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Imaging of HCC

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Abstract

Imaging techniques play a crucial role in the management of patients with liver cirrhosis in whom a nodular hepatic lesion is detected. The most severe complication of patients with liver cirrhosis is the development of a hepatocellular carcinoma (HCC), and the prognosis of the disease depends on the tumoral stage. Surveillance programs based on ultrasonography (US) are recommended in cirrhotic patients with possibility to be treated if an HCC is detected, in order to improve the patient's survival. Nevertheless, early detection and diagnostic confirmation of HCC remains a challenge despite technological advances. The non-invasive criteria to characterize small HCCs in patients with cirrhosis are based on the evaluation of the vascular profile of the lesion. Dynamic multidetector computed tomography (MDCT) and dynamic magnetic resonance imaging (MRI) are the suitable techniques for this purpose. When diagnosis is not achieved, fine US-guided fine needle biopsy (FNB) is indicated. Cellular-MRI contrast agents may have a role in lesions with atypical vascular pattern in which FNB is not feasible. The assessment of the disease extent is another important goal for imaging techniques. Again, dynamic MDCT and dynamic MRI may be used for staging purposes. Although MRI is more accurate in the detection of additional nodules ranging 1–2 cm, both remain relatively insensitive for the detection of tiny satellite nodules below 1 cm. The therapeutic decision can be made in any particular patient on the basis of the tumoral extension, the liver function, and the general status. After curative and palliative therapeutic procedures, the monitoring of the response is mandatory to decide the next approach: to follow-up, to repeat the treatment, to modify the treatment indication, or to suspend the treatment. In this review, we discuss the most recent information on the imaging of HCC.

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Surveillance of hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most frequent primary liver neoplasm, being the major cause of death in cirrhotic patients [1, 2]. The annual incidence of HCC in the cirrhotic population is 3%–5% [3].

The diagnosis after the onset of symptoms, when the tumor stage is already advanced, is associated to a poor prognosis (0%–10% 5-year survival) [4]. However, successful treatments and long-term survival are possible when the HCC is diagnosed promptly (50%–70% 5-year survival) [5].

In order to diagnose the tumor in early stages, when effective therapy might be successfully applied, the population at risk must be enrolled in an appropriate surveillance program. It is necessary therefore, to define the population at risk and to determine the level of incidence of HCC for early detection plan. It has been accepted that surveillance is cost-effective when the risk of HCC is greater than 1.5% per year [6]. Based on this data, all cirrhotic patients and adults with chronic, replicative hepatitis B without cirrhosis should be enrolled in a surveillance program.

Serological tests, as the alphafetoprotein level, have a low sensitivity and they are inadequate for screening [7]. There is now general agreement that the best surveillance tests are the imaging techniques [6]. Ultrasonography (US) is the imaging test most widely used for surveillance because it is not expensive, not invasive, well accepted by patients and can be repeated without risk. The sensitivity and specificity of US for HCC detection in cirrhotic patients is high (60%–80% and 45%–94%, respectively) [8], especially being performed by experienced professionals and using last generation equipments. The sensitivity of CT is also elevated (53%–87%) [8] but its

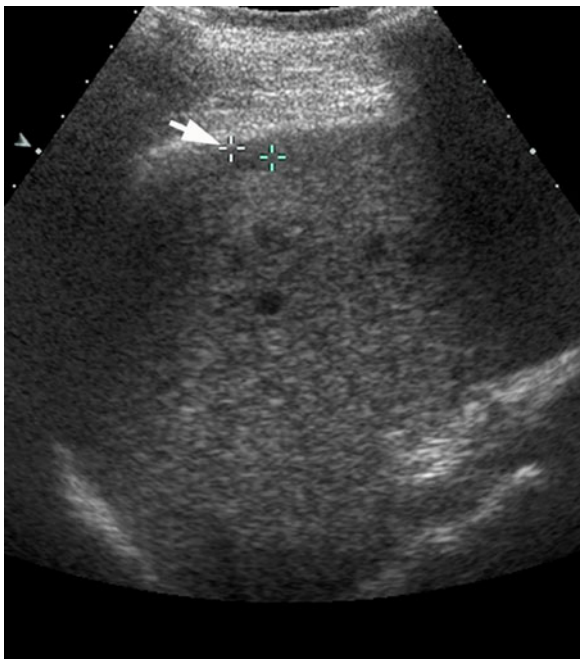


Fig. 1. Sonographic study in a cirrhotic patient shows a small subcapsular hypoechoic nodule corresponding to a dysplastic nodule (*arrow*).

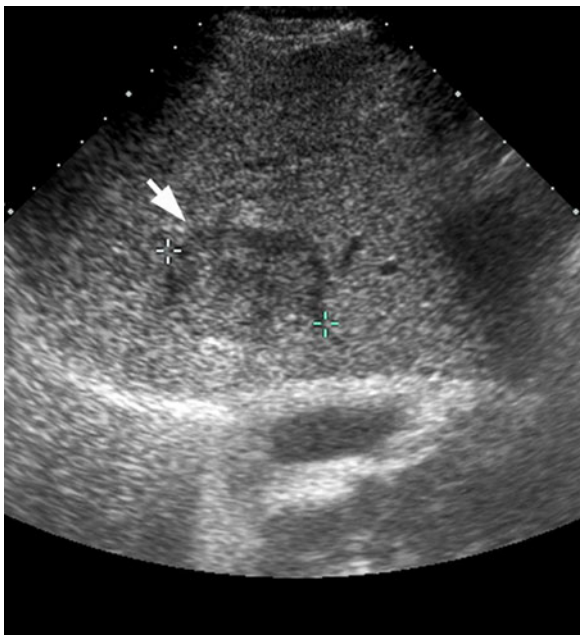


Fig. 2. Large hepatocellular carcinoma in right hepatic lobe sized 52 mm with heterogeneous appearance in sonography with hypoechoic and hyperechoic areas (*arrow*).

usefulness in a surveillance program that required periodical tests is limited by the patients radiation exposure [9]. MRI has higher sensitivity than CT for HCC detection (89%–100%), especially for additional nodules

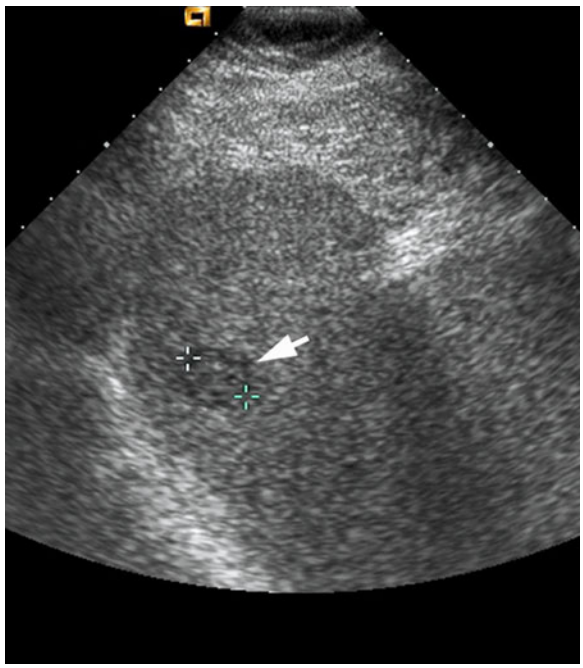


Fig. 3. Surveillance sonography in a cirrhotic patient shows a hypoechoic nodule sized 18 mm (*arrow*). Histological findings on biopsied specimen revealed well-differentiated hepatocellular carcinoma.

between 1 and 2 cm in size (84% vs. 47%) [10]. However, MRI is reserved for characterization purposes, diagnostic confirmation and intrahepatic tumor staging because of its lower availability and high cost [11]. Positron emission tomography (PET) has shown no value in the diagnosis of HCC [12].

The ideal surveillance interval is not known because a prospective comparison of different schedules is lacking in the literature. Based upon of the tumor doubling time, a 6-month schedule is generally recommended; however, a retrospective study comparing 6- or 12-month intervals has demonstrated no changes in survival [13].

The main objective of the surveillance program by US is to identify tumors less than 2 cm because they have low probability of vascular invasion [14] and curative treatments can be applied. However, frequently it is difficult to distinguish small tumors from the nodularity of the cirrhotic liver by US. Professional expertise is essential in order to improve the sensitivity of the technique. Small size and subphrenic location of the tumor decrease the sonographic detection [15]. However, benign nodules like regenerative nodules and dysplastic nodules are very frequent findings in the sonographic studies of cirrhotic patients and, regardless the experience of the physician, may be indistinguishable from small HCC (Fig. 1). The sonographic findings of HCC are nonspecific and may take different appearances. Large tumors are often heterogeneous with hypoechoic and hyperechoic areas and frequently with a hypoechoic rim

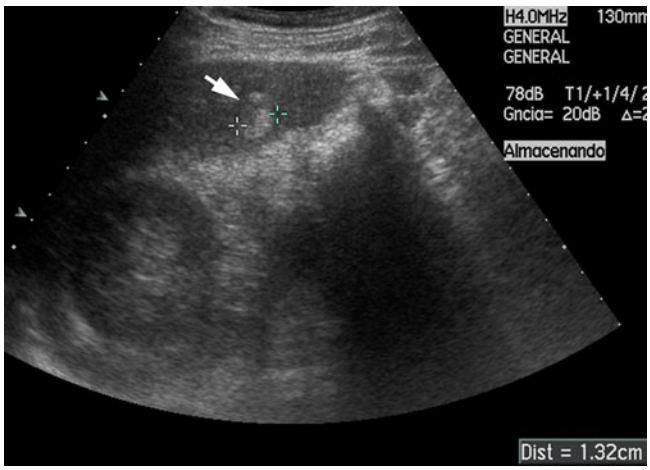


Fig. 4. Small hepatic nodule, 13 mm in size, which shows a hyperechoic area (*arrow*).The lesion proved to be hepatocellular carcinoma at explant correlation.

(Fig. 2). In these cases it may be easy to suggest the diagnosis of HCC. However, small HCCs are less characterized by sonography. Usually they are homogeneously hypoechoic (Fig. 3), but other appearances like mixed or hyperechoic nodules (Fig. 4) if fat is present, are also possible. In these cases, differentiation from other benign or malignant liver lesions (angiomas, metastasis, or cholangiocarcinoma) may be very difficult.

As a rule, any new nodular lesion larger than 1 cm detected on the surveillance US in a cirrhotic liver is suspicious of HCC and more studies should be indicated.

