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UPDATE

Hepatocellular Carcinoma: Diagnosis, staging, and treatment strategy

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Abstract
Hepatocellular carcinoma is a tumor with a high incidence and high mortality. These data justify screening programs to enable curative treatments to improve survival rates. Screening the population at risk (mainly patients with cirrhosis of the liver) should include ultrasonographic examination twice yearly. Given the vascular characteristics of hepatocellular carcinoma, it can be detected using dynamic techniques (contrast-enhanced ultrasonography, CT, and MRI). In cases in which the enhancement pattern is not characteristic, these techniques should be complemented with lesion biopsy.
Once hepatocellular carcinoma is diagnosed, the tumor is staged, and together with the clinical condition of the patient, the stage will determine the most appropriate treatment strategy in each case.

PALABRAS CLAVE
Carcinoma hepatocelular;
Ecografía;
Ecografía con contraste;
Tomografía computarizada;

Carcinoma hepatocelular: diagnóstico, estadificación y estrategia terapéutica

Resumen
El carcinoma hepatocelular es un tumor de elevada incidencia y alta mortalidad. Estos datos justifican los programas de detección precoz para poder aplicar los tratamientos considerados curativos, lo que implicará una mayor supervivencia. La detección precoz debe realizarse mediante ecografía semestral en la población con riesgo de padecer este tipo de tumor, fundamentalmente en pacientes con cirrosis hepática. Debido a sus características vasculares,

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Resonancia magnética;
Diagnóstico precoz;
Diagnóstico por Imagen;
Biopsia;
Tratamiento tumoral

actualmente se puede realizar el diagnóstico de carcinoma hepatocelular por técnicas de imagen dinámicas (ecografía con contraste/TC/RM). En caso que el patrón de captación no sea característico en estas técnicas de imagen debe efectuarse una biopsia de la lesión.
Una vez diagnosticado, se realiza la estadificación del tumor, lo que junto al estado clínico del paciente, determinará la estrategia terapéutica más adecuada en cada caso.

Epidemiology

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and a gradual increase in its incidence has been reported in industrialized countries in recent years.[1] It is currently the sixth most common cancer, with more than one half million cases per year, the third leading cause of death by cancer,[2] and the main cause of death in cirrhotic patients.[3] Its distribution worldwide is heterogeneous and closely related to the presence of different risk factors that are associated with its development. The incidence is the highest in sub-Saharan Africa and Southeast Asia, where infection with the hepatitis B virus (HBV) is endemic and the incidence exceeds 15 cases/100,000 inhabitants/year. Spain presents an intermediate incidence of 5-10 cases/100,000 inhabitants/year, and the most common associated risk factors are chronic infection with the hepatitis C virus (HCV) and alcoholism.[4,5] The development of HCC is mainly observed in the presence of chronic liver disease, and the highest risk (3-7% annually) occurs when the patient develops cirrhosis.[4,5] Effective prevention of death from HCC can be achieved by preventing the acquisition of risk factors (primary prevention). The best example is the drastic fall in the incidence of HCC in Taiwan after the universal implementation of the HBV vaccine.[6]

Unfortunately, once liver cirrhosis has developed, the risk for HCC remains, despite a sustained viral response after treatment.[7] The only effective method of decreasing the mortality associated with HCC is to diagnose the disease early by implementing surveillance programs.[8,9]

Surveillance for early HCC detection

To be effective and impact on survival, before the implementation of a surveillance program the population at risk must be identified, and the types of diagnostic examinations to be used as well as the time intervals between tests should be planned.

1. *The population at risk:* the criteria used for identifying candidates for a surveillance program corresponds to the known risk for tumor development. In that regard, surveillance is recommended in patients with liver cirrhosis of any etiology (i.e., viral, alcohol abuse, hemochromatosis, or autoimmune) who would be candidates for treatment in case of HCC detection.[8,9] In patients with advanced/decompensated cirrhosis (Child-Pugh C state), monitoring is only recommended in cases where the patient is a candidate for liver transplantation. The aim in those patients is to rule out the possibility of advanced HCC, which could contraindicate a transplantation, or to detect the development of HCC that could give priority the patient in the waiting list. Patients with cirrhosis from hepatitis B or C who have been successfully treated by antiviral treatment must be included on the surveillance program because cirrhosis and the risk of developing HCC can persist.[7]

Other candidates at high risk for HCC development are those patients with chronic hepatitis from HBV who has a high replication rate, or familiar history of HCC, or those patients with HIV coinfection. Finally, no data exist regarding the usefulness of surveillance in patients with nonalcoholic steatohepatitis because the natural history of the disease and the real incidence of HCC are not fully understood.[8]

2. *Screening techniques:* the screening examination for early detection during the asymptomatic phase of HCC should be performed using a low-cost technique that has an acceptable sensitivity, is easily repeatable, is widely available, and without associated risks. These criteria allow implementing a surveillance program with an adequate cost for the expected gain of life expectancy and an a good acceptance for the target population. Briefly, the tests availables can be divided into two groups: 1) serological (tumor markers) and 2) imaging techniques.

1) Serological tests: One of the most frequently used tumor markers for HCC surveillance is alpha-fetoprotein (AFP), generally used associated with ultrasounds. The plasma level of this marker is proportional to the size and evolutionary stage of the tumor. Accordingly, only 10% of patients with a tumor smaller than 5 cm present plasma levels that are above 100 ng/ml, which limits the use of AFP in the early detection of the disease. In several studies, AFP has shown a low diagnostic accuracy,[10-12] so its use as a surveillance method is not currently recommended.[8,13,14] Other serological markers, such as glycosylated AFP, des-gamma carboxyprothrombin, and glypican-3, have not shown to be useful and precise tools for diagnosis of HCC, and their use for surveillance purposes are discouraged.[12,15-17]
2) Imaging techniques: The available imaging techniques that are utilized in follow-up examinations are ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI). CTs that are performed every few months over a long period of time can cause elevated radiation levels in patients and are

expensive and not cost-effective.[18] MRI has a greater sensitivity and specificity in the diagnosis of smaller HCC tumors, but due to its cost and availability, it should be reserved only for diagnostic confirmation and staging once the lesion has already been detected by ultrasound.

Ultrasound is the least invasive technique, and it can be repeated periodically with no risk to the patient. It also has high sensitivity (60-80%) and specificity (45-96%) in the diagnosis of HCC if state-of-the-art ultrasound equipment is used and the physicien performing the examination have experience.[19] Therefore, ultrasound is the screening technique of choice. In early cirrhosis or chronic hepatitis, a well-defined nodule would be easily as echogenicity will be different from the rest of the parenchyma. However, in liver with advanced cirrhosis, multinodularity caused by regenerative nodules are common, so a new nodule could go unnoticed.

The fundamental aim of surveillance programs is to identify HCC in its initial phase, preferably when the lesion is less than 2 cm in size, because at this size the lesion is most likely localized and has not produced vascular invasion.[20] In this initial phase, the patient may be cured if treated.

The effectiveness of surveillance programs for early HCC detection has been evaluated by a randomized prospective study that included patients with chronic HBV infection. The patients were randomly assigned to a surveillance group (ultrasound and AFP every six months) or a control group. An increase in the survival rate was demonstrated in the patients included in the surveillance group compared to patients who did not have such follow-up studies.[21] Furthermore, several cost-effectiveness studies have confirmed the benefit of performing follow-up studies with abdominal ultrasound every six months.[22-27] Thus, ultrasound is currently accepted as the technique to be used in the follow-up study of patients at risk for HCC.[8,9]

During its initial phase, HCC is generally single-nodular, although approximately 20% of cases can be multinodular due to the simultaneous appearance of several tumor foci. Small tumors are predominantly hypoechoic, but the presence of fat makes them hyperechogenic in some cases (fig. 1A and B).

