteristics of HCC depend on nodule size. Small nodules of less than 3 cm are frequently hypoechogenic. As they increase in size, they start to acquire isoechogenic characteristics with a peripheral halo or hyperechogenic or heterogeneous characteristics due to the neoformation of blood vessels and intratumoral necrosis. Other possible findings are lateral shadows, a poste-

rior reinforcement and a perilesional halo that corresponds to the presence of a peritumoral fibrous capsule consequent to the compression of the adjacent hepatic parenchyma (8). US can also be used to assess the permeability of vascular structures and the existence of hilar adenopathies suggestive of tumoral extension.

The sensitivity of US for the detection of HCC is directly related to tumor size. Its diagnostic sensitivity for tumors smaller than 1 cm is about 42% (10,11), reaching 95% for tumors of larger size (12).

The combination of Doppler with US can be useful for the identification of portal thrombosis in patients with HCC, with 89 to 92% sensitivity and 100% specificity in the identification of tumor thrombosis (13). The presence of a hepatofugal pulsatile flow inside the thrombus is suggestive of vascular invasion (14). Hepatic arteriography for the identification of portal thrombosis can be avoided when US-Doppler reveals permeability of the portal system (13). In patients with tumors submitted to alcoholization, chemical thrombosis can be differentiated from tumoral thrombosis by means of US-Doppler based on the presence of blood flow in the thrombus. The presence of a pulsatile thrombus rules out the possibility of benign thrombosis (by alcohol), confirming the presence of tumoral invasion of portal vessels. In cases in which doubts persist about the cause of portal thrombosis, fine needle aspirative puncture can be used, a highly sensitive procedure for the confirmation of tumoral thrombosis which also involves low risks of complications (14).

In addition to providing an imaging diagnosis, US can also be used to guide the needle for aspirative puncture or for a biopsy carried out to obtain a tissue fragment from the tumor nodule (8).

Alpha-1 fetoprotein

Under physiological conditions, AFP is synthesized by the embryonic liver, by cells of the vitellin sac and by the fetal intestinal tract. Patients with chronic liver disease, especially those with a high degree of hepatocyte regeneration, can express AFP in blood in the absence of malignant neoplasia.

Measurement of serum AFP levels is not useful for the early detection of HCC because, even though 80% of the patients with HCC have serum AFP concentrations exceeding normal levels (10-20 ng/ml), patients with a high liver regenerative activity may express higher than normal AFP values without having HCC (8,15,16).

AFP serum levels above 400-500 ng/ml are considered to be diagnostic of HCC in cirrhotic patients with focal hepatic lesions (8). However, only 1/3 of patients with HCC have AFP levels higher than 100 ng/ml, with levels above 400 ng/ml being quite infrequent in the presence of small tumors (<5 cm) (8).

Even though they do not reach levels considered to be diagnostic (400-500 ng/ml), progressively increasing AFP concentrations during screening are suggestive of a diagnosis of HCC. These patients should be submitted to helicoidal computed tomography in order to rule out the diagnosis of a tumor. The values and the time interval between AFP measurements needed for them to be considered as "progressively increasing AFP levels" have not yet been established.

With the development of early detection programs, an increase in the number of cases with small tumors and normal AFP levels (29%) has been observed (16). In our experience, 42% of patients with HCC present serum AFP levels within normal limits (3).

At the time of tumor diagnosis, AFP seems to be of prognostic value. This may be due to the fact that well-differentiated tumors express less AFP and patients with normal AFP have a lower incidence of tumoral vascular invasion and tend to present better hepatic function, which is known to be one of the

major prognostic factors for these patients (16-18).

Other tumor markers

Des-gamma carboxyprothrombin (DCP) is another tumor marker used for the diagnosis of HCC. Its diagnostic efficacy has been investigated by various groups, with contradictory results. There are reports of the superiority of DCP over AFP in the diagnosis of HCC, especially in the Orient and in North America. However, studies conducted in Europe have not shown a better performance of DCP compared to AFP. Racial and etiological factors of liver disease may be responsible for the discrepant results. Despite the contradictory results, the combination of the two markers is suggested to increase the diagnostic efficacy. Studies on large patient series and on diverse ethnic populations are needed to clarify the real role of DCP in the diagnosis of HCC.

Other markers such as interleukin-2, urinary tumor growth factor-ß1 and MAGE-4 protein receptors have also been used in research to aid the diagnosis of HCC but their clinical applicability requires scientific confirmation.

In the presence of a diagnostic suspicion by US and/or AFP, the patient should be further investigated by helicoidal computed tomography (CT) and/or magnetic resonance (MR) and, in selected cases, by hepatic arteriography, in order to confirm the suspected diagnosis and determine the stage of the tumor.

Helicoidal computed tomography

After the suspicion of HCC by US in a patient with cirrhosis of the liver, the use of CT is suggested. The sensitivity of CT for the diagnosis of HCC is similar to that of US. Its diagnostic efficacy depends on technical factors, mainly the injection of contrast, and on factors inherent to the tumor, the most important of which are tumor size and vascularization. CT should be performed by the spiral (or helicoidal) technique with intravenous injection of contrast and images should be obtained in the basal, arterial, portal, and equilibrium phases. The main characteristic of HCC detected by CT is the early uptake of contrast in the arterial phase of the exam. Due to the hypovascularization of small-sized tumors, the diagnostic efficacy of CT is reduced in tumors measuring less than 2 cm (19,20). A second phase after the intravenous contrast increases the diagnostic sensitivity when associated with the arterial phase, when the HCC is found to be iso- or hypodense (20). When images and intravenous contrast are associated, a greater capacity to detect HCC is achieved.

