Management of small hepatocellular carcinoma

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Abstract

In the last years the incidence of hepatocellular carcinoma (HCC) is rising in cirrhotic patients worldwide. Due the importance of early and definite diagnosis of HCC, any nodular lesion detected in patients with chronic liver disease should be considered as suspicious for HCC.

The screening and surveillance programs in patients with liver diseases have increased the number of small HCC detected at an early stage, when the therapeutic options available are able to provide benefit. The introduction of new imaging techniques has improved the accuracy of characterizing these nodules. According to the EASL recommendations, contrast-enhanced computed tomography (CT), contrast enhanced ultrasound (US) and magnetic resonance (MR) with different MR-contrast agents are currently used to characterize liver lesions. Imaging guided biopsy is recommended for small nodules or in lesions without typical features (arterial hypervascularization) in at least two imaging techniques. Frequently the differential diagnosis of small nodules is complicated by discordant vascularity and recent studies have also demonstrated the presence of small hypovascular HCC at perfusional US and helical CT. At present, different treatment options can be offered to patients with diagnosis of small HCC at an early stage ; percutaneous techniques, surgical resection and liver transplantation can provide benefit in properly selected patients.

This review describes some critical points regarding the detection, diagnosis and therapeutic management of small nodules of HCC in cirrhotic patients. (Acta gastroenterol. belg., **2006**, 69, **230-235**).

Introduction

The diagnosis of small nodules in cirrhotic liver has become a real challenge for clinicians. In fact, the early characterization of lesions in cirrhotic patients and the correct staging of hepatocellular carcinoma (HCC) are critical prerequisites for assessing correct treatment and achieving optimal outcomes. The crucial point is that the detection of small nodules in a cirrhotic liver does not always correspond to the diagnosis of HCC. The differential diagnosis is complicated by the variable appearance of small liver nodules at imaging techniques and by the coexistence of lesions with different histologic characteristics in the same liver (regenerative, dysplastic and malignant nodules). A recent study has provided some evidence that preneoplastic lesions with uncertain malignant potential can be found in up to 42% of cases in explanted liver, particularly in smaller nodules (11 ± 7 mm vs 29 ± 14) (1). It is also demonstrated that a number of these hepatic lesions may contain a focus of few neoplastic cells (2-4), that will probably evolve into HCC over a few years (5-7).

The introduction of screening and surveillance programs in cirrhotic patients and the improvement of imaging techniques have increased the number of small HCC detected in patients with liver diseases (8). If nodules of HCC are detected and characterized at an early stage, different curative treatments can be offered to patients, including percutaneous destruction, surgical resection and liver transplantation.

Diagnosis of small hepatocellular carcinoma

At present, the distinctive feature of HCC in cirrhosis is considered the detection of arterial hypervascularization at contrast-enhanced imaging techniques, because nonneoplastic lesions still have a prevalent portal vascularization (9-10). According to the EASL document (11) for the clinical management of HCC, nodules larger than 2 cm detected in liver cirrhosis can be considered HCC when a coincident finding of arterial hypervascularization is confirmed by at least two techniques (out of US, CT, MR and angiography) or by the association of one imaging technique showing arterial hypervascularization and a alpha-foetoprotein (AFP) level > 400 ng/mL. In nodules with diameter between 1 and 2 cm, biopsy is strongly recommended because imaging techniques often fail in demonstrating arterial hypervascularization and AFP has a low sensitivity in these cases. Detection of lesions of less than 1 cm in size should raise the suspicion of HCC. In these cases, the recommendation is a strict monitoring of the nodule by repeating US every 3 months, because in these small nodules contrast enhanced imaging techniques are rarely able to give a definite diagnosis. In case the lesion grows over 1 cm, biopsy is indicated, together with the repetition of other imaging techniques.

Different noninvasive imaging techniques, as multislice helical computed tomography (CT), contrast-enhanced harmonic ultrasound (US) and magnetic resonance (MR) with new contrast agents, have facilitated the detection and the characterization of hepatic lesions.