The differential diagnosis of small nodules detected during follow-up examinations must be established with benign lesions: angiomas, hamartomas, regenerative

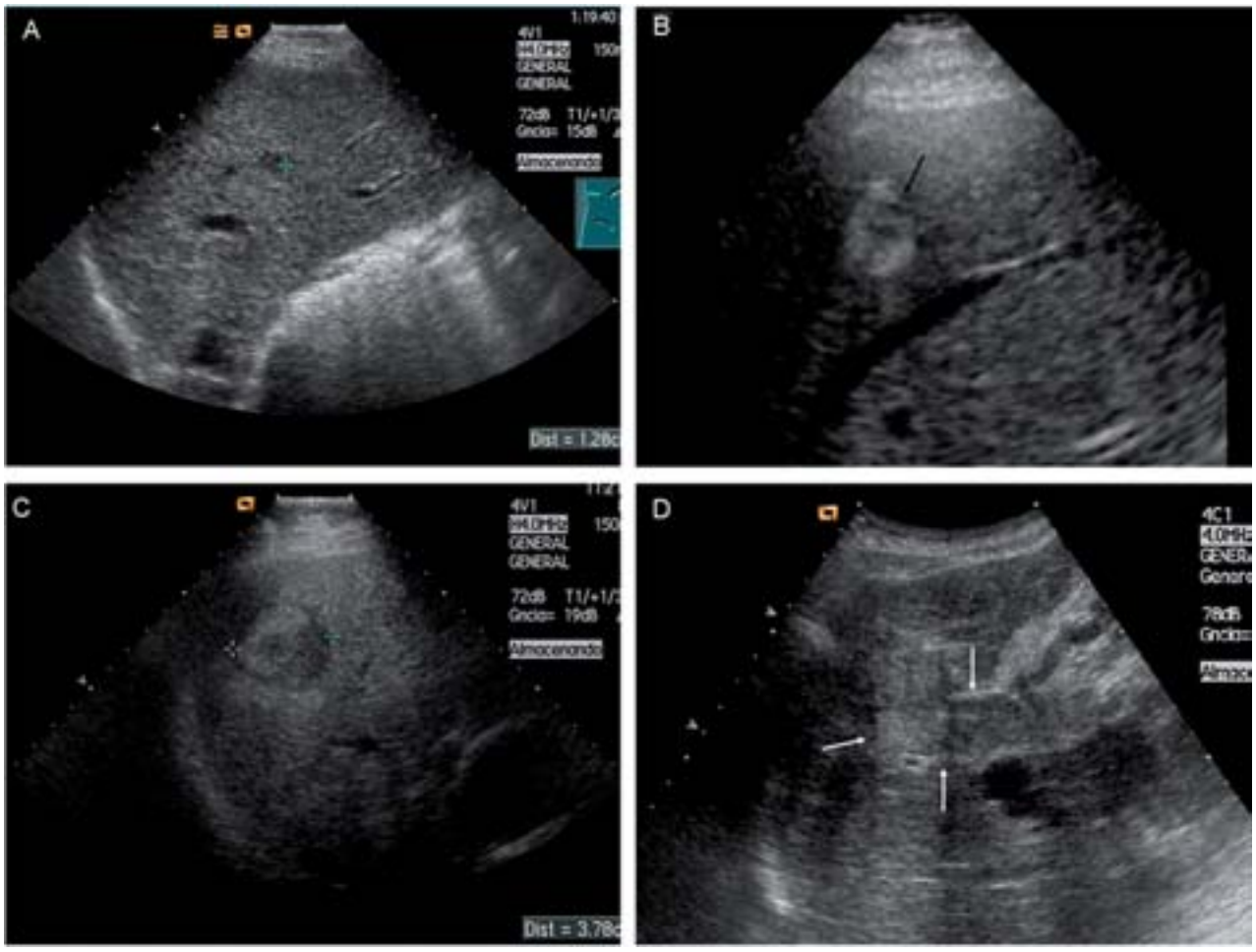

Figure 1 Different patterns of the HCC ultrasound. A) A small hypoechoic nodule that is 13 mm in size in the right hepatic lobe (cursors). B) Echogenic nodule 1.7 cm in size (arrow). C) A heterogeneous nodule that is 3.7 cm in size, with a hypoechoic halo, in the dome of the right lobe (cursors). D) Extensive portal thrombosis that translates to vascular tumoral invasion in a patient with multinodular HCC (arrows).

nodules, and low-grade dysplasia. The malignant lesions that can be found in a patient with liver cirrhosis are primarily HCC, but metastases and peripheral cholangiocarcinomas (PCC) can also be found. The appearance of B lymphomas that are associated with the hepatitis B and C viruses is uncommon, but multiple small hypoechoic can suggest such diagnosis.[28]

HCC is defined by tumor size and aggressiveness. Whereas tumors in the initial phase, which are rarely recognized by imaging techniques, are generally cell clusters without a capsule, tumors of a greater size can have imprecise borders or a well-defined halo. Those with imprecise borders are generally more aggressive and infiltrative tumors, while those with a pseudocapsule resulting from compression by the tumor of the neighboring tissue are expansive tumors that are associated with a better prognosis when they stay within the capsule. However, when the tumor is small (< 2 cm), the halo correspond to the peripheral arterial circulation.

Large tumors are generally heterogeneous because they present interior septae and zones that have different grades of necrosis, vascularization, and fibrosis. They can persist as a single encapsulated lesion (fig. 1C), but in more advanced phases, multiple lesions with semi-precise limits and with vascular invasion are apparent.[29] HCC can invade the hepatic and/or portal veins and produce an increase in the size of the vessel, which results in a solid appearance and arterial vascularization in the interior of the tumoral thrombus (fig. 1D).

3. *The interval between tests:* the ideal interval between each test is unknown. This interval is determined by the rate of tumor growth. The duplication time of HCC is not well established; however, some studies indicate that it is approximately two to four months.[30,31] Several studies have been performed to determine the ideal frequency of tests in terms of cost/effectiveness; Explorations every 3 months detected more nodules than every 6 months but have not impact on early detection and survival since most of these nodules were benign.[32] Annual ultrasounds did not provide worse results than did scans performed every six months, although more evolved lesions were occasionally found in the yearly ultrasounds.[33] Multiple scientific societies have recommended an interval for tests of six months.[8,9,34]

In summary, the experts' recommendations are the following:

- Patients who are at risk for HCC should be monitored by ultrasound every six months.
- AFP should not be used as a marker for surveillance purposes.

Diagnosis of HCC

When a hepatic nodule is detected during an screening US, a conclusive diagnosis should be obtained. Prior to 2000, the diagnostic confirmation of HCC was performed through an anatomopathological study. The risks and limitations of fine needle aspiration biopsies (FNAB) of the liver have led to a search for alternative diagnostic methods. The EASL (European Association for the Study of the Liver) defined in 2000 the first non-invasive diagnostic criteria that allowed a conclusive diagnosis of HCC in cirrhotic patients without the need for cytohistological confirmation in nodules larger than 2 cm.[34] In 2005, the non-invasive diagnostic criteria were revised by the AASLD (American Association for the Study of Liver Diseases) and the redefined criteria were published in clinical practice guidelines for HCC management,[8] and they have been accepted by the EASL and a group of experts from national scientific societies that are implicated in the management of HCC.[9] These criteria are based on the detection of the characteristic vascular pattern defined by the homogenous uptake of contrast in the arterial phase followed by a contrast washout in the venous phase.

With the aim of optimizing the diagnostic strategy, the AASLD guidelines suggest a diagnostic algorithm that is summarized in figure 2, which is based on the performance of dynamic imaging techniques (contrast-enhanced US, multiphase CT, and dynamic MRI). The sequence of tests is determined by the size of the nodule being studied:

1. *Lesion > 2 cm in diameter:* a conclusive diagnosis of HCC can be established if the nodule displays the vascular pattern characteristic of HCC by one dynamic imaging technique (fig. 3). Otherwise, a biopsy is recommended.
2. *Lesion 1-2 cm in diameter:* to avoid controversial readings, the characteristic vascular pattern must be demonstrated by two imaging techniques (fig. 4). Otherwise, a biopsy should be performed.
3. *Lesions < 1 cm:* in the majority of cases, these lesions are benign that do not grow or disappear during follow-up examinations. Furthermore, their correct characterization by imaging techniques or biopsies is, in many instances, impossible. Therefore, upon detection of an infracentrimetric nodule, close follow-up by ultrasound every 3-4 months is recommended. If there has been no growth over a period of up to 2 years, one can revert to routine surveillance. If growth is observed, the flow chart will be followed according to the new size of the tumor.

Interestingly, a small percentage of HCC nodules that are smaller than 2 cm are hypovascular in the arterial phase of dynamic imaging studies, probably because of insufficient development of the arterial network of newly formed blood vessels.[20] Therefore, non-invasive diagnostic criteria can only diagnose HCC that has undergone complete neoangiogenesis, which does not occur often in lesions that are smaller than 2 cm. Thus, biopsies play an important role in the early diagnosis of HCC.