Diagnosis and staging

Small hepatic nodules are frequently found in cirrhotic livers. The International Working Party (IWP) of the World Congresses of Gastroenterology [16] proposed a classification of the hepatocellular nodular lesions found in chronic liver disease into large regenerative nodule (LRN), low-grade dysplastic nodule (LGDN), high-grade dysplastic nodule (HGDN), and HCC. While LRNs is thought to be benign lesions, DNs are considered as preneoplastic lesions and HGDNs are likely advanced precursors of HCC. The IWP also defined the concept of small HCC as a tumor measuring less than 2 cm.

More recent studies support the division of small HCC into two clinicopathological groups: small HCC of distinctly nodular type and small HCC of indistinctly (vaguely) nodular type. The latter is an ill-defined nodule, usually hypovascular on imaging, with well-differentiated malignant cells and with neither tumor cell invasion into the portal vein nor minute intrahepatic metastases in the vicinity of the tumor. These tumors have been termed early HCC and are associated with better long-term survival than small HCC of distinctly nodular type [14]. In order to obtain a refined and updated international consensus on the histopathologic diagnosis of nodular lesions, the International Consensus Group for Hepatocellular Neoplasia (ICGHN) recently published a consensus document that summarizes the results of their meetings [17].

HCC has been proved to develop by multistep carcinogenesis from a LGDN to an over HCC [18–20]. This multistep process implies: (1) a progressive cellular dedifferentiation and (2) the simultaneous development of the neoangiogenesis phenomenon as a result of some changes in the intranodular blood supply such as: progressive decrease of the portal supply, sinusoidal capillarization and increase in the number of anomalous arterial vessels (unpaired arteries or non-triadal arteries). Roncalli et al. [21] demonstrated that both capillary units and unpaired arteries were more numerous in HGDN and malignant lesions compared to LGDNs, regenerative, and cirrhotic nodules. This anomalous arterial vascularization becomes the dominant blood supply in overt HCC lesions and is responsible for the hypervascular pattern seen in the arterial phase of HCC lesions in dynamic imaging studies. More recently, Kitao et al. [22] compared the histopathologic features and the microangioarchitecture in 46 hepatic nodules surgically resected, and demonstrated that the main drainage vessels of HCC change from hepatic veins to hepatic sinusoids to portal veins during multistep hepatocarcinogenesis.

Some authors have studied the value of hepatobiliary contrast agents in the estimation of histological HCC grading. Huppertz et al. [23] evaluated eight HCC patients under MRI with gadoxetic acid. During the hepatobiliary phase, all four grades II or III HCCs showed no contrast enhancement, whereas two of four grade I HCCs showed some enhancement, suggesting potential to differentiate HCCs of different grades. But contradictory results have been reported later by other authors. Frericks et al. [24] reported that, although HCCs are predominantly hypointense relative to the surrounding liver tissue on late hepatobiliary images, most of them, irrespective of grade, retain a small amount of the contrast agent. Recently, Kogita et al. [25] studied 83 histologically proven HCCs and DNs and indicated that reduced Gadoxetic acid uptake might be an early event of hepatocarcinogenesis, preceding portal blood flow reduction. Nevertheless, although the hepatobiliary phase after Gadoxetic acid injection may help estimate histological grading, the authors found difficulties in differentiating HCCs from DNs.

The unequivocal diagnosis of a new detected nodule within a cirrhotic liver during a screening US represents a major clinical challenge. Biopsy confirmation has several limitations. Location of the tumor, clotting disorders, and ascites may prevent a safe needle insertion. In addition, biopsy is not free of risks such as bleeding or seeding and hence, some groups may contraindicate it prior to surgery or transplantation. Finally, it is well

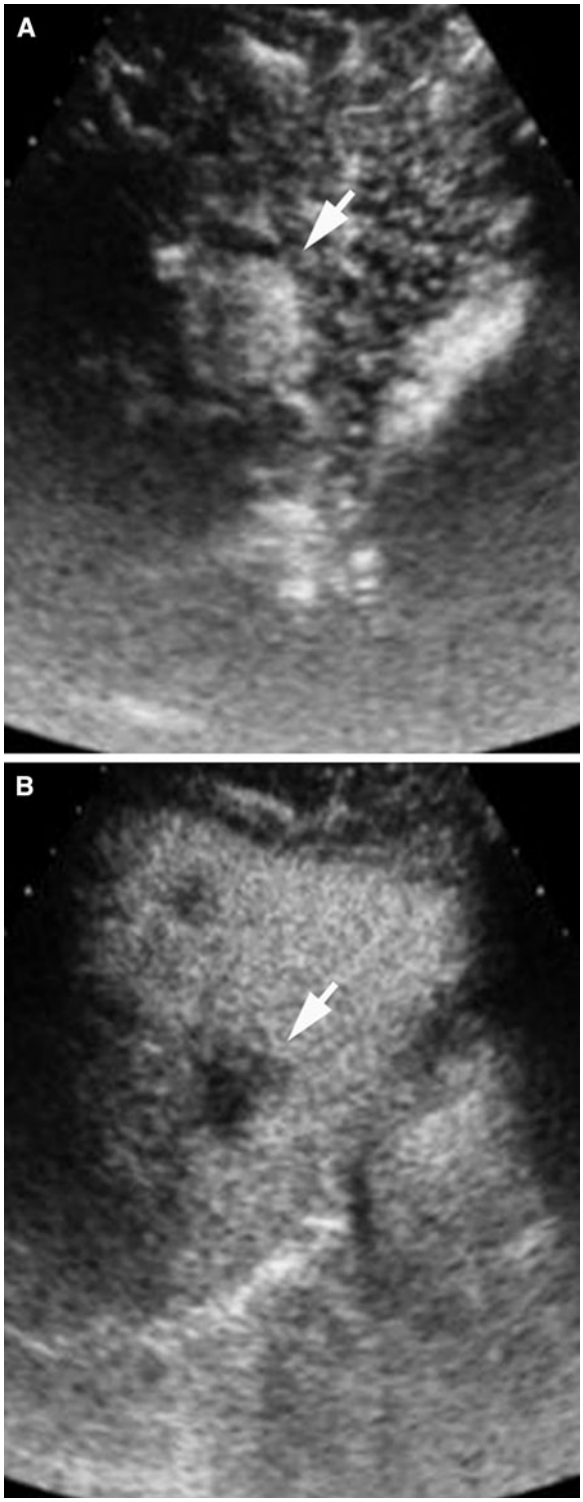


Fig. 5. Intrahepatic cholangiocarcinoma in the left hepatic lobe, in a patient with liver cirrhosis studied by CEUS. **A** Arterial phase: complete homogeneous enhancement of the 22 mm nodule (*arrows*). **B** Portal phase: a clear washout is observed 60 s after contrast injection (*arrows*).

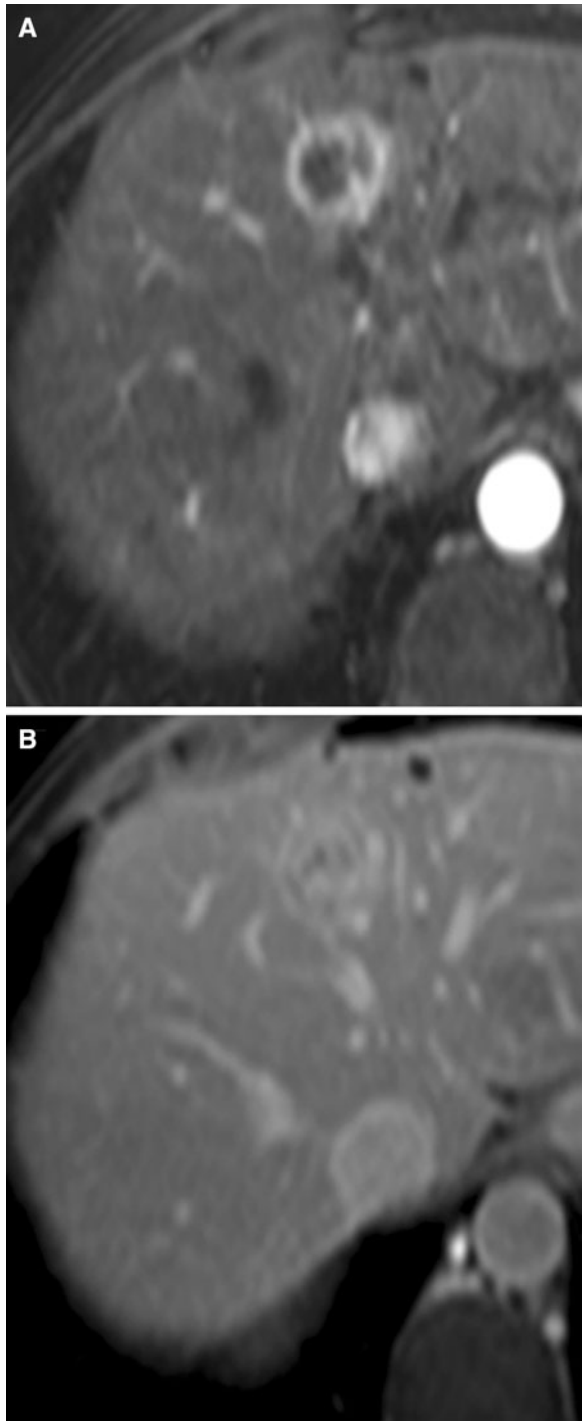
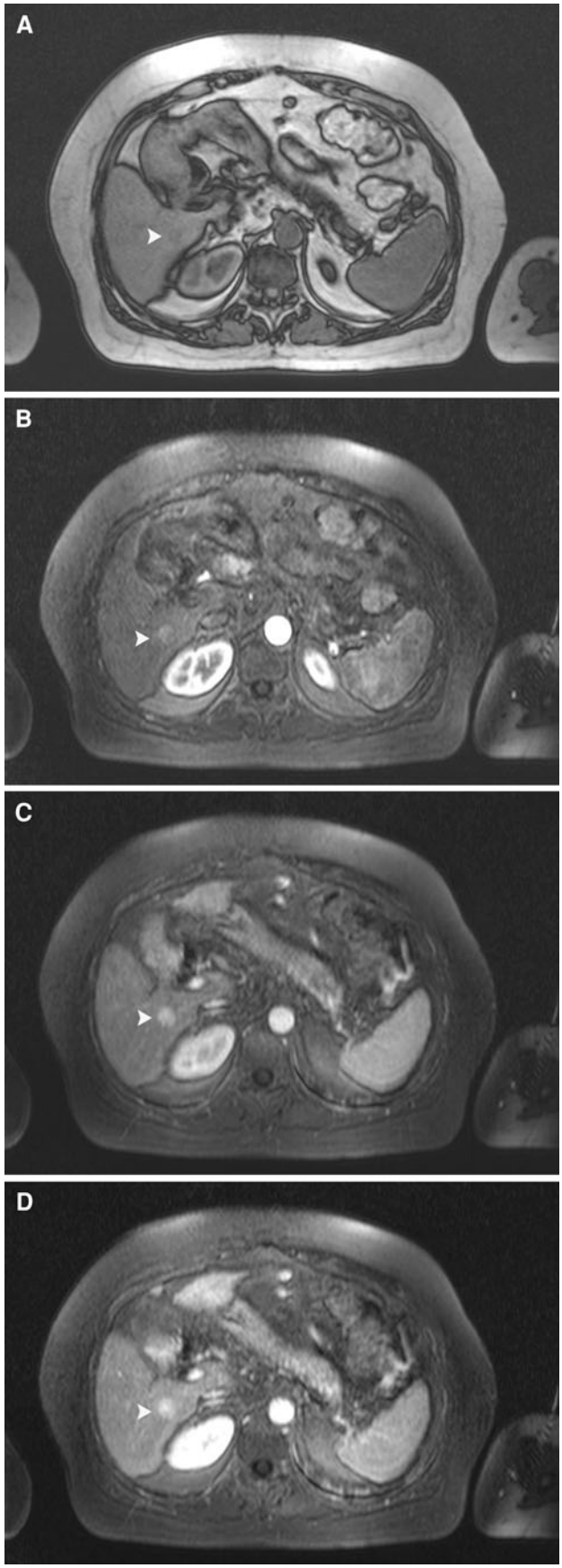