The use of standard CT causes technical difficulties such as respiratory artifacts and difficulty in capturing images during the arterial phase of the contrast dye. To obviate these technical difficulties, the helicoidal (spiral) technique has been used which, due to the rapid image acquisition, permits the capture of sections of the entire liver during a single moment of apnea. This technique increases by about 15% the diagnostic sensitivity for the detection of hepatic tumors smaller than 2 cm compared to standard CT. CT also reveals the presence of tumor involvement of lymph nodes, vascular invasion and extrahepatic involvement with high sensitivity, specificity and diagnostic accuracy.

Intra-arterial injection of lipiodol followed by CT (CT-lipiodol) presents low diagnostic sensitivity (37%) which is not higher than that of helicoidal CT, in addition to being an invasive method (10). Thus, the CT-lipiodol technique has not been routinely used for the diagnosis of HCC.

Magnetic resonance

MR has been used to obtain a better characterization of hepatic lesions sugges-

tive of HCC and also for their differentiation from benign lesions (21). HCC is better evaluated in potentiated sequences in T2, where it frequently appears to be hyperintense (22,23). In potentiated sequences in T1, because of the larger amount of water inside them, which increases the relaxation time, HCC are found to be hypointense. The hyperintensity in T1 may be attributed to the presence of steatosis, to the formation of light cells and to intratumoral copper accumulation. Intravenous injection of paramagnetic contrast (gadolinium-DTPA) is also used to better characterize the lesions. As observed with CT, HCC appears as a hyperdense image with contrast uptake. The sensitivity of MR depends on tumor size. In tumors larger than 2 cm the level of detection is about 95%. However, in tumors smaller than 2 cm this level is reduced to 30% (22). The diagnostic efficacy of MR for the detection of HCC seems to be similar to or even lower than that of CT. However, this imaging technique is very useful for the demonstration of the internal architecture of the tumor, of the tumoral margins, of the presence of a peritumoral capsule, and of intrahepatic vascular invasion (22).

One of the major useful properties of MR is the differential diagnosis from hepatic hemangioma (8). Because of the lack of anatomical limitation, MR and CT are superior to US for the diagnosis of tumors close to the lung and of isoechogenic lesions (15).

Hepatic arteriography

The diagnostic efficacy of hepatic arteriography (HA) depends on tumor size and on the extent of tumor vascularization (19). Small tumors tend to be well differentiated and consequently present low vascularization, thus being difficult to detect by this technique (24). For tumors smaller than 5 cm, HA has 82 to 93% diagnostic sensitivity, 73% specificity and 89% diagnostic accuracy, with these values being even more reduced when the tumors are smaller than 2 cm (24,25).

Only in selected cases is it possible to use laparoscopy for the diagnosis of HCC, since this technique only analyzes the presence of superficial lesions.

The diagnostic accuracy of imaging techniques for the detection of HCC depends on the characteristics of the tumor and on the experience of each study group. In our experience (12,26), the ability to diagnose HCC is 84% for US, 79% for CT, 77% for MR, and 64% for HA. Thus, because of its low cost and availability, we believe that US continues to be the exam of choice for an early diagnosis of HCC, being useful for the monitoring of cirrhotic patients. However, the experience and awareness of the operator is of primordial importance during the execution of the exam.

Cytology and/or histology

Cytologic and/or histopathologic examination of the suspected lesion can also be used for the diagnosis of HCC. The material to be used for cytology is obtained by fine needle aspirative biopsy (FNAB). This is a safe technique with minimal risks of complications due to the procedure, which provides adequate material when performed by trained personnel. Its diagnostic accuracy may vary from 60 to 90% (8,27) depending on the size of the lesion, on the examiner and on the diameter of the puncturing needle. The specificity and positive predictive value of this technique are higher than 90%, reaching 100% in our experience (27).

Histopathological examination is the main method for a sure diagnosis of HCC. A nontumoral liver biopsy is important to rule out or to confirm the presence of liver cirrhosis, since the presence of cirrhosis may contraindicate surgical treatment. The two pathology techniques can be used for the diagnosis of HCC and their combination can increase the diagnostic accuracy (27). To prevent com-

plications, the nodule should always be punctured through the non-tumoral liver, which will serve as a "buffer" preventing bleeding.

Diagnostic criteria

In a recent publication, the European Association for the Study of the Liver (EASL) (28) proposed guidelines and criteria for the diagnosis of HCC in cirrhotic patients (Figure 1). The presence of a nodule larger than 2 cm with hypervascular characteristics detected by at least two imaging techniques confirms the presence of HCC, with no need for cyto-histopathological confirmation. FNAB and/or a biopsy of the suspected lesion with a cutting needle are suggested for cirrhotic patients with nodules smaller than 2 cm, since in about 50% of cases the diagnosis of HCC cannot be confirmed by imaging methods (1).