Biopsies of hepatic nodules are usually performed using ultrasound guidance. Punctures can be performed with either fine needle aspiration (FNA) or with a cutting needle. The choice depends on the preferences of the pathologist. The caliber of the needle used varies between 18-20 G. Unfortunately, the diagnostic performance of biopsy for the early detection of HCC is low. First, in some cases, the puncture cannot be performed due to the location of the nodule, the presence of ascites, or severe coagulation disorders. Furthermore, biopsies of smaller nodules (< 2 cm) are associated with a level of false negatives of up to 30% according to some studies due to sampling errors or difficulties for distinguishing well-differentiated HCC from

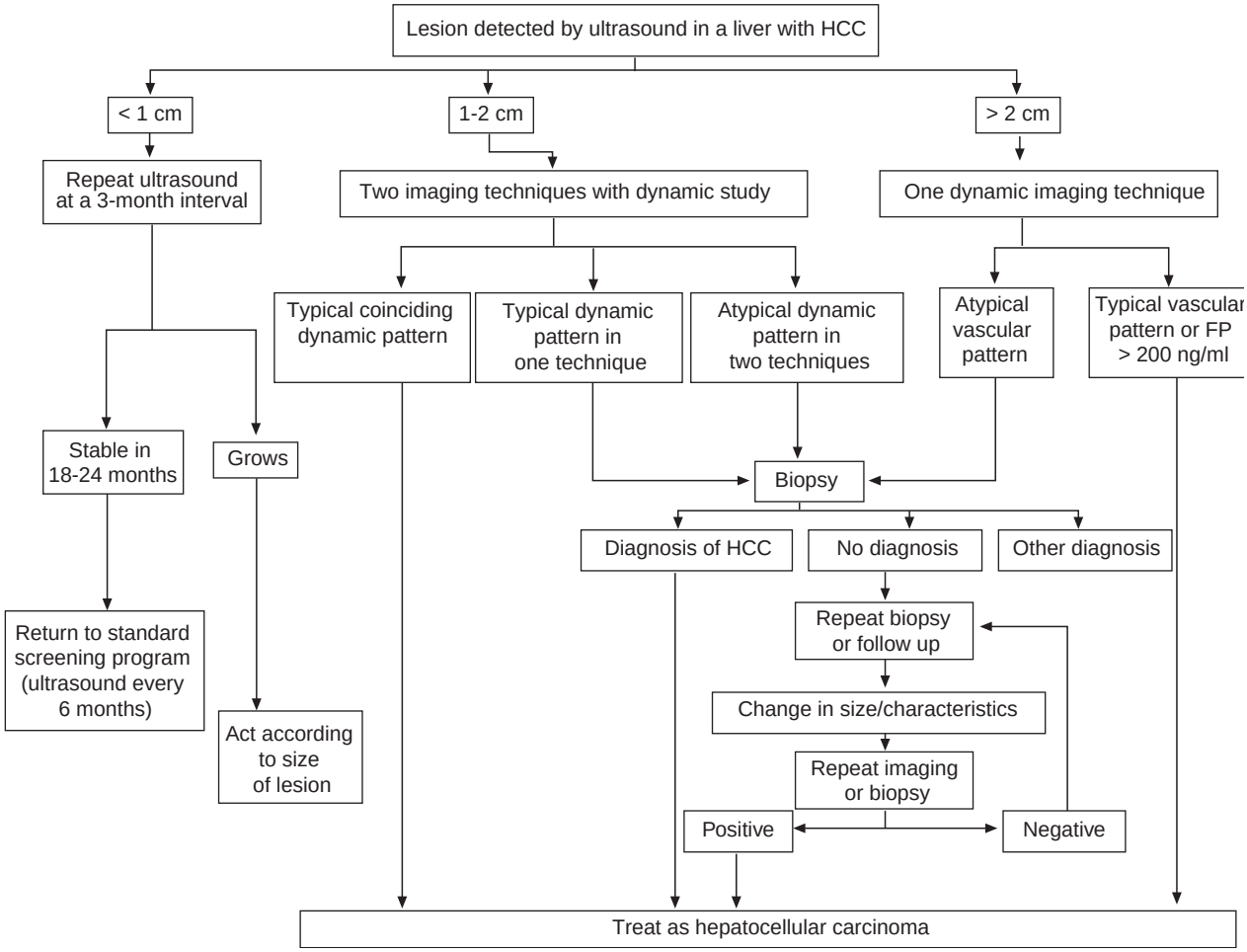

Figure 2 Diagnostic strategy after the detection of a liver nodule in a screening ultrasound in patients with cirrhosis. Reproduction adapted from Bruix and Sherman.[8]

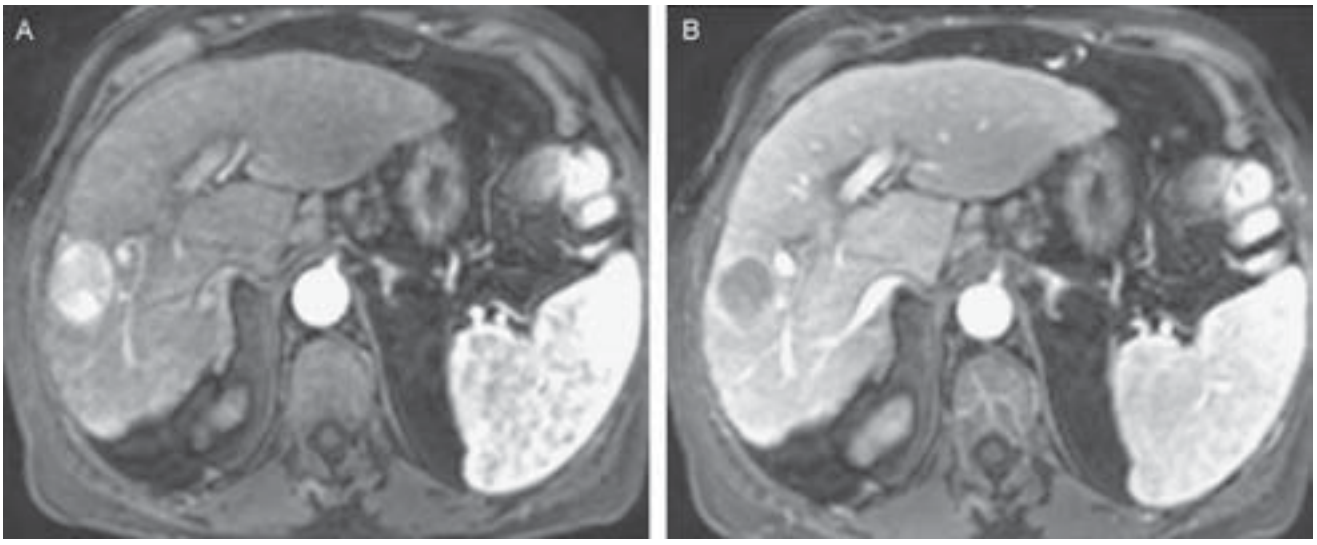

Figure 3 A 30-mm HCC in the right hepatic lobe with a characteristic vascular pattern on a dynamic MRI study. A) In the arterial phase, the lesion is intensely enhanced in relation to the neighboring liver. B) In the portal phase, the nodule washes its contrast more quickly than does the surrounding liver.