Fig. 6. Intrahepatic cholangiocarcinoma in the IV hepatic segment in a patient with liver cirrhosis studied by MRI. **A** The arterial phase shows a nodule with a rim hyperenhancement. **B** At the portal phase progressive uptake of intravenous contrast media is seen until complete enhancement of the lesion.

known that biopsy is flawed by false negative results due to sampling error or to the unfeasibility of confidently distinguishing between dysplastic changes and well-differentiated HCC. This last issue is especially relevant when dealing with small nodules that are commonly composed of well differentiated hepatocytes. This raises the need of well-defined non-invasive criteria that, while



◀ **Fig. 7.** Intrahepatic cholangiocarcinoma in the VI hepatic segment, in a patient with liver cirrhosis. **A** In the plain out-of-phase T1W MRI, a 15 mm hypointense nodule is depicted (*arrowhead*). **B** MRI displays complete homogeneous enhancement of intravenous contrast on arterial phase and stable contrast enhancement in the portal (**C**) and delayed venous phases (**D**).

avoiding the demand for a positive biopsy, would allow a confident diagnosis based on the imaging characterization. To fulfill this need, the European Association for the Study of the Liver (EASL) 2000 Conference proposed a set of non-invasive criteria to establish HCC diagnosis in patients with liver cirrhosis [26] with hypervascular nodules of more than 2 cm in size. In 2005, the American Association for the Study of the Liver diseases (AASLD) guidelines [27] included three imaging techniques suitable to diagnose HCC by non-invasive imaging criteria: contrast-enhanced US (CEUS), dynamic CT, and dynamic MRI. They also recommended more well-defined imaging criteria for the non-invasive diagnosis of HCC nodules, while also reducing the size of the lesions, and nodules between 1 and 2 cm with a specific radiologic hypervascular arterial profile and "washout" in the venous phase observed in two coincident imaging techniques would also be diagnosed as HCC. These new non-invasive criteria were validated in a prospective study that evaluate the accuracy of contrast-enhanced US (CEUS) and dynamic MRI for the diagnosis of solitary nodules <20 mm detected during surveillance in 89 cirrhotic patients with no prior HCC in whom a new solitary 5–20 mm nodule was detected by US. The sensitivity and specificity of conclusive HCC were 61.7% and 96.6%, respectively, for MRI, and 33.3% and 100%, respectively, when MRI and CEUS coincidentally showed conclusive HCC [28]. Accordingly, diagnosis of HCC $<$ 20 mm could be confidently established without requesting a positive biopsy if both CEUS and MRI are diagnostic for HCC in 33% of cases.

Another study provided external validation of the AASLD non-invasive criteria published in 2005. Sangiovanni et al. [29] studied 64 patients with 67 de novo liver nodules (55 ranging 1–2 cm in size) with CEUS, CT, MRI and a fine-needle biopsy (FNB) as a gold standard. They describe a sensitivity of CEUS, CT, and MRI for 1–2 cm HCC of 26%, 44%, and 44%, with 100% specificity, and the typical vascular pattern of HCC was identified in 65% of cases by one single technique vs. 35% by at least two coincidental techniques. They conclude that for hepatic nodules larger than 1 cm in cirrhotic patients, one single imaging technique showing a typical contrast-enhanced pattern confidently allow the diagnosis of HCC, reducing the need for FNB examinations.

Nevertheless, recent data demonstrated that washout may be observed in CEUS in hypervascular liver lesions different from HCC (Fig. 5) [30–32]. Vilana et al. [32]

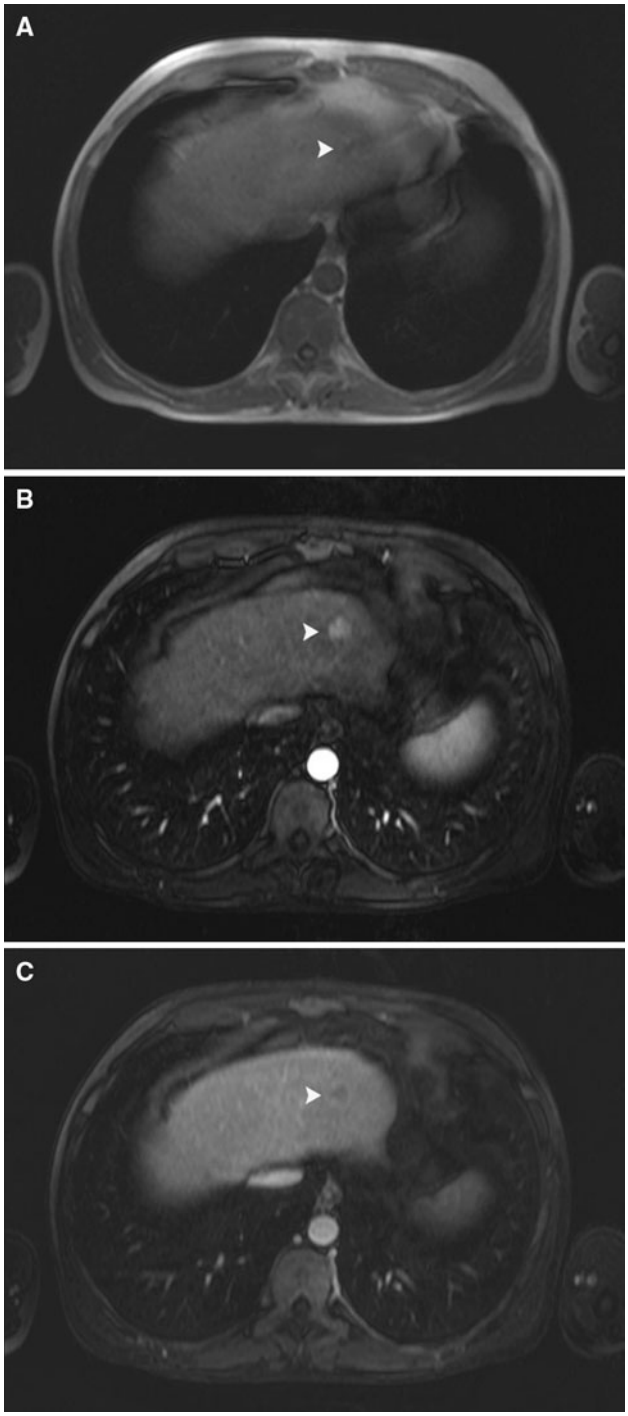


Fig. 8. Well-differentiated HCC 14 mm in size located in the lateral segment of the left hepatic lobe, in a patient with liver cirrhosis. The lesion displays the typical vascular profile of HCC. **A** MRI shows a slightly hypointense nodule (*arrowhead*) in the T1WI. **B** The lesion shows a dramatic homogeneous arterial enhancement (wash-in pattern), **C** with a clear decrease of signal intensity compared to the surrounding liver parenchyma in the portal venous phase (washout) (*arrowhead*).

reported the CEUS findings in 21 cirrhotic patients with histologically confirmed intrahepatic cholangiocarcinoma (ICC) with a median nodule size of 32 mm. All nodules showed contrast enhancement in the arterial phase, homogeneous (10 cases), or peripheral (11 cases). All nodules displayed washout in the venous phase during the first 60 s (10 cases), between 60 and 120 s (5 cases), or after 2 min (6 cases). Ten nodules, five of them larger than 2 cm, displayed homogeneous contrast uptake followed by washout corresponding to the specific pattern of HCC according to the AASLD criteria published in 2005 [27]. The authors conclude that CEUS should not be used as the sole imaging technique to confidently characterize HCC.

The enhancement MRI pattern of ICC nodules in cirrhotic patients has also been studied [33]. Thirty-one histologically confirmed ICC nodules in 25 cirrhotic patients were studied by MRI. The most frequent enhancement pattern observed in the dynamic MRI was the progressive contrast uptake (80.6%) (Fig. 6). Stable contrast enhancement was registered in 19.4% (Fig. 7). None of the ICCs showed a washout pattern. Thus, although ICC may mimic in part the profile observed in those HCC that do not show washout after arterial uptake, since washout in MRI is not observed in ICC, it is the key to use this profile as the specific characteristic allowing non-invasive diagnosis.

As a consequence of these recent data, the AASLD updated the recommendation for non-invasive diagnostic criteria of HCC [6]. They pivot around the required 4-phase dynamic multidetector computed tomography (MDCT) and dynamic magnetic resonance imaging (MRI) (plain, arterial, venous, and delayed phases). CEUS is not further recommended for diagnosis of HCC. Nodules less than 10 mm in size are considered not feasible to be confidently diagnosed and in some cases they may not even correspond to premalignant or malignant foci. Thus, close follow-up by US at intervals from 3 to 6 months is recommended looking for size increase of the lesion over a period up to 2 years. If the lesion shows no changes in the follow-up US after this period of time, the patient can revert to standard surveillance.