The diagnostic criteria (28) are cytological and/or histological criteria, or noninvasive criteria, which include 1) radiologic criterion: two coinciding imaging techniques demonstrating a focal hepatic lesion >2 cm with arterial hypervascularization, or 2) combined criteria: an imaging technique associated with increased serum AFP levels, a focal lesion >2 cm with arterial hypervascularization, and serum AFP levels >400 ng/ml.

The imaging techniques to be evaluated are US, CT, MR, and HA. However, the technology for the execution of all imaging exams suggested by the EASL is not available at all hospital centers. Similarly, the curative therapies also require properly trained specialized teams that are not available at all medical services. This fact leads to two observations: 1) screening with US and AFP should be performed only in cases in which the medical team can offer curative therapies (surgical resection, liver transplantation and percutaneous treatment); 2) the lack of access to helicoidal CT, MR and HA does not exclude the possibility of diagnosing HCC. In this situation we believe that FNAB and/or a biopsy of the lesions should be obtained for a sure diagnosis regardless of tumor size, as long as the patients can be treated with available techniques.

Staging

The main objective of tumor staging is to determine the prognosis of the disease and to

Figure 1. Diagnosis of hepatocellular carcinoma according to the Barcelona-2000 Conference of the European Association for the Study of the Liver (EASL) (28). *Patients who can be submitted to curative treatment if an HCC is diagnosed; **Undefined AFP level; ***Confirmation by pathology or by a noninvasive criterion. AFP = alpha-1 fetoprotein; CT = computed tomography; HA = hepatic arteriography; HCC = hepatocellular carcinoma; MR = magnetic resonance; US = ultrasound.
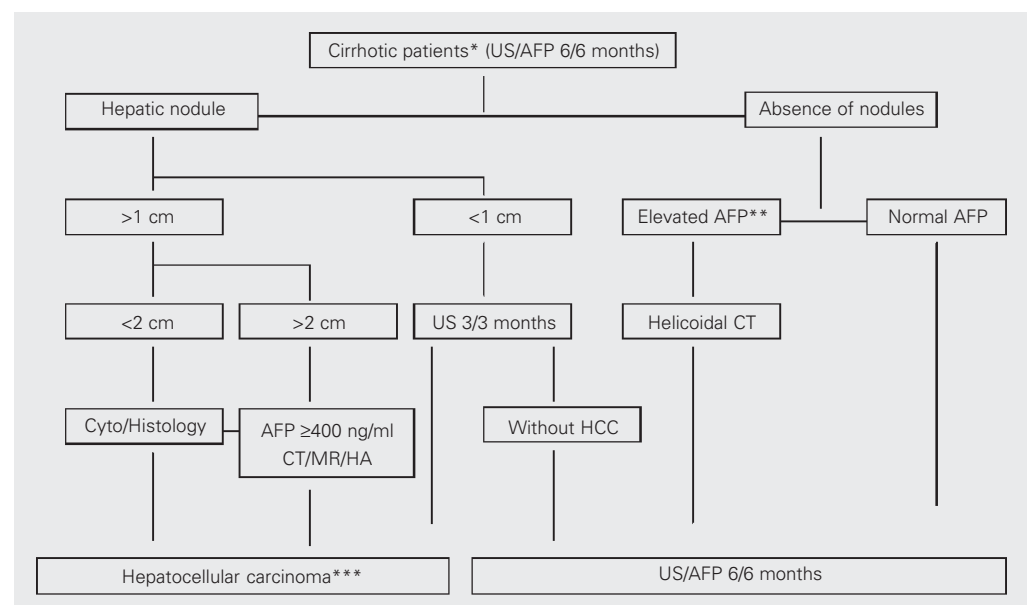
establish the best therapeutic method for the patient. Several factors should be analyzed in cirrhotic patients with HCC. Prognosis and treatment mainly depend on the degree of hepatic dysfunction, tumor stage and general patient condition. It should be kept in mind that most patients with HCC have associated cirrhosis of the liver, this being a factor frequently as important or even more important than tumor stage.

Various classifications have been adopted to stage HCC. The first was developed in 1985 by Okuda et al. (5) (Table 1) in a study on 850 patients with HCC using data concerning tumor size (> or < than 50% of the liver size), serum bilirubin levels (> ou <3 mg/dl), serum albumin levels (> or <3 g/dl), and the presence of ascites, classified HCC into three stages. The mean survival rate for patients with stages I, II and III was 11.5, 3 and 0.9 months, respectively, without considering the treatment variable. When the patients submitted to surgical resection of the tumor were analyzed, survival reached 25.6 months for patients with Okuda stage I.

Several other prognostic classifications of HCC are currently being used:

Barcelona Clinic Liver Cancer (BCLC) Group (29) (Table 2). This classification takes into consideration hepatic function, portal hypertension, bilirubins, symptoms related to the tumor, tumor morphology, presence of distant metastases, or vascular invasion. This is the only classification that correlates prognostic data with therapeutic possibilities.

TNM classification (30) (Table 3). This classification considers the size and number of nodules, vascular invasion, and bilobar involvement. Hepatic function is not considered as a factor in staging, although it is an important factor for the prognosis of these patients. Evaluation of this classification in patients submitted to liver transplantation did not show benefits in prognostic terms for patients with HCC (30). The inclusion of the hepatic fibrosis factor in staging by TNM has been recently suggested.