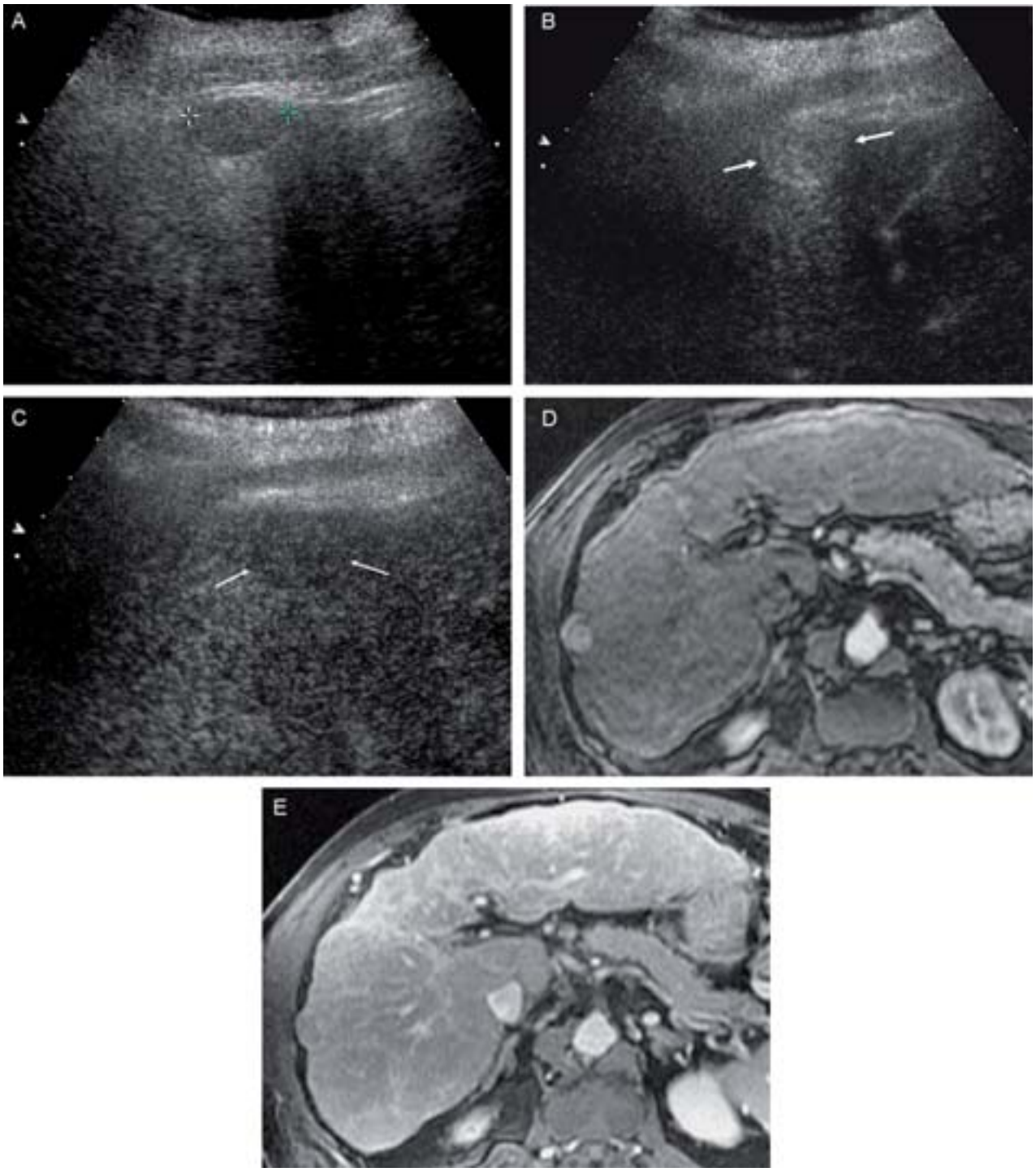

Figure 4 A 16-mm subcapsular HCC nodule in the right hepatic lobe with a typical vascular pattern that is observed in two imaging techniques. A) Hypoechoic nodule in the baseline ultrasound study (cursors). B) In the arterial phase, the CEUS confirms the hypervascular nature of the lesion (arrows). C) CEUS: washout in venous phase (arrows). D) The arterial phase of the dynamic MRI shows arterial uptake of the lesion. E) MRI: the venous phase shows contrast washout of the nodule.

other premalignant lesions (for example, dysplastic nodules).[10,35,36] The use of immunohistochemical techniques[37,38] or molecular techniques[39] has been proposed with the aim of improving the diagnostic performance of biopsies; however, the utility of these proposed methods should be validated in clinical practice. Therefore, a negative biopsy does not rule out the possibility of HCC, and a repeat biopsy or strict follow-up examinations of the lesion should be considered.

These recommendations have recently been validated in a prospective study conducted in our unit. This study included 89 cirrhotic patients who had a single new nodule of

between 5 and 20 mm in size that was detected during an screening ultrasound.[10] A baseline contrast-enhanced ultrasound (CEUS), dynamic MRI, and biopsy (gold-standard technique) were performed; the biopsy was repeated in case of an initial negative result. When a conclusive diagnosis could not be obtained, strict follow-up was performed using CEUS every 3 months and MRI every 6 months to rule out the possibility of HCC. The final diagnoses of the lesions were 60 HCC, 1 cholangiocarcinoma, and 28 benign lesions. Regarding the characteristic vascular pattern (hypervascularization in the arterial phase and washout in the venous phase), the sensitivity and specificity were 61.7% and 96.6%, respectively, for MRI and 51.7% and 93.1%, respectively, for CEUS. If the finding of the typical pattern by both techniques was required, the specificity was 100%, but the sensitivity was 33.3%.[10] Additionally, the first biopsy presented a false negative rate of 30%. Therefore, this study validated the utility of non-invasive criteria for the diagnosis of HCC, confirmed the need to demonstrate the characteristic pattern in the two imaging tests to avoid false diagnoses of HCC, and lastly, showed that the absence of arterial vascularization in a dynamic study or a negative biopsy did not rule out a diagnosis of HCC.

In recent years, advances in the use of imaging techniques in the diagnosis of HCC have been achieved. MRI scans employing organ-specific contrasts, like SPIO, which is captured by the Kuppfer cells, and hepatobiliary contrast agents that are captured by the hepatocytes, have shown a diagnostic performance that is similar to that of multidetector CT for the detection of HCC lesions, although these studies are not specifically designed to examine lesions of smaller sizes.[40-43] Discrepancies exist regarding whether the type of arterial contrast uptake of HCC can be related to the grade of tumor differentiation. Previous studies performed by contrast-enhanced ultrasound[44] or CT[45] describe such a relationship, but other studies, such as a recent study by Frericks et al. performed with MRI and the contrast agent Gd-EOB-DTPA, have not validated it.[43] Frericks et al. described a typical vascular pattern of HCC after the injection of Gd-EOB-DTPA (arterial contrast uptake and venous washout), which was similar to the vascular profile described when an extracellular paramagnetic contrast agent is used. However, this pattern has also recently been described in three high-flow hemangiomas, which limits its reliability.[46] Thus, data that consider specific MRI contrast agents as the primary method of diagnosis in patients with HCC do not exist.

Another important advance in the field of diagnostic imaging of HCC has been the development of CEUS. This technique allows for the characterization of nodular lesions that are detected by ultrasound,[47] and it is useful as an ideal complement for confirming findings obtained by MRI/CT.[48]

Some considerations must be noted that concern the different imaging techniques that are used to establish the diagnosis. First, the ultrasound contrast agents that are currently utilized are purely intravascular, unlike contrast agents employed in CT and MRI, which can pass into the interstitial space. This can produce discordant results for some of the hepatic lesions that are studied with CEUS or CT/MRI.[49] Likewise, some contrast uptake patterns that can be observed during the follow-up examinations of a cirrhotic patient, should be outlined. Regenerative nodules, low-grade dysplasia, and hammartomas do not present arterial uptake. Angiomas characteristically present peripheral arterial uptake that become complete and homogeneous in delayed phases. Angiomas of smaller sizes may occasionally present complete arterial uptake, and they may remain hyper-isointense with respect to the parenchyma in delayed phases (fig. 5).

High-grade dysplasia generally presents arterial uptake and remains isointense in the portal and delayed phases because, unlike HCC, it conserves the portal vascularization. Hepatic metastases generally present arterial uptake, which is usually ring-like, followed by a rapid clearance of the contrast agent in venous phases, this finding is associated with malignancy. PCC also generally presents peripheral, ring-like arterial uptake, but in some cases, especially when it is smaller in size, complete arterial nodular uptake can be present and followed by a washout in the venous phase on CEUS technique. This image can be indistinguishable from HCC.[50,51] The absence of contrast washout in the delayed phase of the MRI in PCC helps to distinguish them from HCC (fig. 6).[52]

Occasionally, benign and malignant lesions are simultaneously detected in the same patient. In these cases, dynamic imaging techniques can help us to differentiate them and to identify the target lesions for diagnostic biopsies and percutaneous treatments (fig. 7).

Tumoral extension study

Appropriate tumor staging is essential for deciding on the most appropriate therapy for each patient. Detection of additional nodules and/or vascular invasion is a key aspect for the HCC staging because both conditions reflect an advanced tumor stage, and therefore, discarding the chance of curation after therapy. MRI is the technique of choice for the detection of additional smaller lesions, being superior to helical CT for detecting nodules between 1 and 2 cm in size.[53] Despite technological advances, additional lesions that are less than 1 cm in size present an unresolved diagnostic problem because the diagnostic accuracy of CT and MRI for the detection and characterization of these lesions is less than 50%.[53] The vascular tumor invasion is generally presented as an extensive thrombosis that, in some cases, can present arterial hypervascularization. The use of dynamic techniques (CEUS, CT, and MRI) can help to identify intratumoral arterial vascularization and to distinguish it from benign thrombosis and portal cavernoma (fig. 8). In ambiguous cases, a fine needle aspiration biopsy of the thrombus can establish its malignant nature.[54] Extrahepatic dissemination is less common in the initial stages of the disease. Nonetheless, the use of a thoracic CT should rely on clinical criteria. Bone metastases are generally symptomatic, and if suspected, they should be ruled out by a bone scan. Cerebral metastases are seldom found.