Nodules larger than 10 mm found on screening US should be studied either by 4-phase dynamic MDCT or dynamic MRI. If a specific vascular profile is demonstrated (wash-in the arterial phase followed by wash-out in the portal venous or delayed phases) in one single imaging technique, the diagnosis of HCC can be established, and the lesion should be treated (Fig. 8). If this vascular pattern is not observed, then a second dynamic imaging technique or a nodule biopsy should be performed. If the biopsy is negative, the lesion should be followed-up by imaging techniques every 3–6 months until it disappears, or it enlarges or changes its vascular profile to a typical HCC pattern. If the lesion grows but

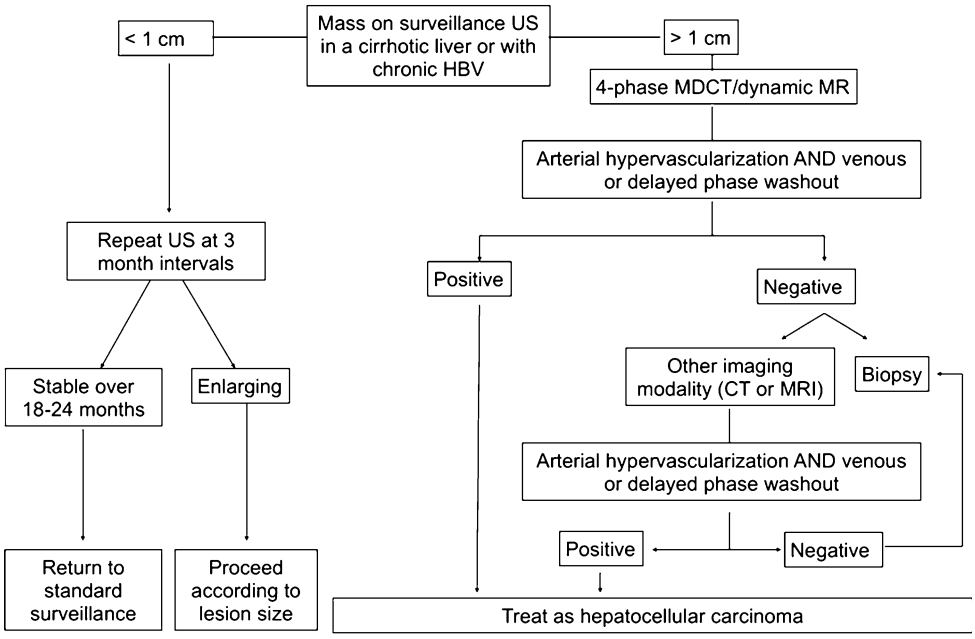


Fig. 9. Algorithm for investigation of small nodules found on screening in patients at risk for HCC (MDCT: multidetector CT). (from the AASLD Guidelines for the management of HCC, http://www.aasld.org/practiceguidelines).

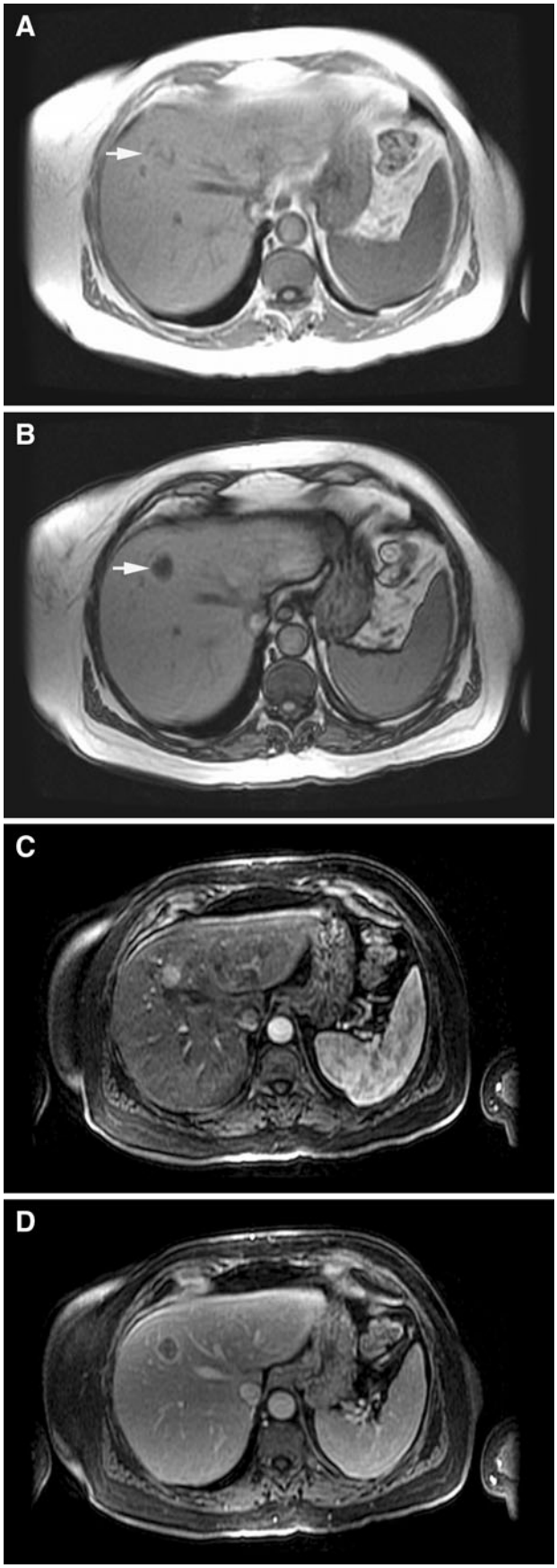
does not show a typical wash-in/was-out pattern, then a repeated biopsy is recommended. Furthermore, when the biopsy specimen can not clearly show HCC changes, the tissue should be stained with all the available markers to improve diagnostic accuracy.

The updated AASLD guidelines for the non-invasive criteria for the diagnosis of HCC (Fig. 9) include three major changes compared to the imaging criteria published in 2005: (1) CEUS has been eliminated as a diagnostic technique suitable for the characterization of HCC lesions because it may produce false positive findings for HCC in patients with intrahepatic cholangiocarcinoma. US should be reserved for detection purposes along the screening programs, for guiding the FNB when it is required, to apply an ablative percutaneous treatment if indicated and to evaluate the local therapeutic response after these local therapies, (2) The recommendation to obtain a second imaging technique required to diagnose HCC nodules of 10–20 mm in size even when the lesion had a typical vascular profile in the first imaging technique has been eliminated. This allows to increase the sensitivity of the non-invasive criteria for nodules larger than 10 mm maintaining a specificity close to 100%, and (3) The non-invasive criteria to diagnose HCC lesion may be applied not only in patients with liver cirrhosis but also in patients with long term chronic HBV infection [6].

It should be noted that the typical vascular profile of HCC lesions has been described and validated in dynamic imaging techniques using extracellular contrast media. Thus, the wash-in (the lesion enhances more densely or intensely than the surrounding liver parenchyma in the arterial phase) and wash-out (the lesion appears less dense or intense than the surrounding liver parenchyma in the venous phase) phenomena, is related with the particular pharmacokinetics and biodistribution of the extracellular contrast media. On the other hand, it should be stressed that although the characteristic imaging appearance of HCC, including small HCC, is a hypervascular lesion that shows washout in the portal or delayed venous phase, DNs and most early HCCs are hypovascular lesions probably because of the insufficient development of an extensive network of newly formed vessels [34].

Other imaging features on dynamic CT and MRI may support the diagnosis of HCC. Tumor capsule is identified as a hyperdense or hyperintense thin peripheral rim enhancement in the delayed venous phase images [35], although this finding is not commonly present in small tumors. Fatty metamorphosis in HCC detected by T1W-in/out-MRI sequences has been reported in a 14% of the HCC patients [36]. Although these findings, if present, are very specific (Fig. 10), they have shown a low sensitivity and up to now, they have not been demonstrated to improve the sensitivity of the standard non-invasive criteria for the diagnosis of HCC based on the enhancement (wash-in/out) pattern.

Diffusion-weighted (DW) MRI is a functional study susceptible to differences in water mobility useful for tissue characterization by probing tissue microstructural changes, quantified as the apparent diffusion coefficient (ADC). This technique has been tested to diagnose HCC lesions and it has shown encouraging results. Vandecaveye et al. [37] conducted a prospective study to evaluate the accuracy of DW-MRI in differentiating HCC from benign cirrhotic lesions compared with conventional dynamic contrast-enhanced MRI in 55 cirrhotic patients. They obtained a sensitivity of DW-MRI of



◀ **Fig. 10.** Moderately differentiated 17 mm HCC located in the left hepatic lobe in a patient with liver cirrhosis. **A** The lesion shows fatty content in the in/out T1WI (*arrow*). It is hyperintense in the image obtained in phase (**B**) and it shows an important decrease of signal intensity in the out of phase images. **C** The nodule shows a typical HCC vascular profile with a clear arterial enhancement and **D** also a clear washout in the venous phase and a thin rim around the nodule corresponding to a peritumoral pseudocapsule.

95.2% for detection of malignant lesions compared to 80.6% for conventional MRI, and the improved accuracy was most beneficial for differentiating malignant lesions smaller than 2 cm.

MRI with liver-specific contrast agents such as superparamagnetic iron oxide particles, which target Kupffer cells [38], or gadobenate dimeglumine and gadoxetic acid, which are suitable for dynamic studies and are taken up by hepatocytes, have been found to have diagnostic accuracy in the detection of HCCs similar to that of MDCT [39, 40]. The delayed hepatocyte-specific phase after the injection of gadoxetic acid presents a superior liver enhancement compared to that obtained with gadobenate dimeglumine, probably because of the high liver-specific uptake of gadoxetic acid (approximately 50% of the injected dose is taken up by hepatocytes, against the 5% for gadobenate dimeglumine) [41]. The mechanism of enhancement of HCC on gadoxetic acid hepatobiliary phase MRI has been recently studied [42], and the hepatocyte selective enhancement is induced by expression patterns of transporters which may result in accumulation of gadoxetic acid in the cytoplasm of tumor cells or in the lumina of pseudoglands. HCC with high gadoxetic acid enhancement is characterized by bile accumulation in tumors.