French classification (31) (Table 4). This classification includes as prognostic factors

Table 1. Okuda classification of hepatocellular carcinomas (5).

	Negative	Positive
Tumor size	<50% of liver	>50% of liver
Ascites	Absent	Present
Serum albumin	>3 g/dl	<3 g/dl
Bilirubin	<3 mg/dl	>3 mg/dl

Okuda I: No positive factor; Okuda II: 1 or 2 positive factors; Okuda III: 3 or 4 positive factors.

Table 2. Barcelona Clinic Liver Cancer (BCLC) Group classification of hepatocellular carcinomas (29).

Stage	PST	Tumor stage	Okuda	Portal hypertension	Total bilirubin	Child-Pugh
A						
A1	0	Single	I	No	Normal	
A2	0	Single	I	Yes	Normal	
A3	0	Single	I	Yes	Altered	
A4	0	3 <3 cm	I–II			A–B
B	0	>5 cm Multinodular	I–II			A–B
C	1-2	Vascular invasion and/or metastasis	I–II			A–B
D	3-4	Any stage	III			C

PST = Performance status test.

the Karnofsky index, serum bilirubin levels, AFP, alkaline phosphatase, and the presence of portal thrombosis detected by US. The score ranges from 0 to 11. The 1- and 2-year survival rate was 72 and 51% for low risk patients (score 0), 34 and 17% for patients of

intermediate risk (score 1 to 5), and 7 and 3% for high risk patients (score ≥6), respectively. It should be pointed out that this classification was based on the analysis of patients (47%) submitted to some type of treatment. In addition, mean patient survival was only 4.3 months, suggesting selection of patients with an advanced stage of the disease.

Chinese University Prognostic Index (32) (Table 5). This index includes the TNM classification associated with serum levels of bilirubin, alkaline phosphatase, AFP, presence of ascites, and absence of clinical symptoms at the time of diagnosis. The score ranges from -7 to 12. The mean survival is 10 months for low risk patients (score ≤1), 3.7 months for patients at intermediate risk (score from 2 to 7), and 1.4 months for high risk patients (score ≥8). It should be pointed out that the patients analyzed in the cited study were Chinese, most of them (79%) with cirrhosis of the liver due to hepatitis B virus. Of the patients evaluated, 41.6% were submitted to some antitumoral treatment which might have interfered with data assessment. The low mean survival for these patients (19 weeks) may also suggest the selection of patients with advanced tumors.

Cancer of the Liver Italian Program (17) (Table 6). This program includes hepatic function, tumor morphology, presence of thrombosis of the portal vein, and serum AFP levels. It should also be pointed out that part of the patients were submitted to either regional (57%) or systemic (18%) treatment, a fact that may change the data of this prognostic system. The tumors of the patients are divided into 7 stages (0 to 6). Mean survival is 35, 8 and 3 months for stages 0, 2 and 4-6, respectively (18).

As is the case for diagnosis, population differences also influence the prognostic models. In contrast to other types of tumors in which the neoplasia is responsible for mortality, in HCC, cirrhosis of the liver is the main factor related to patient survival. In general, hepatocellular function is consid-

Table 3. TNM classification of hepatocellular carcinomas (30).

Classification	Definition
T1	Solitary tumor ≤2 cm in the widest diameter without vascular invasion.
T2	Solitary tumor ≤2 cm in the widest diameter with vascular invasion; or multiple tumors limited to one lobe, none of them >2 cm in the widest diameter, without vascular invasion; or solitary tumor >2 cm in the widest diameter, without vascular invasion.
T3	Solitary tumor >2 cm in the widest diameter with vascular invasion; or multiple tumors limited to one lobe, none of them >2 cm in the widest diameter, with vascular invasion; or multiple tumors limited to one lobe, some of them >2 cm in the widest diameter, with or without vascular invasion.
T4	Multiple tumors in more than one lobe; or tumor(s) invading a large portal branch or one or more suprahepatic veins. Solitary tumor >2 cm in the widest diameter with vascular invasion.

Stage of TNM classification

I	T1 / N0 / M0
II	T2 / N0 / M0
III A	T3 / N0 / M0
III B	T1 / N1 / M0
	T2 / N1 / M0
	T3 / N1 / M0
IV A	T4 / any N / M0
IV B	any T / any N / M1

T = tumor; N = nodes; M = metastasis; N0 = without regional lymph nodes; N1 = with regional lymph nodes; M0 = without distant metastasis; M1 = with distant metastasis.

Table 4. French classification of hepatocellular carcinomas (31).

	0	1	2	3
Karnofsky index (%)	≥80			<80
Bilirubin (µmol/l)	<50			≤50
Alkaline phosphatase (MNL)	<2		≥2	
Alpha-1 fetoprotein (µg/l)	<35		≥35	
Portal obstruction (US)	No	Yes		

Karnofsky index >80% = complete patient autonomy; MNL = maximum normal limit; US = ultrasound. Group A (low risk): 0 point; group B (intermediate risk): 1-5 points; group C (high risk): ≥6 points.

ered to represent one of the major variables related to patient survival. In addition, hepatic dysfunction determines the type and efficacy of the treatment proposed.