Therapeutic strategy

Once the diagnosis has been made, a prognostic assessment must be undertaken that allows us to inform the patient and his/her family of the patient's life expectancy, to choose

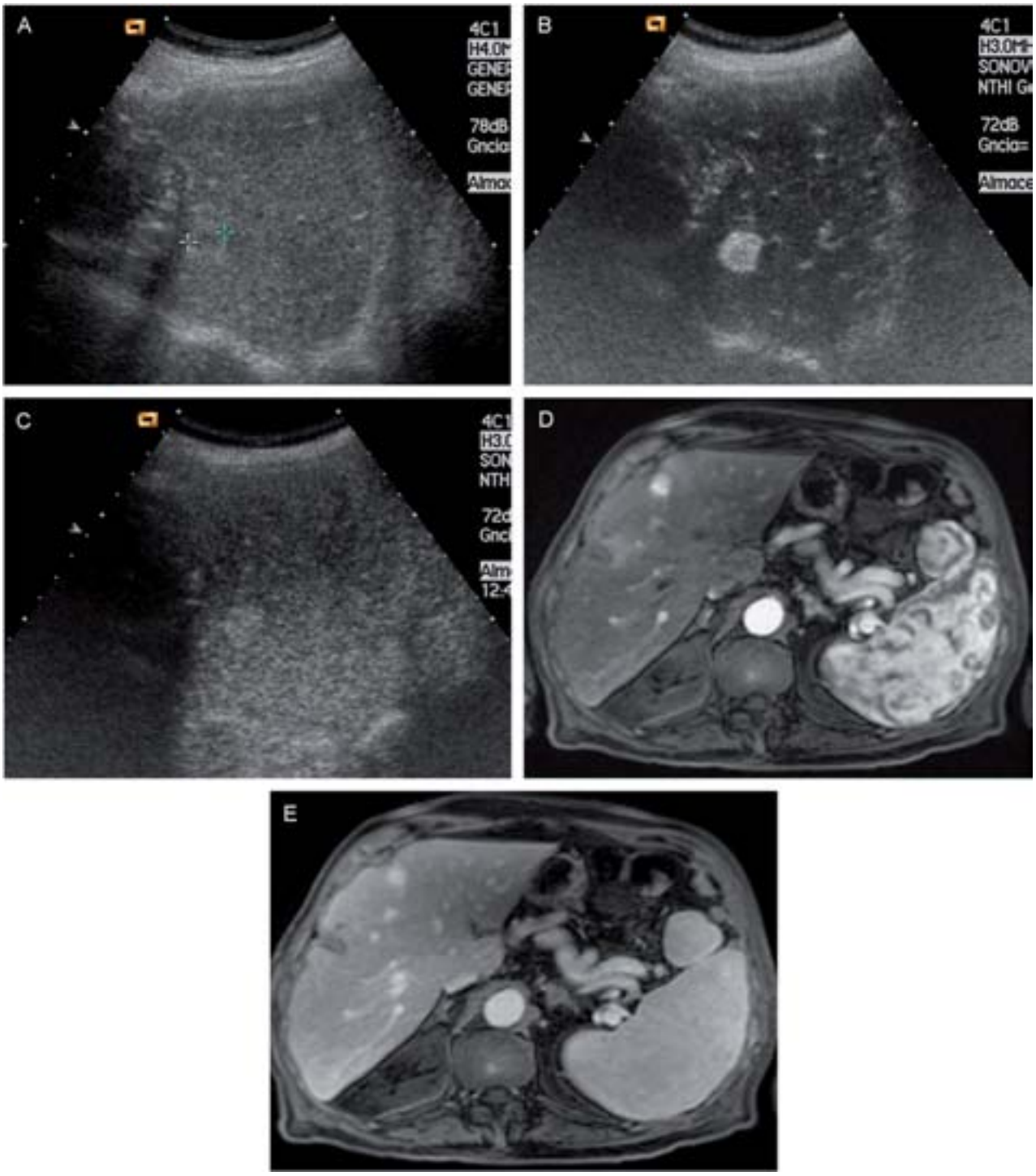

Figure 5 A lesion detected in the semi-annual screening ultrasound of a cirrhotic patient. A differential diagnosis should be done between hemangioma or HCC. A) In the baseline ultrasound, an echogenic, 17 mm nodular image with a more hypoechoic center is observed (cursors). B) CEUS: in the arterial phase, the lesion presents clear and complete contrast uptake. C) CEUS: in the delayed venous phase, the lesion remains hyperechogenic, which is uncharacteristic of HCC and supports the diagnosis of a benign lesion. D) Complete nodular uptake of the lesion in the arterial phase of the MRI. E) In the delayed venous phase, persistent uptake is identified. The lesion was characterized as a hemangioma.

the most appropriate therapeutic option and to evaluate its response HCC is frequently associated with cirrhosis in the majority of cases, and the degree of liver function impairment determines the therapeutic options and survival independent of the presence of HCC, the evaluation of this aspect is mandatory. Additionally, the presence of symptoms has shown a great prognostic value,[55] and as to the grade of the functional liver reserve, it determines the applicability

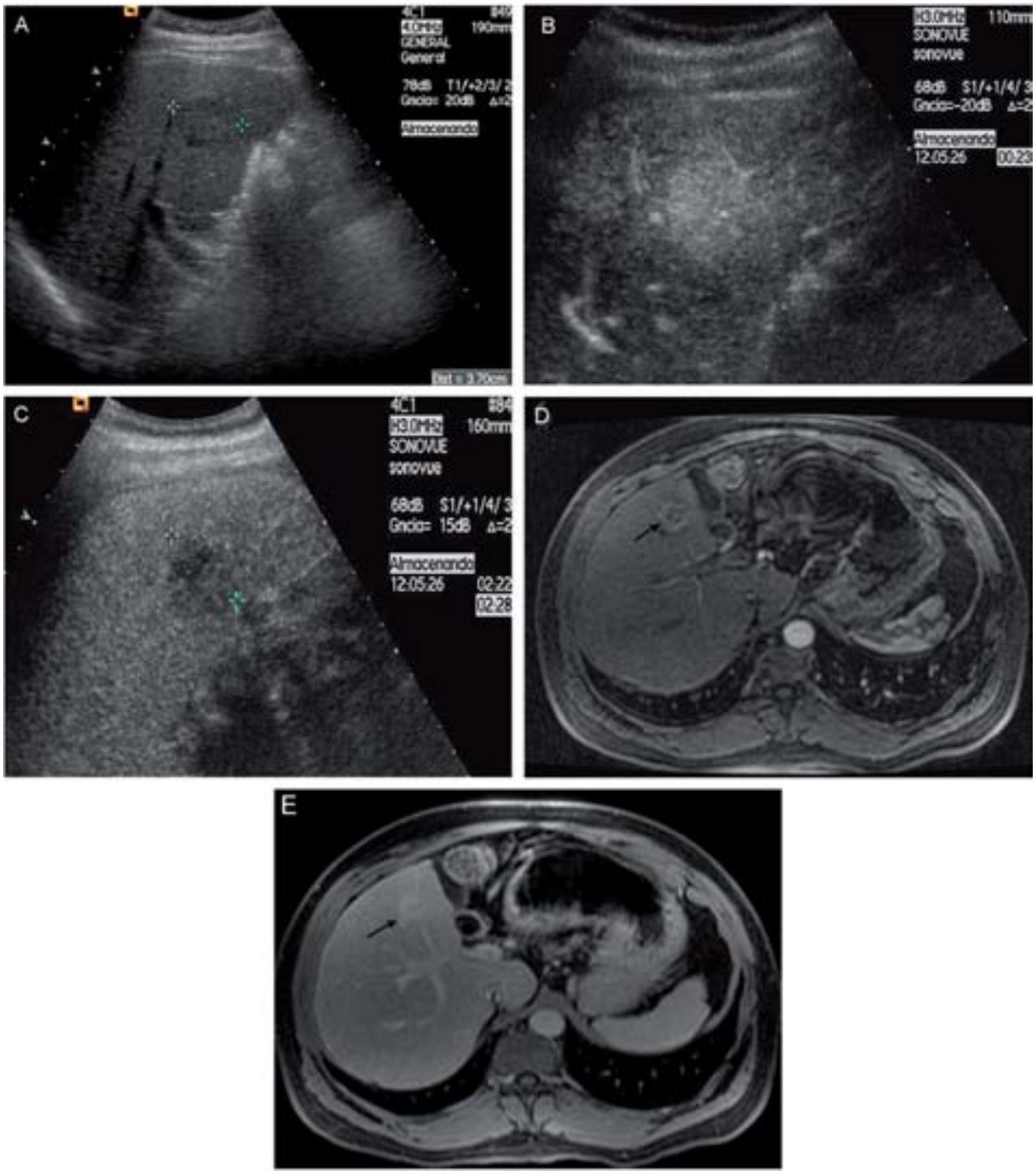

Figure 6 A patient with cirrhosis secondary to HCV infection with a hepatic lesion that was diagnosed as an intrahepatic cholangiocarcinoma by a percutaneous biopsy. In this case, the vascular pattern on CEUS was indistinguishable from HCC. A) In the baseline ultrasound, a 37 mm, hypoechoic nodules was identified in the right liver lobe (cursors). B) In the arterial phase of CEUS, the nodule displayed a homogeneous contrast uptake. C) In the delayed phase the CEUS showed contrast washout. D) In the arterial phase of the MRI, an almost complete uptake of the lesion is observed. E) Persistence of the uptake is identified in the delayed venous phase of MRI.