A recent study compared the performance of ferucarbotran and gadoxetic acid-enhanced MRI using a 3T unit, and both showed a similar diagnostic accuracy for the preoperative detection of HCC [43].

The added value of hepatobiliary phase images in the evaluation of HCC is unclear. Although sensitivity of the dynamic study increases with the addition of hepatobiliary phase images, it did not reach statistical significance [44]. Nevertheless, there are some data indicating the usefulness of gadoxetic acid in the differentiating of small HCC from hypervascular pseudolesions in patients with chronic liver disease [45, 46].

Once the diagnosis of HCC is established, the next crucial step is to define the staging of the disease to be able to offer the optimal treatment to every particular case. In HCC patients the prognosis assessment is a complex issue because it is related not only to the tumoral extension demonstrated in the imaging techniques, but also to the underlying liver function and performance status. Thus, the therapeutic approach should be faced based on tumoral extension and also on clinical aspects.

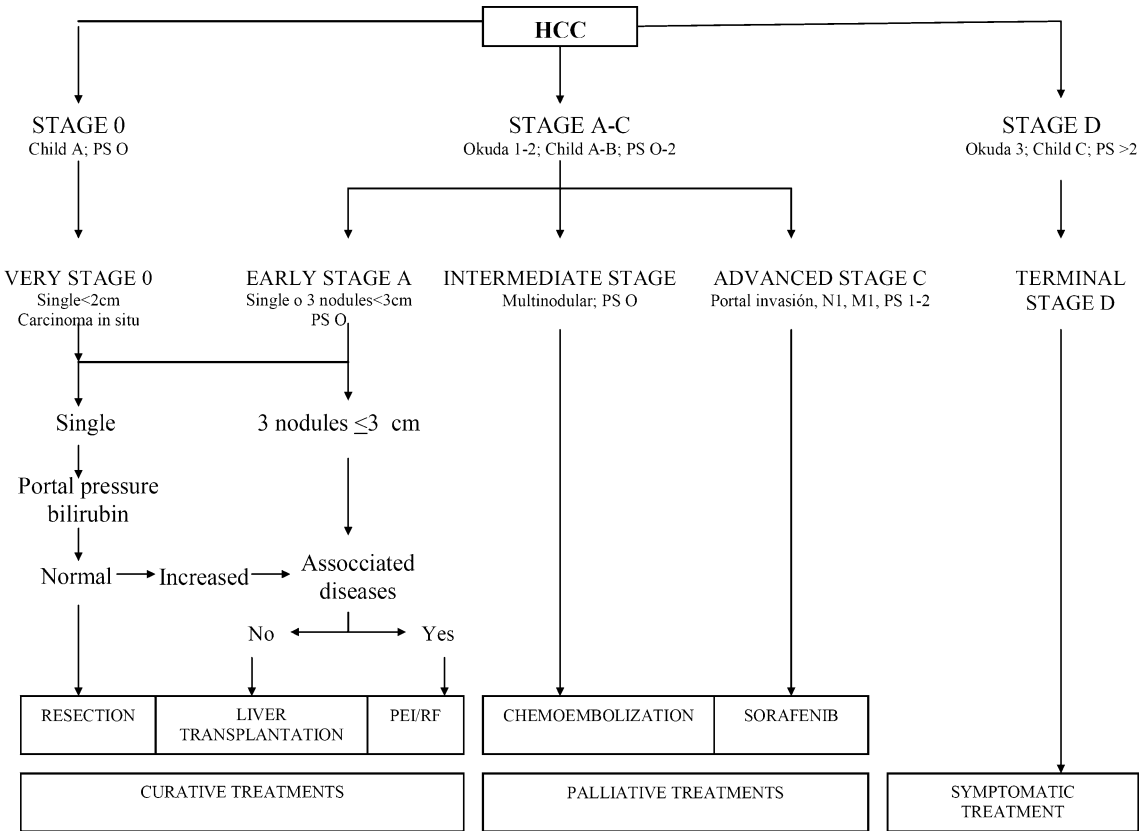


Fig. 11. The BCLC staging system and treatment allocation (From the AASLD Guidelines for the management of HCC, http://www.aasld.org/practiceguidelines).

Up to now, the only proposal to link staging with prognostic prediction and treatment indications is the BCLC approach [47] (Fig. 11). Thus, the role of imaging techniques in the staging of HCC once the diagnosis of the tumor is reached has two aspects: first, to determine the size, number and location of the lesions, and to detect vascular invasion and distant metastases. And second, to assess the presence of portal hypertension and its associated clinical manifestations (for instance, ascites). Typically, CT and MRI are the techniques used for staging purposes. Burrel et al. [10] correlated the MRI findings and the liver explant in 29 HCC patients treated with liver transplant to establish whether MRI is superior to helical CT scan for HCC staging. CT and MRI detected all nodules above 20 mm in size and both were inefficient to detect nodules less than 10 mm, but MRI detected a high proportion of nodules between 10 and 20 mm (sensitivity of 84%), significantly better than triphasic helical CT (sensitivity of 47%). CT of the thorax is also routinely indicated and other procedures such as bone scan are appropriate in selected cases.

Evaluation of response to treatment

The accurate evaluation of response to treatment is a key aspect in cancer therapy, because objective response in HCC after treatment may become a surrogate marker of improved survival.

Although surgical treatment in patients with HCC is the standard for curative care, most are not candidates for resection. Consequently, most patients with HCC in the early and intermediate stages undergo loco-regional therapies, including percutaneous ablation, mainly percutaneous ethanol injection (PEI) and radiofrequency (RF) and embolization procedures (trans-arterial chemoembolization—TACE—and trans-arterial radioembolization).

The evaluation of surgery is not subject to controversy. Due to the risk of recurrence, especially during the first 2 years after surgery (up to 65%) mainly due to dissemination rather than metachronous tumor [48], follow up of these patients is strongly recommended. However, there is no specific recommendation concerning the best imaging modality nor the best interval time for this purpose.

Conversely, assessment of tumor response after loco-regional treatment is important in determining treatment efficacy and in guiding future strategies. For that reason, is important to have uniform, reliable and reproducible criteria for it assessment.

More recently, sorafenib, an antiangiogenic–antiproliferative systemic drug, has demonstrated an increase of

survival and a delay in time to progression in patients with advanced HCC. However, criteria for its response assessment, as well as other new molecular targeted drugs that are currently used in clinical trials, have not been still well established.

Imaging criteria in the assessment of treatment response

The World Health Organization (WHO) published the first criteria to evaluate the response to treatment [49]. However, in the subsequent years, several interpretation problems appeared, mainly related to the number of target lesions that could be included to assess the response. Additionally, confusion was also generated about the use of three-dimensional measurements after the introduction of CT and MRI, resulting in important discordances among research groups. As a result the WHO criteria were no longer recommended.

With the aim of unifying criteria of response assessment, the National Cancer Institute published the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines in 2000 [50]. RECIST criteria included important changes such as unidimensional tumor measurement, specification of minimum size to select target lesions, and definition of the objective response.

RECIST criteria are based on the measurement of the greatest dimension of all target lesions, and response is categorized as a complete response (CR) (the disappearance of all target lesions), a partial response (PR) (a decrease superior to 30% in the sum of the greatest dimension of target lesions), progressive disease (PD) (an increase of more than 20% in the sum of the greatest dimension of target lesions and/or the appearance of new lesions and/or unequivocal progression of existing non-target lesions), and stable disease (SD) (not enough shrinkage nor sufficient increase to qualify as a PR or as PD, respectively).

Despite the improvement of RECIST compared with WHO criteria, it has been demonstrated that their applicability in the setting of HCC is less than optimal [51], because in patients with HCC, the aim of all effective loco-regional therapies, including ablation and trans-arterial embolization, is not tumor shrinkage of the lesion but the necrosis of the tumor.

RECIST criteria are based on the measurement of tumor burden by unidimensional determination of the major diameter of the tumor, disregarding tumor necrosis due to treatment, which is the objective of all effective loco-regional therapies widely used for HCC.

Therefore, in 2000, a panel of experts on HCC of the EASL agreed that estimating the reduction in viable tumor volume, recognized as non-enhanced areas using dynamic imaging techniques should be considered the optimal method for assessing local response to treatment in patients with HCC [26]. Hence, most authors reporting results of locoregional therapy for HCC evaluate tumor response according to this recommendation. Residual disease is defined as persistence of enhancing areas inside the treated lesions seen at first study after locoregional treatment, while post-treatment recurrence is defined as the identification of a new focus of tumoral enhancement after the initial achievement of CR by imaging techniques [52].

Recently, a modified RECIST (mRECIST) for HCC had been proposed [53] (Table 1). In mRECIST for HCC, similar to conventional RECIST, overall patient response is a result of the combined assessment of target lesions, non-target lesions, and new lesions. The mRECIST for HCC has introduced modifications to RECIST in the assessment of tumor response for target lesions, as follows: CR is considered when the disappearance of any intratumoral arterial enhancement in all target lesions is observed; PR: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions; PD: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the start of treatment; and SD: any cases that do not qualify for either PR or PD. All assessments should be performed in the arterial phase for an optimal evaluation. The disappearance of intratu-

Table 1. Assessment of target lesion response: conventional RECIST and mRECIST assessment for HCC

	RECIST	mRECIST for HCC
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Progressive disease	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease

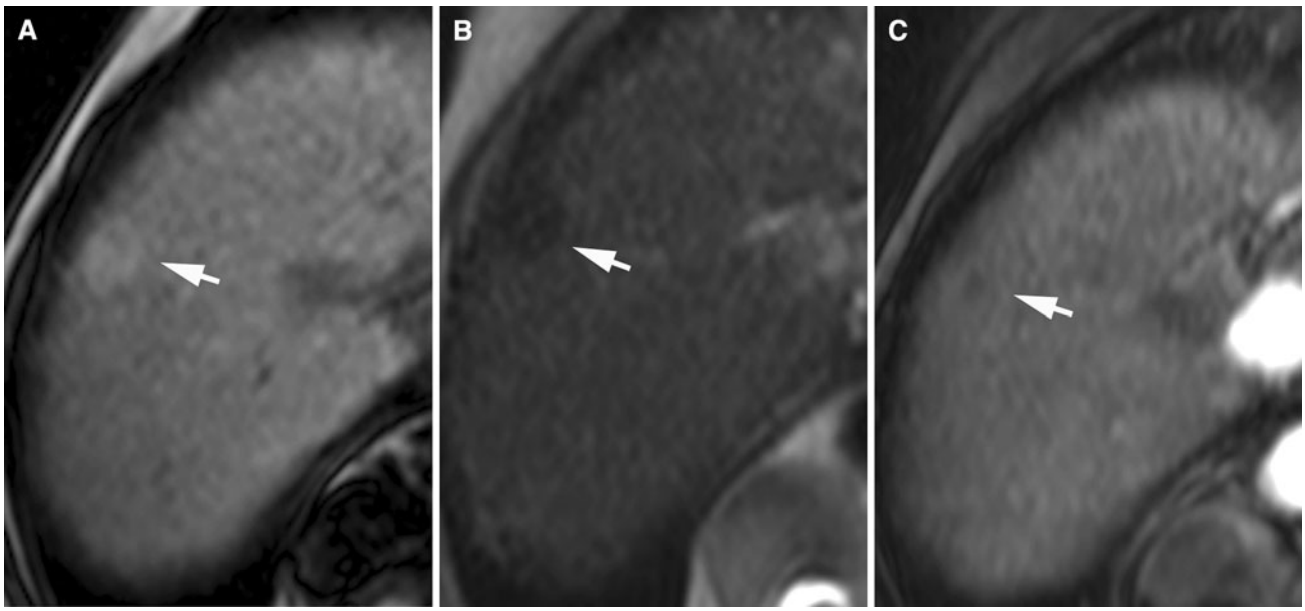


Fig. 12. MRI of a cirrhotic liver with an HCC after successful ablation with ethanol injection. **A** Lesion shows hypersignal on T1 (*arrow*) secondary to coagulative necrosis, sequences and **B** hyposignal on T2 sequences probably due to process of dehydration *(arrow)*. **C** After extracellular contrast administration, the lesion does not display areas of enhancement, which is indicative of complete response after treatment (*arrow*).

moral arterial enhancement in non-target lesions should be considered equivalent to the disappearance of non-target lesions. Finally, detection of a new hepatic nodule will be classified as HCC if it has at least 1 cm in diameter and displays typical vascular profile for HCC on dynamic CT or MRI. In addition, atypical lesions larger than 1 cm can be considered as new HCC lesions by evidence of at least 1 cm interval growth in subsequent scans.

Imaging evaluation after tissue ablation

Percutaneous HCC ablation may be performed by different techniques, either chemical ablation (ethanol or acetic acid injection) or thermal ablation (tumor heating with radiofrequency electrodes, laser fibers or microwave antennas; or tumor freezing with chryotherapy), being the RF ablation the most widely accepted and the most effective method for HCC ablation [54, 55]. Coagulative necrosis is achieved when temperature exceeds 50°C [56]. Lesion size and tumor location are influencing factors for treatment response. Complete necrosis of HCC may be achieved in lesions up to 5 cm in size in one or multiple treatment sessions, obtaining the best rates of treatment response in lesions smaller than 3 cm [57].

The objective of monitoring tumor response after ablation by imaging is the early detection of remaining residual disease as well as early tumoral recurrence. Both dynamic CT scan and dynamic MRI have demonstrated high accuracy in this setting. Lesions successfully treated

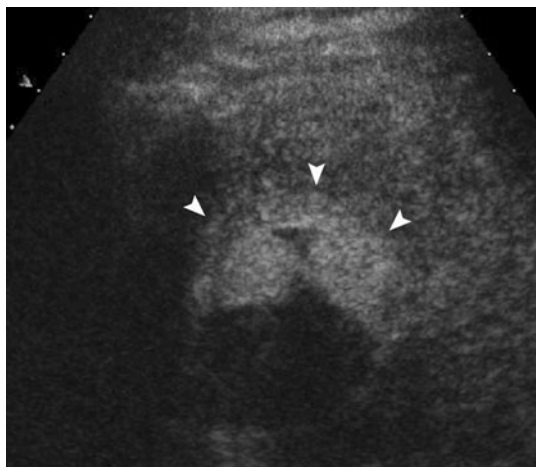


Fig. 13. Hepatic HCC treated with ablation. Contrast-enhanced ultrasonography at the arterial phase obtained after treatment. Residual tumoral area shows evident uptake of intravenous contrast (*arrowheads*) while the necrotic area do not enhances.

usually appear hypointense on T2-weighted MRI sequences probably due to a dehydration process secondary to ablation. On T1W sequences, treated HCC may have heterogeneous hyperintense signal due to coagulative necrosis (Fig. 12). On CT, the zone of ablation is often hypodense, although areas of hyperattenuation may be seen due to protein coagulation. The ablation area may remain stable in size or may show an involution, and in some cases vanish completely.

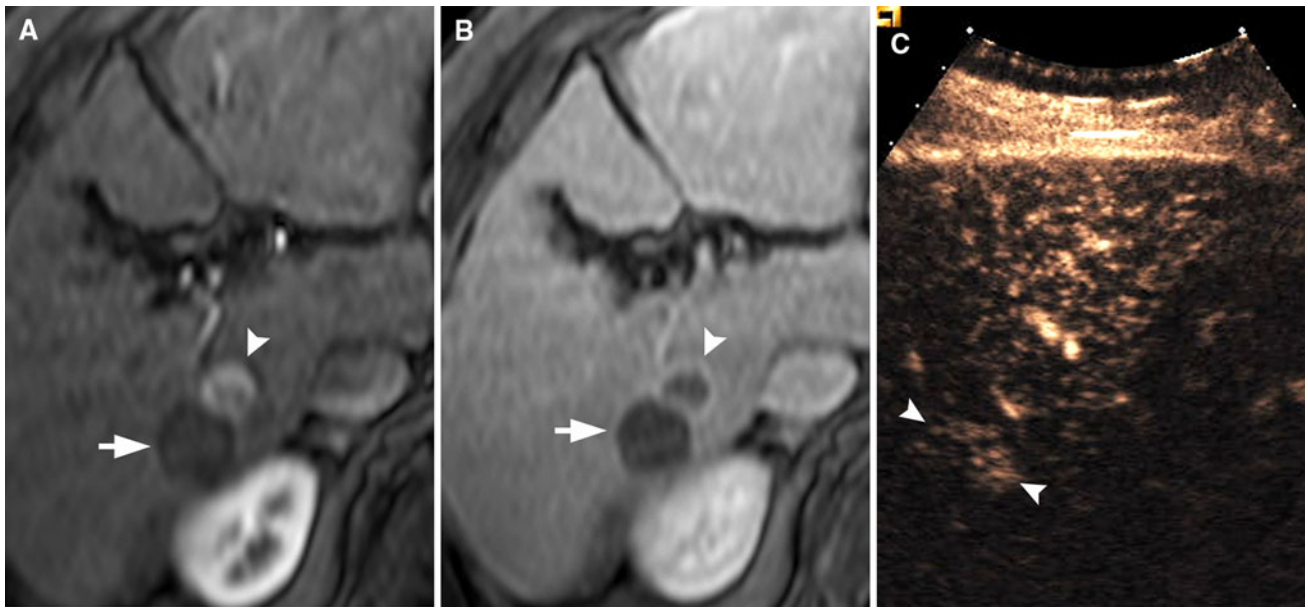


Fig. 14. Recurrence of HCC with nodular pattern. Enhanced images on MRI on arterial (**A**) and delayed phases (**B**) show a necrotic lesion in the right hepatic lobe (*arrow*) and nodular arterial enhancement in the periphery of the lesion with an evident washout in delayed phase (*arrowheads*) corresponding to the recurrent tumor. **C** The same lesion seen at contrast-enhanced ultrasonography also shows a nodular enhancement in the arterial phase (*arrowheads*).

The hallmark of treatment success is the loss of enhancing areas inside the tumor by CT or MRI. In expert hands, CEUS has also demonstrated a high diagnostic accuracy in the assessment of percutaneous ablation treatment response [58] (Fig. 13).

There are two main patterns of enhancement suggestive of residual or recurrent tumor: (1) the nodular-pattern, which appears as a nodular area of enhancement along the periphery of the ablated lesion (Fig. 14); and (2) the halo-pattern, that appears as an irregular and thick enhancing area around the ablative zone (Fig. 15). Since the persistence of viable tumor or recurrence is usually located along the periphery of the ablation zone, the margins of the treated lesions should be carefully examined on subsequent CT or MRI. A thin, less than 5 mm peripheral rim enhancement may be seen during the follow-up studies on CT, MRI or CEUS. It is likely due to inflammatory changes and hyperemia and can persist several months after treatment [59]. Arterio-venous shunts caused by needle introduction or thermal damage may result in peripheral wedge-shaped enhancing areas seen during the arterial phase of dynamic studies. These perfusion abnormalities are expected to disappear after the initial follow-up studies. Areas of hepatic capsule retraction and/or peripheral bile duct dilatation can also be seen after treatment.

There is no uniform consensus on the most appropriate follow-up schedule. Many groups perform the first imaging study at 1 month and then subsequent serial imaging studies every 3–6 months to detect possible recurrences [60].

Imaging evaluation after TACE

The TACE combines the delivering of high concentrations of chemotherapeutic agents directly in the tumor bed followed by embolization of feeding tumoral arteries. The most widely employed chemotherapeutic agents are cisplatin or adriamicin. Both classically are emulsified in lipiodol, an iodinated oil-based medium that is retained in hepatic tumoral cells. In recent years, with the aim of optimizing the discharge of cytostatic drugs in the tumor, embolization particles able to load the cytostatic drug have been developed. These microparticles, known as drug-eluting beads (DEB), are able to deliver higher doses of chemotherapy selectively inside the tumor in comparison to classical arterial embolization [61].

Changes on MRI T1W and T2W sequences after effective TACE are similar to those seen after ablation. The absence of intravenous contrast uptake after TACE is indicative of the presence of areas of intratumoral necrosis, while intratumoral contrast uptake should be considered as viable tumor [62] (Fig. 16). It is important to highlight that after lipiodol-based TACE, multiple areas of lipiodol of different size may be seen retained in the tumoral area. This fact represents a limitation for effective tumor assessment by CT due to the high density of lipiodol (about 500 HU) that can mask arterial enhancement at CT. In consequence, CT may overesti-

Fig. 15. Recurrence of HCC with halo pattern in the posterior segment of the right hepatic lobe previously treated with ablation. The CT scan at the arterial phase after intravenous contrast administration shows a peripheral halo-shaped enhancement (*arrowhead*) indicating the presence of residual viable tumor.

mate the extent of necrosis area when lipiodol is employed. MRI may overcome this limitation, as no relevant artifacts generated by lipiodol have been reported. Thus, MRI is preferred to CT as follow-up examination after lipiodol-based TACE. With the introduction of DEB, CT, and MRI have similar accuracies for detection of viable tumor [63].