Another factor just as important is the presence of neoplastic vascular invasion. Four of the classifications presented earlier consider the presence of vascular invasion to be a factor related to survival, indicating tumor dissemination. However, in most cases, vascular invasion is diagnosed only during histopathological analysis, i.e., after the application of therapeutic procedures such as resection and liver transplantation. Unfortunately, currently available imaging methods are not sufficient for the diagnosis of tumoral thrombosis of small hepatic vessels.

Serum AFP levels are also considered to be of prognostic value in three classifications. Due to the low general survival rates of the patients evaluated by these classifications, it is possible that selection of patients with advanced tumors occurred, since early HCC tend not to express high AFP levels.

One of the great benefits of tumor classification, in addition to providing an estimate of survival, is the selection of patients who can be submitted to treatment. The treatments currently used for HCC have shown an effect on patient survival, especially surgical and percutaneous therapies. However, none of the classifications available considers this variable (treatment). On this basis, the new classifications should evaluate the treatment options as a prognostic factor and correlate the tumor stages with the form of treatment to be adopted. The only classification that tries to correlate tumor stage with treatment is that of the Barcelona Group (BCLC). However, this classification still awaits prospective validation. Regional multicenter studies on large patient series are needed to clarify the best time and types of treatment for each patient with HCC.

The main sites of HCC metastases are the adrenal glands, the bones and the lungs. Thus, it is imperative to perform bone scin-

tigraphy and chest and abdomen tomography to rule out tumor dissemination. Although uncommon, brain metastasis may occur (33). For patients who benefit from radical or curative treatment, mainly liver transplantation, we believe that skull tomography should be performed routinely to ex-

Table 5. Chinese University Prognostic Index (CUPI) classification of hepatocellular carcinomas (32).

Variable	Score
TNM classification	
I and II	-3
III A and III B	-1
IV A and IV B	0
Asymptomatic at diagnosis	-4
Ascites	3
AFP ≥500 ng/ml	2
Bilirubin (µmol/l)	
<34	0
34-51	3
>51	4
Alkaline phosphatase ≥200 IU/l	3

Score ≤1: low risk; score 2-7: intermediate risk; score ≥8: high risk. Risk of death within 3 months: >70% (high risk); 30 to 70% (intermediate risk); <30% (low risk). AFP = alpha-1 fetoprotein. For stages of the TNM classification, see legend to Table 3.

Table 6. Cancer of the Liver Italian Program (CLIP) classification of hepatocellular carcinomas (17).

Variable	Points
Child-Pugh	
A	0
B	1
C	2
Tumor morphology	
Uninodular and extension <50%	0
Multinodular and extension ≤50%	1
Diffuse (massive) or extension >50%	2
Alpha-1 fetoprotein	
<400	0
≥400	1
Thrombosis of the portal vein	
No	0
Yes	1

CLIP classification: 0 to 6 points.

clude the presence of brain metastases.

Treatment

The small number of patients with the same tumor stage impairs the execution of randomized and controlled studies, with a consequent difficulty in reaching a reliable conclusion about the best treatment for HCC. However, the consensus is that for effective treatment the tumor must be detected in the early phases of development. A tumor is considered to be in an early stage when its size does not exceed 2 cm. However, single tumors of less than 5 cm or up to three nodules, none of which exceeds 3 cm, are considered to be candidates for curative treatment. With follow-up programs for cirrhotic patients by US and AFP, the number of patients that can be submitted to curative treatment has increased. Tumors diagnosed in advanced phases, with vascular invasion, multinodular, and with distant metastases cannot be treated with the objective of improving patient survival. However, despite the programs of early detection of HCC, only 1/3 of patients with HCC will benefit from treatment considered to be curative. In our experience, we were able to perform radical treatment in 25% of patients with HCC (3).

The fibrolamellar variant of HCC is more common among non-cirrhotic young patients. Due to the slow evolution and low metastasis rates of this tumor, the treatment of choice is surgical resection even for tumors of large volume since the hepatic functional reserve needed for the procedure is maintained and the remaining liver in most cases is normal. When the tumor is not resectable, liver transplantation may be indicated. However, most HCC are not of the fibrolamellar variant and occur in the presence of cirrhosis, with consequent impairment of treatment. Thus, we shall comment on the treatment of HCC in patients with cirrhosis.

Surgical treatments (surgical resection and liver transplantation) and percutaneous treatment (alcoholization, radiofrequency and microwaves) are considered to be curative or radical. A 74% 5-year survival rate can be reached by patients submitted to liver transplantation (Table 7).

Surgical resection

Surgical resection is considered to be the option of choice for the treatment of patients with HCC. However, due to the frequent occurrence of postoperative hepatic decompensation, this treatment modality should be indicated only for patients with preserved

Table 7. Survival after radical treatment of hepatocellular carcinoma.