of the different available treatments. Therefore, prognostic systems that only consider the tumoral extension, such as the TNM,[56] liver function, such as the Child-Pugh[57] or the MELD[58] system, or the presence of symptoms, such as the ECOG Performance Status classification[59] or the Karnofsky[60] index, are imprecise for evaluating the prognosis of patients affected by HCC and are only useful for detecting terminal disease. In recent years, multiple staging systems have

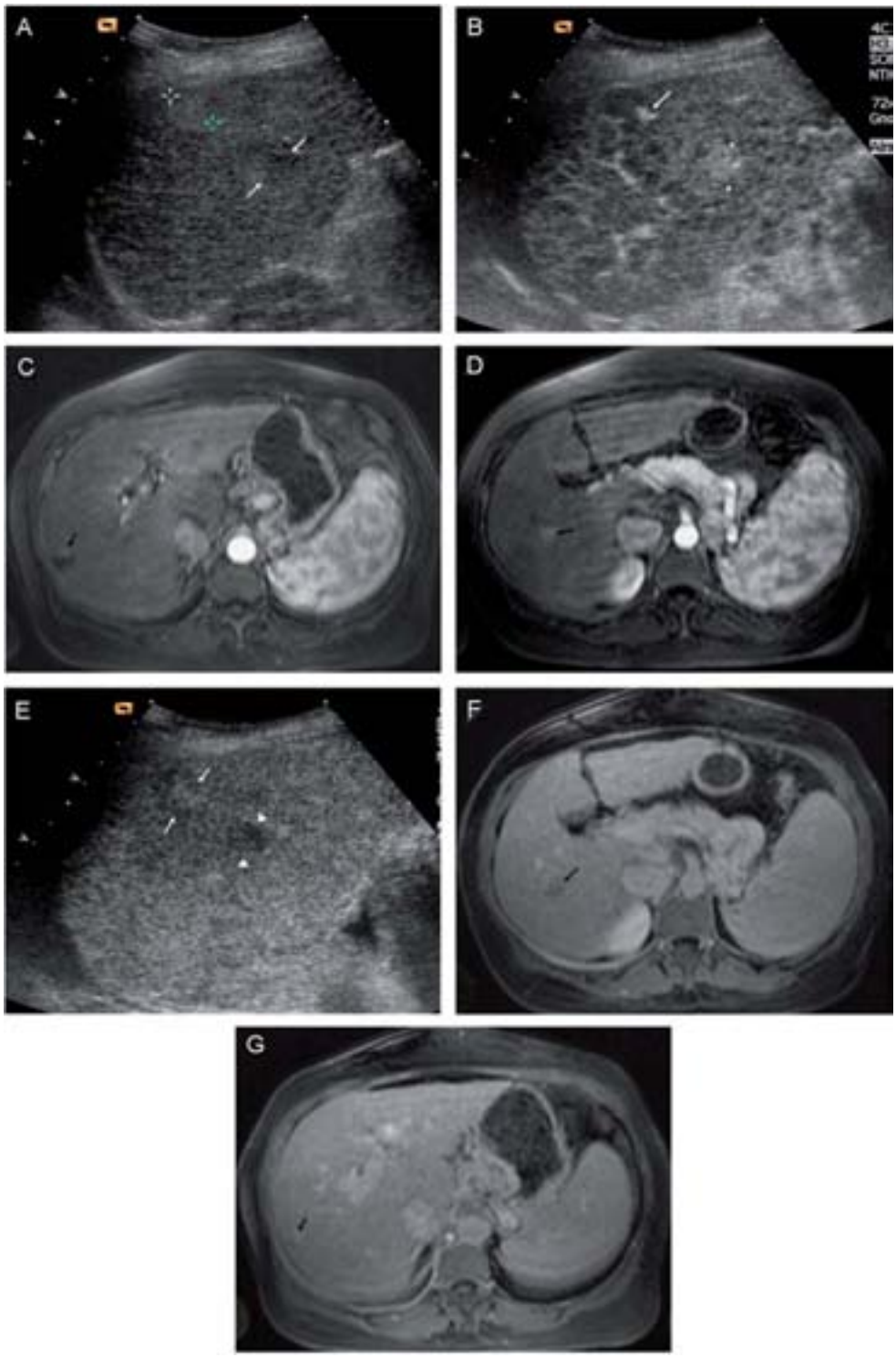

Figure 7 Simultaneous detection of two lesions: a benign lesion (hemangioma) subcapsular and a malignant lesion (HCC) in a patient with cirrhosis. The lesions were studied using CEUS and MRI. A) In the baseline ultrasound, two juxtaposed lesions are observed in the right liver lobe; one of them is lightly echogenic and more subcapsular (cursors), and the other is more hypoechoic and is located deeper (arrows). B) In the arterial phase of CEUS, the administration of a contrast agent allows for the observation of two different uptakes. In the subcapsular lesion, peripheral nodular uptake appears (arrow), whereas in the profound lesion, complete uptake is observed (tip of arrow). C) In the arterial phase of the MRI, the same peripheral nodular uptake is observed in the subcapsular lesion (arrow). D) In the arterial phase of the MRI, complete uptake of the profound lesion is confirmed (arrow). E) In the delayed venous phase of CEUS, the subcapsular lesion stays iso-hyperechogenic with respect to the rest of the parenchyma (arrows), while the profound lesion shows a clear contrast washout (tip of arrow). F) In the venous phase of the MRI, a contrast washout of this profound lesion is also observed (arrow). G) In the delayed venous phase of the MRI, the subcapsular lesion remains isointense compared to the surrounding parenchyma.