Imaging assessment of tumoral response after radioembolization

Arterial radioembolization with Yttrium-90 loaded microspheres enables selective delivery of high dose of internal radiation to the HCC, avoiding damage to the surrounding cirrhotic liver parenchyma.

Changes in tumor enhancement according to the previously mentioned EASL criteria assess the tumor response more accurately than WHO or RECIST criteria. In addition, it is important to check for the presence of areas of nodular enhancement in the periphery of the lesion, or the presence of a peripheral rim-enhancement

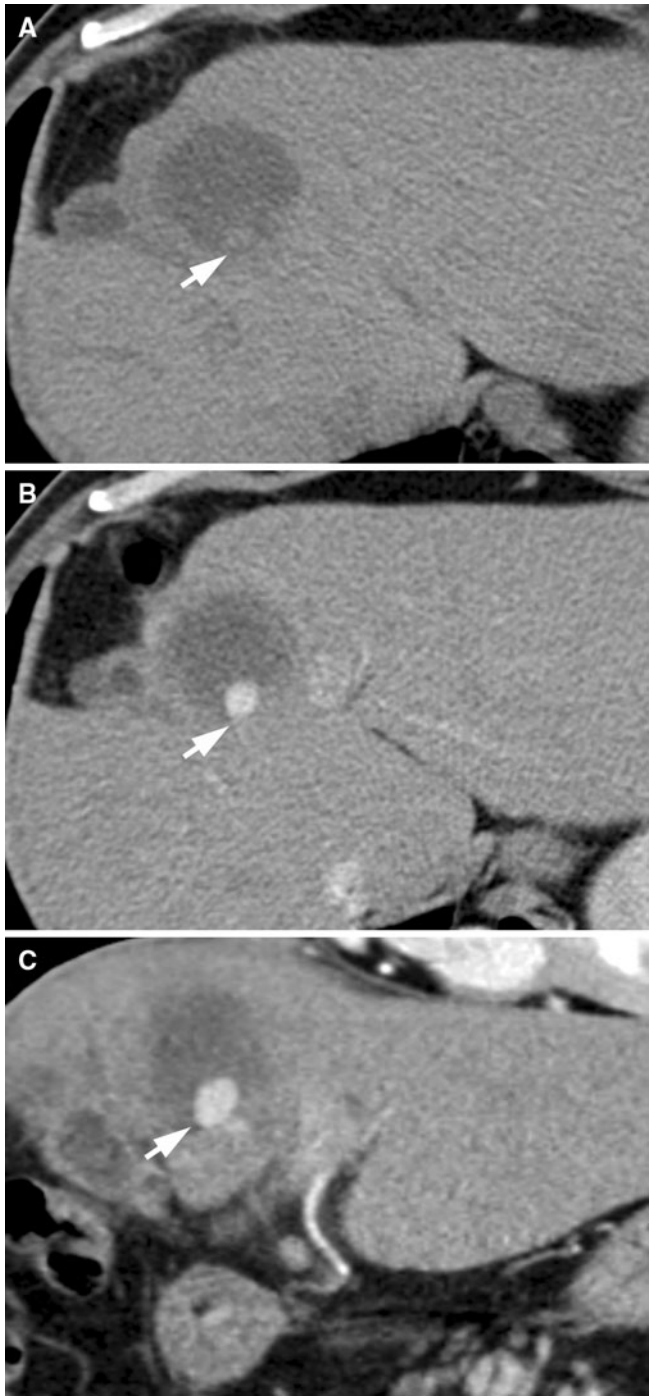


Fig. 16. HCC treated with TACE. **A** CT scan before and **B** after intravenous contrast administration on axial and **C** coronal planes show a residual solid area in the periphery that enhances suggesting residual tumor (*arrows*).

(less than 5 mm of thickness). The former is likely indicative of higher rate of recurrence, while the latter is likely indicative of CR. It is important to point out that the complete necrosis of an HCC after radioembolization may appear several months after the therapeutic procedure, and it is expected that intratumoral necrotic areas

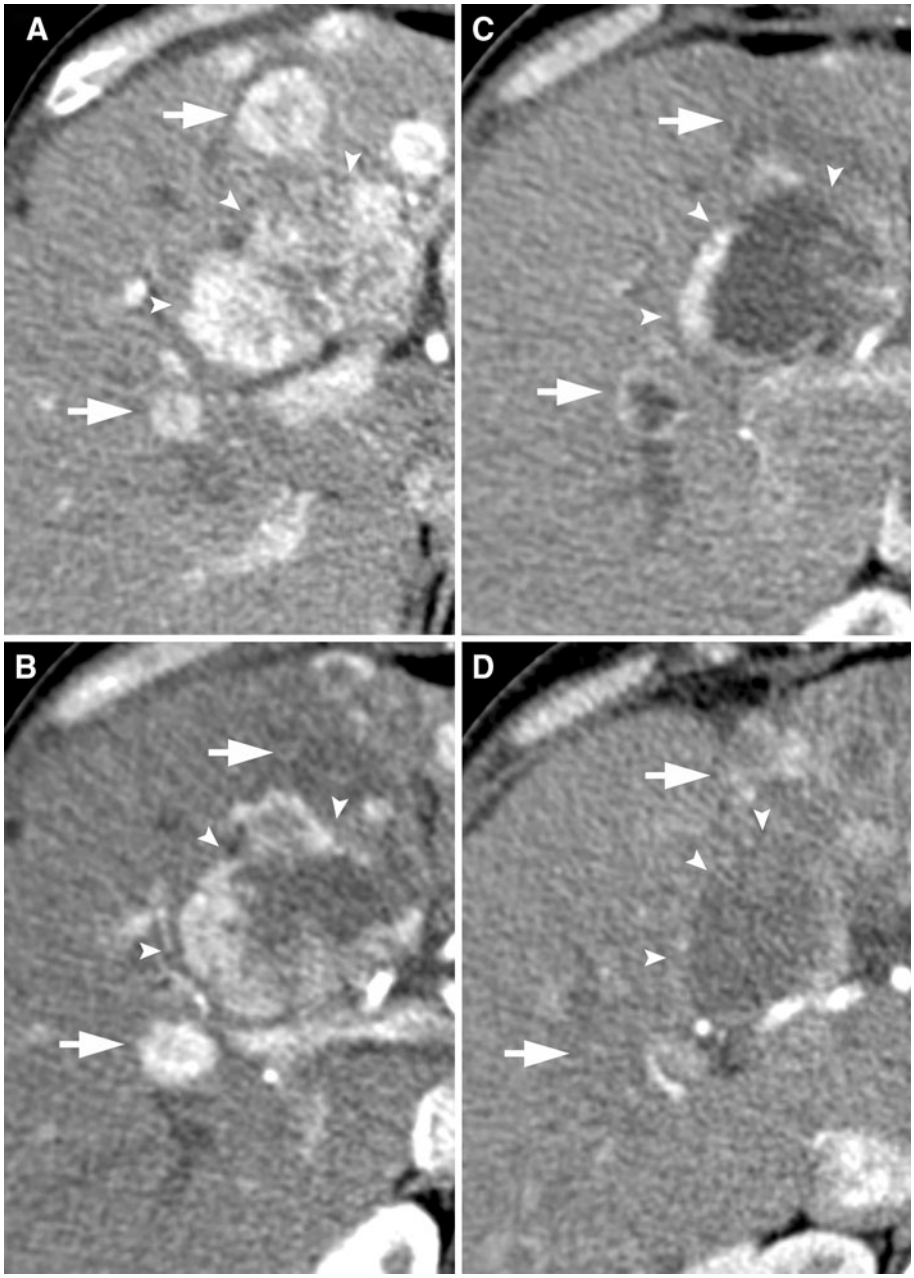


Fig. 17. Changes on CT scan after radioembolization with ^{90}Yttrium in a patient with multifocal HCC. **A** CT scan before treatment shows a large hyperenhancing mass at the arterial phase and peripheral smaller nodules located on right hepatic lobe can be seen. **B** Consecutive CT scan 8 weeks after treatment, **C** 16 weeks and **D** 24 weeks after treatment depict that main lesion (*arrowheads*) displays progressive areas of intratumoral necrosis and satellite lesions (*arrows*) turn also to hypovascular during the follow-up.

progressively increase in subsequent follow-up studies (Fig. 17) [64, 65].

Imaging assessment of tumoral response in advanced HCC undergoing new-agents

Sorafenib, an oral tyrosine kinase inhibitor blocking the Raf/MEK/ERK pathway and VEGFR 2 and PDGFR-beta with antiproliferative and antiangiogenic effects, has been demonstrated to improve the survival of patients with advanced HCC through a delay in tumor progression [66, 67]. The efficacy of treatment was detected by an increase of the time to progression rather than an objective response. For this reason, it is important to stress that the benefit of sorafenib has been obtained despite the lack of relevant tumor shrinkage, thus tumor response according to RECIST or WHO criteria were rarely found. Therefore, currently there are not reliable image criteria to assess the sorafenib efficacy.