	N	1 year	2 years	5 years
Surgical resection				
Fong et al.,1999 (35)	100	83	–	42
<5 cm	–	–	57	–
Llovet et al.,1999 (36)				
No PH and TB NL	35	91	87	74
PH and TB NL	15	93	59	50
PH and TB >1	27	74	35	25
Arii et al.,2000 (34)				
Stage 1 <2 cm	1318	–	88	71
Stage 1 2-5 cm	2722	–	–	58
Yamamoto et al.,2001 (37)	58	97	84	61
Liver transplantation				
Figueras et al.,1997 (41)	38	82	75	63
França,1997 (12)/Llovet et al.,1998 (26)	58	84	74	74
Jonas et al.,2001 (42)	120	90	–	71
Yao et al.,2001 (44)				
≤pT2	46	91	–	72
Alcoholization				
Livraghi et al.,1995 (50)				
<5 cm				
Child A	293	98	79	47
Child B	149	93	63	29
Child C	20	64	0	0
Arii et al.,2000 (34)				
Stage 1 <2 cm	767	–	81	54
Stage 1 2-5 cm	587	–	–	39
Yamamoto et al.,2001 (37)	39	100	82	59
Radiofrequency				
Buscarini et al.,2001 (52)				
≤3.5 cm	88	89	62	33

NL = normal value; PH = portal hypertension; TB = total bilirubin.

hepatic function. Non-judicious patient selection for surgical resection may not lead to increased survival when surgical treatment is compared to the natural history of HCC or even to other less invasive therapies (34-37). The Child-Pugh classification and indocyanine green clearance have been used to assess the extent of liver function impairment before the indication of the surgical procedure. The presence of portal hypertension represented by the portal pressure gradient (difference between occluded and free hepatic venous pressure) ≥10 mmHg has been used as one of the main factors predictive of hepatic decompensation after surgical resection (36). This suggests that resection should be indicated for patients without portal hypertension. When it is not possible to measure portal pressure by the angiographic route, an invasive method which is not available at most services in Brazil, other signs of portal hypertension can be determined, such as splenomegaly, presence of esophageal varices upon upper gastrointestinal endoscopy, and a platelet count of less than 100,000/mm^3, and used as criteria to rule out resection (36).

A single tumor measuring less than 5 cm in patients with preserved hepatic function and in sufficiently good clinical conditions to withstand the procedure is the criterion most often used to indicate resection. Nodules larger than 5 cm present a higher probability of invasion of the tumor capsule, with the presence of satellite nodules indicating local tumor dissemination.

Only about 10% of patients have these tumoral characteristics, with a consequent infrequent indication of surgical resection (38). Tumor localization, especially in a perihilar situation, may be a criterion for contraindication of resection regardless of the characteristics of the tumor. Intraoperative US should be routinely used both to define the safety margins and to exclude other lesions not visualized by preoperative imaging techniques (39).

The survival rate after resection can reach 97% for the 1st year and 74% for the 2nd, depending on residual hepatic reserve and tumor staging (39). When possible, conservative surgery should be performed, such as segmentectomy or sub-segmentectomy which will preserve a functioning liver mass. Tumor recurrence is observed in about 12, 60 and 70% of patients after 1, 3 and 5 years, respectively (36,38) and is related to the presence of satellite nodules and tumor differentiation (40). Recurrence may be local or may consist of the appearance of metachronic tumors since the cirrhotic liver, especially when involved by extensive inflammatory activity, continues to be a risk factor. Tumor size (>5 cm), vascular invasion, the presence of satellite nodules, bilobar involvement, and the involvement of regional lymph nodes are considered to be factors related to tumor recurrence (36,38).

Liver transplantation

Liver transplantation is the treatment of choice in cases of HCC limited to the liver that cannot be submitted to surgical resection due to poor hepatic function or to technical impossibility. Liver transplantation not only eliminates the neoplasia, but can also cure the base liver disease. Some authors adopt post-resection tumor recurrence as an indication for liver transplantation. Others adopt liver transplantation as the treatment of choice before resection. When strict selection criteria are used, such as a single, small tumor (<5 cm) without satellite nodules, without vascular invasion, without invasion of regional lymph nodes, without distant metastases, and without an indication for resection, a satisfactory survival can be obtained (12,26,41-44). In our experience (12,26), with single tumors smaller than 5 cm, the possibilities of survival reach 84, 74 and 74% in the 1st, 2nd and 5th years after liver transplantation, with a rate of tumor recurrence of only 3.5%. These survival rates

are similar to those observed for liver transplantation in patients without neoplasias (41,45). Thus, the ideal candidate for liver transplantation is a patient with a single HCC smaller than 5 cm or with up to 3 nodules, none of them larger than 3 cm, without signs of neoplastic invasion of the portal system or of distant metastases.

Despite its advantages, the procedure also involves some disadvantages. The lack of donors with a consequent increase in the time on the waiting list, the high cost of the procedure, the possibility of tumor recurrence, the frequent postoperative infections, the high rates of perioperative morbidity, and the quality of postoperative life are aspects that should be taken into account at the time when the decision for an indication of liver transplantation is made.

Pre-liver transplantation co-adjuvant treatment in order to prevent tumor progression until the time for the surgical procedure has been adopted at some transplant centers where the time on the waiting list is more than 6 months. The real efficacy of these treatments for patient prognosis is still a matter of controversy. Some groups use arterial embolization with or without chemotherapy as co-adjuvant pre-liver transplantation treatment and localized chemotherapy post-liver transplantation (46). The combination of techniques, such as embolization and alcoholization, has demonstrated a satisfactory antitumoral effect and may be useful for co-adjuvant treatment before liver transplantation (47).