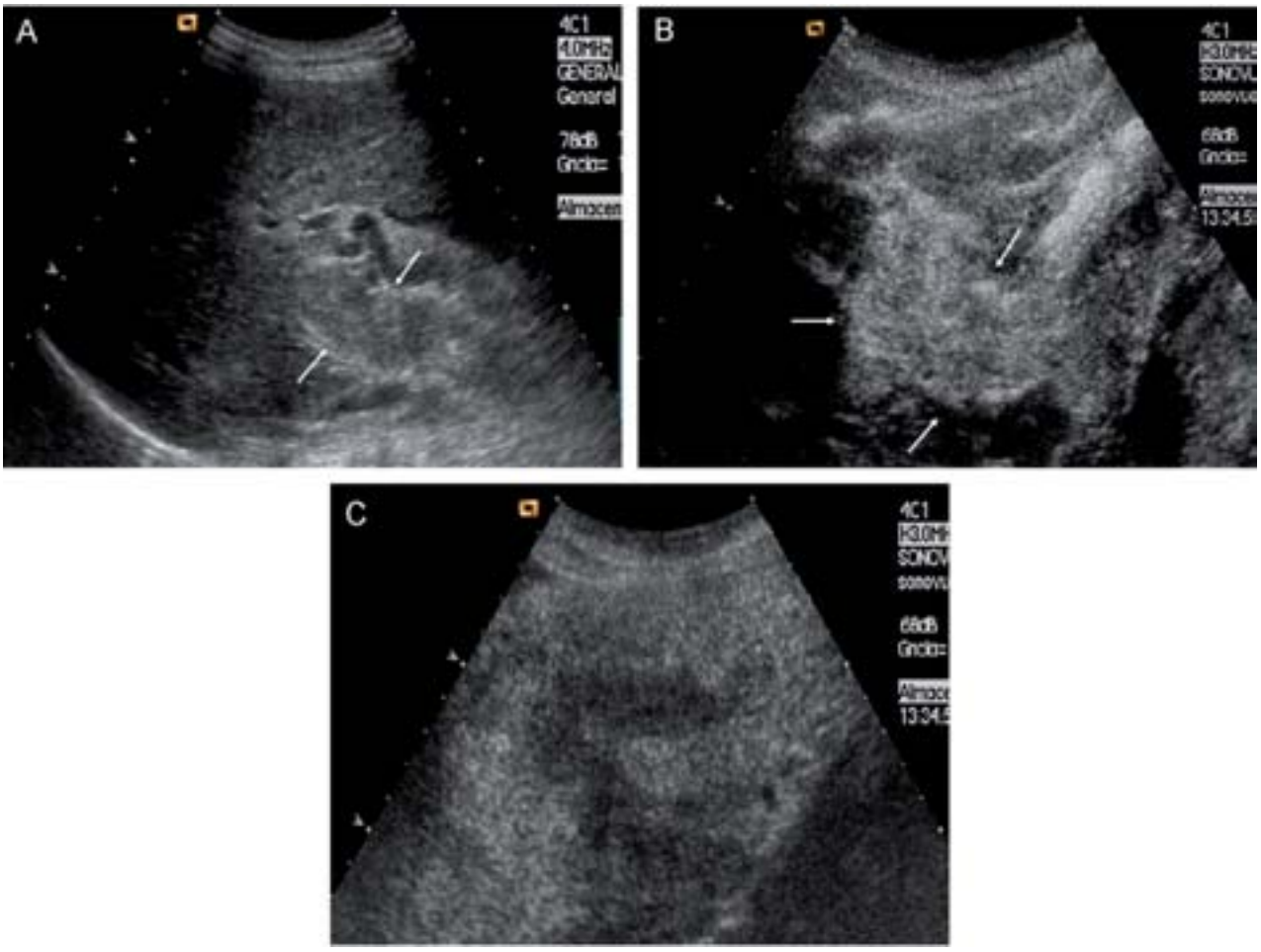

Figure 8 Patient with HCC and portal tumoral thrombosis. A) In the baseline ultrasound a solid thrombus with an expansive aspect occupying the principal trunk and the right portal branch (arrows) is identified. B) After administering an ultrasound contrast agent, intense intratumoral contrast uptake appears in the arterial phase, which demonstrates the tumoral nature of the thrombosis. C) In the late venous phase, a contrast washout of the previous intravascular tumoral uptake is displayed with respect to the rest of the liver parenchyma.

appeared that consider factors associated with tumoral extension and liver function.[61] Of all of the current systems, the only one that associates the stage of the disease with the therapeutic recommendation and has been validated in Europe,[62,63] the United States[64], and Asia is the Barcelona Clinic Liver Cancer (BCLC) system (fig. 9).[65] Recognized for its predictive ability and its utility in the treatment decision process, the BCLC system has been recommended by AASLD[8,66] and by Spanish clinical guidelines.[9]

The BCLC system includes variables associated with the tumoral burden (size and number of lesions, presence of vascular invasion, and/or extrahepatic disease), liver function (Child-Pugh classification), and the presence of symptoms (ECOG Performance Status). It distinguishes four main prognostic groups, each with an associated therapeutic recommendation (fig. 9):

- Early stage (Stage A): This group includes asymptomatic patients with preserved liver function (Child-Pugh A and B) with a solitary HCC or a maximum of 3 nodules, each with a maximum diameter of 3 cm. In these cases, curative treatments can be applied, and the expected survival at 5 years is 50-75%. In brief, candidates for surgical resection are patients that are affected by solitary HCC with preserved liver function with normal bilirubin (< 1 mg/dl) and without clinically relevant portal hypertension.[67] A subgroup of patients that have an excellent prognosis are those with a solitary HCC that is less than 2 cm (very early HCC, stage 0), that corresponds with the concept of carcinoma *in situ*,[20] and surgical resection or percutaneous ablation have a high probability of offering a cure. In patients affected with multifocal HCC ($n \leq 3$) and/or patients who present liver dysfunction, the recommended treatment is a liver transplantation. Finally, in patients who are not eligible for a liver transplantation, the primary treatment recommendation is percutaneous ablation.
- Intermediate stage (Stage B): Patients with multinodular tumors that exceed the previously described criteria. They have no vascular or extrahepatic invasion but have a generally conserved state of liver function. The only treatment that has demonstrated a benefit in terms of

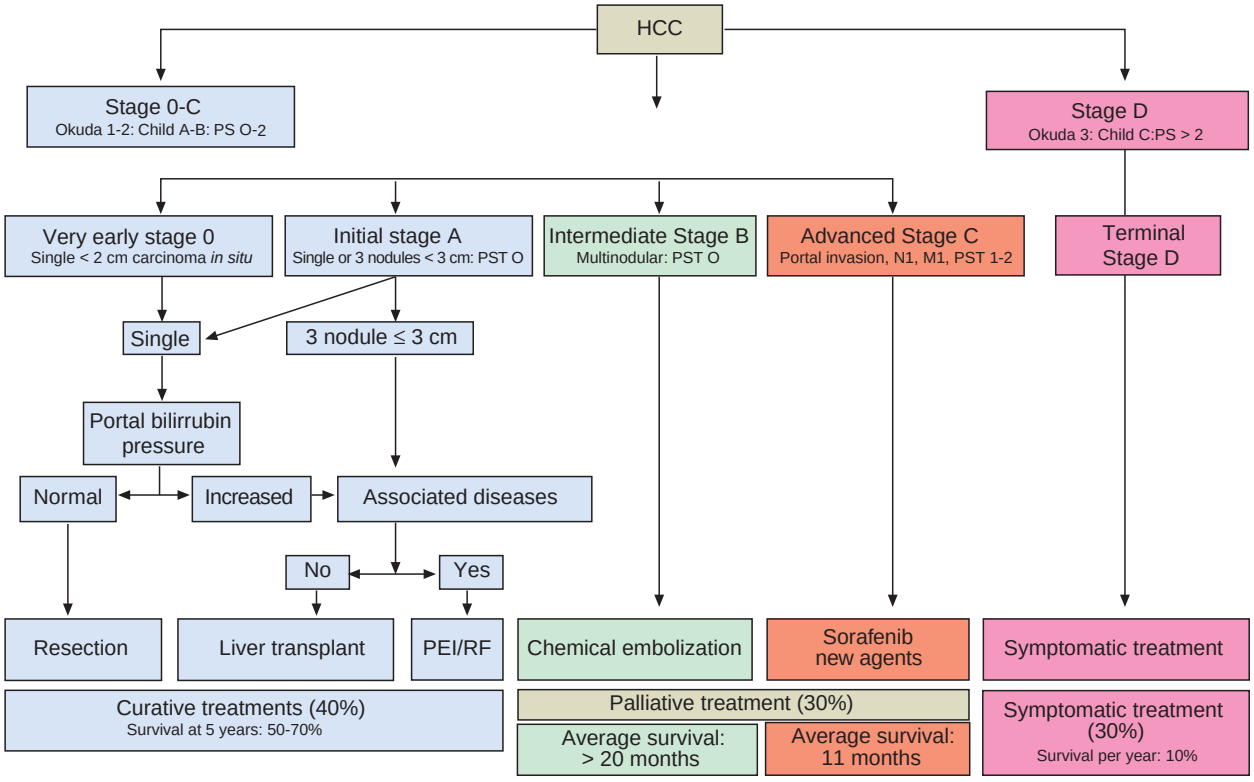

Figure 9 BCLC (Barcelona Clinic Liver Cancer) staging system. Adapted from Forner et al.[9]

survival is transarterial chemoembolization[68], and the median expected survival is longer than 20 months.

- Advanced stage (Stage C): In this stage, patients have conserved liver function but present HCC with vascular and/or extrahepatic invasion or with mild affectation of the general state. Until now, no effective treatment was available, and these patients were candidates for participating in clinical trials to evaluate new therapeutic options. Of all of the evaluated agents, the only drug that has demonstrated a benefit in terms of survival is sorafenib.[69,70] Presently, sorafenib constitutes the only available palliative treatment in this stage.[9,66]
- Terminal stage (Stage D): These patients present severe impairment in their general condition and/or compromised liver function (Child-Pugh C) not candidates for a liver transplantation. The average survival period is less than 3 months, and only symptomatic treatment should be indicated.

Authorship

Ramon Vilana: Study design; redaction and critical revision of part of the chapter; final approval of the version sent for publication.

The rest of the authors were involved in the acquisition of data, design, and redaction of part of the work.

The authors have read and approved the final version of the document.

Conflict of interest

The authors declare no conflict of interest.

References

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340: 745-50.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74-108.
3. Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology. 2006;43:1303-10.
4. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127 (5 Suppl 1):S5-S16.
5. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(5 Suppl 1):S35-50.
6. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al, Taiwan Childhood Hepatoma Study Group. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. N Engl J Med. 1997;336:1855-9.
7. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, Mazzella G, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45:579-87.

8. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42:1208-36.
9. Forner A, Ayuso C, Isabel Real M, Sastre J, Robles R, Sangro B, et al. Diagnosis and treatment of hepatocellular carcinoma. Med Clin (Barc). 2009;132:272-87.
10. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008;47:97-104.
11. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol. 2001;34: 570-5.
12. Marrero JA, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, et al. Alpha-fetoprotein, Des-gamma Carboxyprothrombin, and Lectin-Bound Alpha-fetoprotein in Early Hepatocellular Carcinoma AFP, DCP, and AFP-L3 in Hepatocellular carcinoma. Gastroenterology. 2009.
13. Sherman M. Alphafetoprotein: an obituary. J Hepatol. 2001; 34:603-5.
14. Forner A, Reig M, Bruix J. Alpha-fetoprotein for hepatocellular carcinoma diagnosis: the demise of a brilliant star. Gastroenterology. 2009;137:26-9.
15. Shiraki K, Takase K, Tameda Y, Hamada M, Kosaka Y, Nakano T. A clinical study of lectin-reactive alpha-fetoprotein as an early indicator of hepatocellular carcinoma in the follow-up of cirrhotic patients. Hepatology. 1995;22:802-7.
16. Marrero JA, Su GL, Wei W, Emick D, Conjeevaram HS, Fontana RJ, et al. Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in american patients. Hepatology. 2003;37:1114-21.
17. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, et al. Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. Gastroenterology. 2003;125:89-97.
18. Brenner DJ, Hall EJ. Computed tomography–an increasing source of radiation exposure. N Engl J Med. 2007;357:2277-84.
19. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol. 2003;39:1076-84.
20. Kojiro M, Roskams T. Early Hepatocellular Carcinoma and Dysplastic Nodules. Semin Liver Dis. 2005;25:133-42.
21. Zhang B, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. J Med Screen. 1999;6:108-10.
22. Wong LL, Limm WM, Severino R, Wong LM. Improved survival with screening for hepatocellular carcinoma. Liver Transpl. 2000;6:320-5.
23. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut. 2001;48:251-9.
24. Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology. 2004;126:1005-14.
25. Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. Am J Med. 1996;101:422-34.
26. Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. Am J Gastroenterol. 2003;98:679-90.
27. Lin OS, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. Aliment Pharmacol Ther. 2004;19:1159-72.
28. Caturelli E, Bartolucci F, Biasini E, Vigliotti ML, Andriulli A, Siena DA, et al. Diagnosis of liver nodules observed in chronic liver disease patients during ultrasound screening for early detection of hepatocellular carcinoma. Am J Gastroenterol. 2002;97:397-405.
29. Maroto A, Bru C, Bruix J, Bianchi L, Ayuso C, Gilabert R, et al. Características ecográficas del carcinoma hepatocelular; Análisis de una serie de 125 caso. Radiologia. 1987;29:569-73.
30. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology. 1992;16: 132-7.
31. Ebara M, Hatano R, Fukuda H, Yoshikawa M, Sugiura N, Saisho H. Natural course of small hepatocellular carcinoma with underlying cirrhosis. A study of 30 patients. Hepatogastroenterology. 1998;45(Suppl 3):1214-20.
32. Trinchet J. Screening for hepatocellular carcinoma (HCC) in patients with cirrhosis. A multicenter randomized trial comparing two periodicities of ultrasonographic (US) screening, 3 months vs 6 months. J Hepatol. 2007;46(Suppl 1):S56.
33. Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnu L, Zoli M, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol. 2002;97:734-44.
34. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al, European Association for the Study of the Liver. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. J Hepatol. 2001;35:421-30.
35. International Consensus Group for Hepatocellular Neoplasia. The International Consensus Group for Hepatocellular Neoplasia consists of: Masamichi Kojiro IRW, Venancio Alves, Sunil Badve, Charles Balabaud, Pierre Bedosa, Prithi Bhathal, Paulette Pathologic diagnosis of early hepatocellular carcinoma: A report of the international consensus group for hepatocellular neoplasia. Hepatology. 2009;49:658-64.
36. Bru C, Maroto A, Bruix J, Faus R, Bianchi L, Calvet X, et al. Diagnostic accuracy of fine-needle aspiration biopsy in patients with hepatocellular carcinoma. Dig Dis Sci. 1989;34: 1765-9.
37. Di Tommaso L, Franchi G, Park YN, Fiamengo B, Destro A, Morenghi E, et al. Diagnostic value of HSP70, Glypican 3, and Glutamine Synthetase in hepatocellular nodules in cirrhosis. Hepatology. 2007;45:725-34.
38. Di Tommaso L, Destro A, Seok JY, Balladore E, Terracciano L, Sangiovanni A, et al. The application of markers (HSP70 GPC3 and GS) in liver biopsies is useful for detection of hepatocellular carcinoma. J Hepatol. 2009;50:746-54.
39. Llovet JM, Chen Y, Wurmbach E, Roayaie S, Fiel MI, Schwartz M, et al. A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. Gastroenterology. 2006;131:1758-67.
40. Kim SH, Choi D, Lim JH, Lee WJ, Kim MJ, Lim HK, et al. Ferucarbotran-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol. 2005;184:1069-76.
41. Kim YK, Kim CS, Chung GH, Han YM, Lee SY, Chon SB, et al. Comparison of gadobenate dimeglumine-enhanced dynamic MRI and 16-MDCT for the detection of hepatocellular carcinoma. AJR Am J Roentgenol. 2006;186:149-57.
42. Jung G, Breuer J, Poll LW, Koch JA, Balzer T, Chang S, et al. Imaging characteristics of hepatocellular carcinoma using the hepatobiliary contrast agent Gd-EOB-DTPA. Acta Radiol. 2006;47:15-23.
43. Frericks BB, Loddenkemper C, Huppertz A, Valdeig S, Stroux A, Seja M, et al. Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. AJR Am J Roentgenol. 2009;193:1053-60.

44. Jang HJ, Kim TK, Burns PN, Wilson SR. Enhancement patterns of hepatocellular carcinoma at contrast-enhanced US: comparison with histologic differentiation. Radiology. 2007; 244:898-906.
45. Yoon SH, Lee JM, So YH, Hong SH, Kim SJ, Han JK, et al. Multiphasic MDCT enhancement pattern of hepatocellular carcinoma smaller than 3cm in diameter: tumor size and cellular differentiation. AJR Am J Roentgenol. 2009;193: W482-9.
46. Doo KW, Lee CH, Choi JW, Lee J, Kim KA, Park CM. "Pseudo washout" sign in high-flow hepatic hemangioma on gadoxetic acid contrast-enhanced MRI mimicking hypervascular tumor. AJR Am J Roentgenol. 2009;193:W490-6.
47. Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS)-update 2008. Ultraschall Med. 2008;29:28-44.
48. Catala V, Nicolau C, Vilana R, Pages M, Bianchi L, Sánchez M, et al. Characterization of focal liver lesions: comparative study of contrast-enhanced ultrasound versus spiral computed tomography. Eur Radiol. 2007;17:1066-73.
49. Wilson SR, Kim TK, Jang HJ, Burns PN. Enhancement patterns of focal liver masses: discordance between contrast-enhanced sonography and contrast-enhanced CT and MRI. AJR Am J Roentgenol. 2007;189:W7-W12.
50. Chen LD, Xu HX, Xie XY, Xie XH, Xu ZF, Liu GJ, et al. Intrahepatic cholangiocarcinoma and hepatocellular carcinoma: differential diagnosis with contrast-enhanced ultrasound. Eur Radiol. 2009.
51. Vilana R, Forner A, Bianchi L, Garcia-Criado A, Rimola J, Rodriguez de Lope C, et al. Intrahepatic peripheral cholangiocarcinoma in cirrhosis patients may display a vascular pattern similar to hepatocellular carcinoma on contrast-enhanced ultrasound. Hepatology. 2010;51:2020-9.
52. Rimola J, Forner A, Reig M, Vilana R, de Lope CR, Ayuso C, et al. Cholangiocarcinoma in cirrhosis: Absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology. 2009;50:791-8.
53. Burrel M, Llovet JM, Ayuso C, Iglesias C, Sala M, Miquel R, et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. Hepatology. 2003;38:1034-42.
54. Vilana R, Bru C, Bruix J, Castells A, Sole M, Rodes J. Fine-needle aspiration biopsy of portal vein thrombus: value in detecting malignant thrombosis. AJR Am J Roentgenol. 1993;160:1285-7.
55. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999;29:62-7.
56. Greene F, Page D, Fleming I, Fritz A, Balck C, Haller D, et al. Cancer Staging Handbook. AJCC, editor. New York: Springer Verlag; 2002.
57. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-9.
58. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70.
59. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. Br J Cancer. 1993;67:773-5.
60. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? Eur J Cancer. 1992;28A: 1328-30.
61. Forner A, Reig ME, Rodriguez de Lope C, Bruix J. Current Strategy for Staging and Treatment: The BCLC Update and Future Prospects. Semin Liver Dis. 2010;30:61-74.
62. Cillo U, Bassanello M, Vitale A, Grigoletto FA, Burra P, Fagiuoli S, et al. The critical issue of hepatocellular carcinoma prognostic classification: which is the best tool available? J Hepatol. 2004;40:124-31.
63. Grieco A, Pompili M, Caminiti G, Miele L, Covino M, Alfei B, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. Gut. 2005;54:411-8.
64. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology. 2005;41:707-16.
65. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329-38.
66. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100:698-711.
67. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology. 1999;30:1434-40.
68. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003;37:429-42.
69. Llovet J, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-90.
70. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10:25-34.