Preliminary results derived from some active researches suggest a promising role of functional techniques, namely perfusion-CT/MRI or diffusion-MRI for detecting early response to sorafenib treatment or other new-molecular targeted therapies [68, 69]. On the other hand, the previously proposed mRECIST for HCC is expected to provide a reliable method for assessing tumor response in advanced HCC treated with new molecular targeted therapies. However, these new criteria

should be prospectively validated before being widely accepted.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Sangiovanni A, Prati GM, Fasani P, et al. (2006) The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. Hepatology 43:1303–1310
3. Llovet JM, Bruix J (2008) Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 48:S20–S37
4. Llovet JM, Burroughs A, Bruix J (2003) Hepatocellular carcinoma. Lancet 362:1907–1917
5. Llovet JM, Fuster J, Bruix J (1999) Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 30:1434–1440
6. Bruix J, Sherman M (2010) Management of hepatocellular carcinoma: an update. American Association for the Study of Liver Diseases. http://www.aasld.org/practiceguidelines. Retrieved 4 October 2010.
7. Sherman M (2001) Alphafetoprotein: an obituary. J Hepatol 34:603–605
8. Bolondi L (2003) Screening for hepatocellular carcinoma in cirrhosis. J Hepatol 39:1076–1084
9. Brenner DJ, Hall EJ (2007) Computed tomography—an increasing source of radiation exposure. N Engl J Med 357:2277–2284
10. Burrel M, Llovet JM, Ayuso C, et al. (2003) MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. Hepatology 38:1034–1042
11. Lencioni R, Cioni D, Pina C, Crocetti L, Bartolozzi C (2005) Hepatocellular carcinoma. Imaging diagnosis. Semin Liver Dis 25:162–170
12. Teefey SA, Hildeboldt CC, Dehdashti F, et al. (2003) Detection of primary hepatic malignancy in liver transplant candidates: prospective comparison of CT, MR imaging, US and PET. Radiology 226:533–542
13. Trevisani F, De NS, Rapaccini G, et al. (2002) Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 97:734–744
14. Kojiro M, Roskams T (2005) Early hepatocellular carcinoma and dysplastic nodules. Semin Liver Dis 25:133–142
15. Lee MW, Kim YJ, Park HS, et al. (2010) Targeted sonography for small hepatocellular carcinoma discovered by CT or MRI: factors affecting sonographic detection. AJR Am J Roentgenol 194: W396–W400
16. Terminology of nodular hepatocellular lesions. International Working Party. Hepatology 22:983–993 (1995)
17. Kojiro M, Wanless IR, Alves V, et al. (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 658–664
18. Hayashi M, Matsui O, Ueda K, et al. (1999) Correlation between the blood supply and grade of malignancy of hepatocellular nodules associated with liver cirrhosis: evaluation by CT during intraarterial injection of contrast medium. AJR Am J Roentgenol 172:969–976
19. Efremidis SC, Hytiroglou P (2002) The multistep process of hepatocarcinogenesis in cirrhosis with imaging correlation. Eur Radiol 12:753–764
20. Kudo M (2009) Multistep human hepatocarcinogenesis: correlation of imaging with pathology. J Gastroenterol 44:112–118
21. Roncalli M, Roz E, Coggi G, et al. (1999) The vascular profile of regenerative and dysplastic nodules of the cirrhotic liver: implications for diagnosis and classification. Hepatology 30:1174–1178
22. Kitao A, Zen Y, Matsui O, Gabata T, Nakamura Y (2009) Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography-radiologic-pathologic correlation. Radiology 252:605–614
23. Huppertz A, Haraida S, Kraus A, et al. (2005) Enhancement of focal liver lesions at gadoxetic acid-enhanced MR imaging: correlation with histopathologic findings and spiral CT—initial observations. Radiology 234:468–478
24. Frericks B, Loddenkemper CH, Huppertz A, et al. (2009) Qualitative and quantitative evaluation of hepatocellular carcinoma and cirrhotic liver enhancement using Gd-EOB-DTPA. AJR Am J Roentgenol 193:1053–1060
25. Kogita S, Imai Y, Okada M, et al. (2010) Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 20(10):2405–2413
26. Bruix J, Sherman M, Llovet JM, et al. (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421–430
27. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
28. Forner A, Vilana R, Ayuso C, et al. (2008) Diagnosis of hepatic nodules ≤20 mm in cirrhosis. Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma (HCC). Hepatology 47:97–104
29. Sangiovanni A, Manini MA, Iavarone M, et al. (2010) The diagnostic and economic impact of contrast imaging technique in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 59:570–571
30. Bhayana D, Kim TK, Jang HJ, Burns PN, Wilson SR (2010) Hypervascular liver masses on contrast-enhanced ultrasound: the importance of washout. AJR Am J Roentgenol 194:977–983
31. Chen LD, Xu HX, Xie XY, et al. (2010) Intrahepatic cholangiocarcinoma and hepatocellular carcinoma: differential diagnosis with contrast-enhanced ultrasound. Eur Radiol 20:743–753
32. Vilana R, Forner A, Bianchi L, et al. (2010) Intrahepatic peripheral cholangiocarcinoma in cirrhotic patients may display a vascular pattern similar to hepatocellular carcinoma on contrast enhanced ultrasound. Hepatology 51:2020–2029
33. Rimola J, Forner A, Reig M, et al. (2009) Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by MR avoids misdiagnosis of hepatocellular carcinoma. Hepatology 50:791–798
34. Bolondi L, Gaiani S, Celli N, et al. (2005) Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 42:27–34
35. Ishigami K, Yoshimitsu K, Nishihara Y, et al. (2009) Hepatocellular carcinoma with a pseudocapsule on gadolinium enhanced MR images: correlation with histopathologic findings. Radiology 50:435–443
36. Martín J, Sentís M, Zidan A, et al. (1995) Fatty metamorphosis of hepatocellular carcinoma: detection with chemical shift gradient-echo MR imaging. Radiology 195(1):125–130
37. Vandecaveye V, De Keyzer F, Verslype Ch, et al. (2009) Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. Eur Radiol 19:2456–2466
38. Kim YK, Kwak HS, Kim CS, et al. (2006) Hepatocellular carcinoma in patients with chronic liver disease: comparison of SPIO-enhanced MR imaging and 16-detector row CT. Radiology 238:531–541
39. Kim YK, Kim CS, Chung GH, et al. (2006) Comparison of gadobenate dimeglumine-enhanced dynamic MRI and 16-MDCT for the detection of hepatocellular carcinoma. AJR Am J Roentgenol 186:149–157
40. Kim SH, Kim SH, Lee J, et al. (2009) Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 192:1675–1681
41. Filippone A, Blakeborough A, Breuer J, et al. (2010) Enhancement of liver parenchyma after injection of hepatocyte-specific MRI contrast media: a comparison of gadoxetic acid and gadobenate dimeglumine. J Magn Reson Imaging 31:356–364
42. Tsuboyama T, Onishi H, Kim T, et al. (2010) Hepatocellular carcinoma: hepatocyte-selective enhancement at gadoxetic acid-enhanced MR imaging—correlation with expression of sinusoidal and canalicular transporters and bile accumulation. Radiology 255(3): 824–833
43. Lee JY, Kim SH, Jeon YH, et al. (2010) Ferucarbotran-enhanced magnetic resonance imaging versus gadoxetic acid-enhanced magnetic resonance imaging for the preoperative detection of hepato-

cellular carcinoma: initial experience. J Comput Assist Tomogr 34(1):127–134
44. Ahn SS, Kim MJ, Lim JS, et al. (2010) Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 255:459–466
45. Motosugi U, Ichikawa T, Sou H, et al. (2010) Distinguishing hypervascular pseudolesions of the liver from hypervascular hepatocellular carcinomas with gadoxeticacid-enhanced MR imaging. Radiology 256(1):151–158
46. Sun HY, Lee JM, Shin CH, Lee DH (2010) Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas (≤2 cm in diameter) from arterial enhancing pseudolesions. Special emphasis on hepatobiliary phase imaging. Invest Radiol 45:96–103
47. Bruix J, Llovet JM (2009) Major achievements in hepatocellular carcinoma. Lancet 373:614–616
48. Llovet JM, Schwartz M, Mazzaferro V (2005) Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 25(2):181–200
49. World Health Organization (1979) *WHO handbook for reporting results of cancer treatment*. Geneva (Albany, N.Y.: World Health Organization; sold by WHO Publications Centre USA)
50. Therasse P, Arbuck SG, Eisenhauer EA, et al. (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92(3):205–216
51. Forner A, Ayuso C, Varela M, et al. (2009) Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer 115(3):616–623
52. Goldberg SN, Grassi CJ, Cardella JF, et al. (2005) Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 235(3):728–739
53. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30(1):52–60
54. Cho YK, Kim JK, Kim WT, Chung JW (2010) Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology 51(4):1284–1290
55. Orlando A, Leandro G, Olivo M, Andriulli A, Cottone M (2009) Radiofrequency thermal ablation vs. percutaneous ethanol injection for small hepatocellular carcinoma in cirrhosis: meta-analysis of randomized controlled trials. Am J Gastroenterol 104(2):514–524
56. Dodd GD 3rd, Soulen MC, Kane RA, et al. (2000) Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics 20(1):9–27
57. Lu DS, Yu NC, Raman SS, et al. (2005) Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology 234(3):954–960
58. Vilana R, Bianchi L, Varela M, et al. (2006) Is microbubble-enhanced ultrasonography sufficient for assessment of response to percutaneous treatment in patients with early hepatocellular carcinoma? EurRadiol 16(11):2454–2462
59. Kim SK, Lim HK, Kim YH, et al. (2003) Hepatocellular carcinoma treated with radio-frequency ablation: spectrum of imaging findings. Radiographics 23(1):107–121
60. Sala M, Llovet JM, Vilana R, et al. (2004) Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 40(6):1352–1360
61. Hong K, Kobeiter H, Georgiades CS, Torbenson MS, Geschwind JF (2005) Effects of the type of embolization particles on carboplatin concentration in liver tumors after transcatheter arterial chemoembolization in a rabbit model of liver cancer. J Vasc Interv Radiol 16(12):1711–1717
62. Takayasu K, Arii S, Matsuo N, et al. (2000) Comparison of CT findings with resected specimens after chemoembolization with iodized oil for hepatocellular carcinoma. AJR Am J Roentgenol 175(3):699–704
63. Kloeckner R, Otto G, Biesterfeld S, et al. (2010) MDCT versus MRI assessment of tumor response after transarterialchemoembolization for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 33(3):532–540
64. Riaz A, Kulik L, Lewandowski RJ, et al. (2009) Radiologic-pathologic correlation of hepatocellular carcinoma treated with internal radiation using yttrium-90 microspheres. Hepatology 49(4):1185–1193
65. Salem R, Thurston KG (2006) Radioembolization with 90yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 2: special topics. J Vasc Interv Radiol 17(9):1425–1439
66. Llovet JM, Ricci S, Mazzaferro V, et al. (2008) Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359(4):378–390
67. Cheng AL, Kang YK, Chen Z, et al. (2009) 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 10(1):25–34
68. Sahani DV, Holalkere NS, Mueller PR, Zhu AX (2007) Advanced hepatocellular carcinoma: CT perfusion of liver and tumor tissue–initial experience. Radiology 243(3):736–743
69. Schraml C, Schwenzer NF, Martirosian P, et al. (2009) Diffusion-weighted MRI of advanced hepatocellular carcinoma during sorafenib treatment: initial results. AJR Am J Roentgenol 193(4):W301–W307