Strategies to increase the number of donors are of great importance. "Domino" and split liver transplants are options used to increase the number of organs for transplantation. Living donor liver transplantation should also be considered for patients with HCC in groups in which time on the waiting list is more than 7 months (39). The use of an "expanded" criterion for living donor liver transplantation in HCC has been discussed. This criterion is based on the following features (39): single tumor <7 cm or up to 3 nodules, none >5 cm or up to 5 nodules, none >3 cm or a partial response to any of the treatments fulfilling standard criteria. However, these criteria still need validation and should not be used in routine clinical practice.

Immunosuppressive agents such as cyclosporine and tacrolimus are known to be stimulators of hepatic regeneration. However, their interference with tumor progression is still a matter of controversy.

Percutaneous treatment

Several types of percutaneous treatment are available for HCC, all of them aiming at destruction of the tumor with a safety margin of non-tumoral liver. The techniques most commonly used are alcoholization and radiofrequency. However, substances such as boiling saline solution and acetic acid can also be used. Coagulation by radiofrequency, microwaves, laser therapy, and electrocauterization are percutaneous techniques used for the treatment of HCC. Percutaneous ethanol injection (PEI) is the technique for which most experience has been obtained, with various studies showing its efficacy.

Absolute alcohol causes cell dehydration and extensive coagulative cell necrosis in addition to leading to thrombosis of the intratumoral vessels. PEI is a procedure of easy execution, good tolerability and low cost, which can be applied during repeated sessions (48,49). Using ultrasound, the alcoholization needle is introduced until it reaches the nodule. A 22-G needle or a needle with specific side perforations for the procedure is used. After reaching the tumor, always under US visualization, the injection of absolute alcohol is started. The amount of alcohol injected per session depends on tumor size and tolerability on the part of the patient, ranging from 1 to 10 ml, with an average of 5 ml per session. Larger volumes are inadvisable because of the risk of the occur-

rence of an extensive area of hepatic necrosis. However, injection of a large volume of alcohol in a single session without the occurrence of marked side effects has been reported in the literature. The number of alcoholization sessions depends on the size and consistency of the tumor and on the distribution of alcohol through the tumor. The final objective of this treatment is to obtain total HCC necrosis.

Serious complications are rare. Pain during the procedure is common and is related to alcohol reflux towards the hepatic capsule or to alcohol escape through the portal vein, visualized by US during the procedure. In our routine we do not use sedation or systemic analgesia before PEI. There have been reports of hemoperitoneum, pleurisy, hemobilia, hepatic abscess, cholangitis, and hepatic decompensation (50). Portal thrombosis may also occur after PEI as a consequence of vascular invasion by the tumor or of chemical thrombosis caused by alcohol. Differentiation of these events can be obtained using US-Doppler or FNAB of the thrombus (14).

A single tumor smaller than 3 cm or up to three nodules, none of them larger than 3 cm, without extrahepatic metastases and with only slightly deteriorated hepatic functional reserve (Child-Pugh A and B) and without surgical indication (34,37,48) are the major indications for PEI.

The therapeutic efficacy of PEI depends on various factors. Vilana et al. (49), in an analysis of alcoholization of tumors measuring less than 5 cm, observed that tumors smaller than 3 cm gave a better response and concluded that the success of PEI is related to tumor size at the beginning of treatment, as also reported by others. PEI may have a therapeutic efficacy similar to resection or even to liver transplantation, especially when patients with poor hepatic function are selected for surgical treatment (48).

Local recurrence is observed in 17% of cases. The appearance of new lesions after treatment may reach 60% at 2 years and 80% at 5 years and is related to tumor size, inadequate necrosis, presence of pretreatment intrahepatic metastases, or even to the appearance of metachronic lesions during patient follow-up (49,50).

Depending on the degree of hepatic dysfunction, the survival of patients submitted to PEI may reach 85% in the first year, 60% in the third, and 30% in the fifth, rates similar to those obtained with surgical resection (34,37,48,50).

Radiofrequency has also been used successfully for patients with HCC. The indications are similar to those for PEI (51). No randomized studies comparing the two percutaneous techniques in terms of antitumoral effect and patient survival are available. The advantage of radiofrequency over PEI is the smaller number of sessions needed to obtain tumor necrosis. However, PEI is less expensive and is easy to perform, requiring no hospitalization. Radiofrequency should be avoided in superficial lesions because of the risk of tumoral dissemination through the path of the needle. The 5-year survival rate for patients submitted to radiofrequency is about 33% (52). The option for PEI and radiofrequency depends on the experience of each group.

Transarterial embolization or chemoembolization

Since HCC is a tumor predominantly irrigated by the arterial system of the liver, blockade of the blood supply to the tumor is used as treatment. The surgical route has been abandoned due to its severe side effects and has been replaced with the use of arterial obstruction by a peripheral route using interventionist radiology. Tumors that cannot be submitted to radical treatment are considered for transarterial embolization (TAE)/ chemoembolization (TACE). Usually, patients with multiple diffuse tumors or single tumors larger than 5 cm, with barely deterio-

rated hepatic function are the main candidates for treatment by TAE (28).

Using fluoroscopy, the tumor nourishing artery is located and selective obstruction with gelatin particles or preformed polyvinyl microparticles is started after advancing the catheter as close as possible to the HCC. This procedure may be combined with the use of chemotherapeutic agents such as doxorubicin, epirubicin, mitomycin, or cisplatin in combination or not with lipiodol, a substance retained by neoplastic cells. These combinations seem to improve the antitumoral effect, although in most cases they do not improve patient survival (53).

In a recent study, Llovet et al. (54) demonstrated improved survival of patients submitted to TACE compared to control patients (no antitumoral treatment). Patients with multinodular HCC and asymptomatic with respect to the tumor, without vascular invasion or distant metastases, with preserved hepatic function (preferentially Child-Pugh A) and not considered to be candidates for liver transplantation may benefit from TACE.

Thrombosis of the portal vein and hepatofugal portal flow are considered to be a contraindication of TAE due to the risk of severe hepatic insufficiency after the procedure. The post-embolization syndrome, characterized by fever, abdominal pain, nausea and vomiting, and frequently self-limited, is observed in most patients submitted to TAE or TACE. Fifteen to 30% of the patients may present severe symptoms such as gallbladder infarction by embolization of the cystic artery, arteritis, thrombosis of the intima layer of the hepatic artery, pulmonary edema, pancreatitis, or even hepatic insufficiency due to poor hepatic function. For this reason, this therapeutic modality is avoided in Child-Pugh C patients (53,55). A higher frequency of post-embolization syndrome and of gastrointestinal toxicity tends to occur in cases in which lipiodol is used as the chemotherapeutic vehicle. Antibiotic prophylaxis should not be routinely applied to patients submitted to TAE (56).

TAE can reduce the size of the tumor, leading to ischemic necrosis of more than 80% of the HCC, while the cells that infiltrate the tumoral capsule and the portal vein continue to be viable. Relapses are also frequent. In cases of relapse or persistence of viable cells, the procedure can be repeated or post-TAE PEI can be performed (55). However, the probability of maintenance of this level of therapeutic response is about 10% at 2 years. Larger tumors tend to respond to TAE at higher frequency, probably due to the hypervascularization of larger HCC (53). Both TAE and TACE should be periodically repeated. The time interval has not been defined, but the suggestion is to repeat the procedure every 3 to 6 months.

Patients with a single tumor larger than 3 cm that cannot be treated surgically may benefit from the combination of TAE and PEI. The combination of these two therapeutic techniques is based on the persistence of viable neoplastic cells after TAE, especially at the periphery of the lesion, where the predominant circulation seems to be the venous one (47). In addition, large tumors require larger amounts of alcohol to be necrotized. Thus, when TAE is performed first, necrosis of the central part of the HCC is obtained, and PEI is later performed at the periphery. This combination of techniques seems to be effective in reducing tumor size and increasing patient survival (57,58).

TACE has been used as co-adjuvant treatment when the patient is on the waiting list for liver transplantation (46). In our experience, the combination of TAE and PEI has shown a good antitumoral effect in patients who are on the waiting list for liver transplantation (47).

However, the possibility of tumor dissemination after treatment, detected by the presence of messenger RNA for AFP (58) and by a higher incidence of pulmonary metastases after TAE, should be considered at the time when a decision has to be made

about co-adjuvant treatment in addition to radical therapy.

Evaluation of the therapeutic response

The therapeutic response to percutaneous methods (PEI and radiofrequency) and to TAE is determined by using CT in the arterial phase, at least 1 month after the procedure. Before this period, areas suspected of tumor viability may be detected, corresponding to areas of peritumoral edema caused by the therapeutic procedure. The persistence of a hyperdense image in the arterial phase is suggestive of tumor viability. The absence of contrast uptake is indicative of tumor necrosis. In MR, the loss of signal intensity in potentiated sequences in T2 and after the administration of paramagnetic contrast in potentiated sequences in T1 is also suggestive of tumor necrosis. US-Doppler has been used for the control of treatment with satisfactory results. The presence of an intratumoral pulsatile flow indicates the persistence of viable tumor cells. However, the absence of a Doppler signal does not rule out the possibility of tumor viability.

A quarterly US, measurement of serum AFP and dynamic CT at 6- to 8-month intervals are suggested for post-treatment follow-up. The absence of an increase in the lesion, in AFP levels or in contrast uptake by CT is indicative of successful treatment. The World Health Organization adopts the following criteria for response to treatment (59):

Complete response: complete disappearance of known lesions and no occurrence of new lesions as evaluated during two observations separated by an interval of at least 4 weeks.

Partial response: reduction of the tumor mass ≥50% as evaluated during two observations separated by an interval of at least 4 weeks.

Stable disease: not classified as complete response, partial response or progressive disease

Progressive disease: an increase ≥25% in the tumoral mass of one or more known lesions or appearance of new lesions.

Serum AFP levels can be used as a parameter of response to treatment only in cases in which their levels were elevated before the procedure. Elevation of their levels after treatment is suggestive of tumor recurrence.

Other therapies

In HCC, both estrogen and androgen receptors can be found on the membrane of neoplastic cells, theoretically justifying hormonal therapy for this type of neoplasia. The use of antiestrogens has been suggested for the treatment of HCC. However, tamoxifen, a non-steroid antiestrogen, did not prove to be useful in improving the quality of life of patients with HCC even when administered at high doses (60).

Radiotherapy, systemic chemotherapy and the use of interferon have not shown satisfactory results in terms of antitumoral effect or survival of patients with HCC (14).

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