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Ultrasonography

Ultrasonography has been for long time one of the most important imaging techniques used for the detection and characterization of liver lesions. The introduction of Doppler ultrasonography and of ultrasonographic contrast agents has strongly improved the potential of this technique in the characterization of nodules in cirrhotic liver, based on the assessment of their vascular pattern. More recently, several studies have emphasized the potential role of contrast-enhanced harmonic US (12-14), because the introduction of contrast agents offers an accurate visualization of perfusional patterns of hepatic lesions in all the vascular phases. The use of second generation contrast agents together with specific low energy US technology offers the advantage of limiting bubble destruction, thus allowing continuous real-time US imaging of the liver during contrast vascular perfusion ("perfusional angiosonography") (15-18).

Contrast-enhanced perfusional angiosonography is superior to conventional Color and Power Doppler in displaying pathological vascularization of nodules and shows a good diagnostic agreement with spiral CT (19). In comparison to spiral CT, perfusional ultrasonography offers the advantage of being simpler ; this technique may be proposed for an immediate characterization of nodules detected at US. At present, the perfusional US limitation is that it cannot display the whole liver during the same examination and that it cannot depict deeply-seated lesions. Nowadays perfusional angiosonography could be considered as second imaging technique to confirm arterial hypervascularity also in small HCCs ; in fact, this new method is highly sensitive both in large and small liver nodules (97.3% in HCCs > 3 cm, 90% in HCCs between 1 and 3 cm, and 66% in HCCs < 1 cm) (19). It has been recently emphasized that relative hypodensity in the portal phase following arterial hypervascolarization (washout) increases the specificity of the vascular findings at CT scan (20). Similarly, in agreement with other authors, in our series most HCCs were slightly hypoechoic in the late phases, but this pattern cannot be considered a specific diagnostic criterion in the absence of arterial hypervascularity. However, it is known that a subset of small well differentiated HCCs may be hypovascular (21) and will consequently result as non-typical for HCC, at imaging techniques.

Recent studies have confirmed that HCC with hypovascular pattern can be detected in cirrhotic liver and particularly in nodules of 1-2 cm (21-23). These small hypovascular nodules and hepatic lesions with equivocal vascular patterns (hypervascular at only one technique), without a pathological diagnosis of malignancy, represent a real clinical challenge.

Computed tomography

CT is considered one of the standard techniques for the detection and characterization of nodules in liver with cirrhosis ; several studies have been performed in order to calculate sensitivity and specificity of multiphasic helical CT in the diagnosis of HCC. The results of recent and older studies are often different and this reflect the technological advances of CT imaging methods, particularly with the advent of helical CT. The high acquisition speed allows the detection of the arterial phase of contrast imaging and has greatly improved the ability of CT to detect small lesions (24-26). However, the results of these studies are sometimes disappointing, because the gold standard for the diagnosis of HCC or other liver lesions is usually based on the findings at partial hepatic resection or at other imaging studies (with or without biopsy) and not always based on the pathological examination of explanted livers. Incidental HCCs that were missed on imaging techniques, especially small lesions (27), have been in fact frequently found in explanted livers.

The results of sensitivity and specificity of CT obtained in different studies are summarized in Table 1 ; they confirm that the ability of CT to detect and characterize large HCC have dramatically increased in the last years, but the identification and diagnosis of small hepatic nodules remains a critical problem.

The problem of differential diagnosis of small lesions is complicated by hypovascular nodules, pseudolesions and transient hepatic attenuation differences (THAD). These areas are attenuation differences of liver tissue appearing during contrast-enhanced dynamic CT, not always corresponding to liver lesions ; generally they are highly attenuated on the hepatic arterial phase and normally attenuated on the portal venous phase, reflecting a change in the dual blood supply of the liver adjacent to the lesions. THADs could be erroneously interpreted as benign or malignant hepatic lesions (hemangioma, focal nodular hyperplasia, pyogenic abscess, focal eosinophilic necrosis, HCC, cholangiocarcinoma and hepatic metastasis). The correct identification of these areas is essential to avoid false-positive diagnosis and to not overestimate the extent of the disease (28).

Magnetic resonance

The role of MR in the detection and characterization of liver lesions is increasing in the last years ; this technique provides good contrast resolution and possibility of multiplanar evaluation of the liver. The diagnostic sensitivity of this technique ranges from 33% to 77% (29) ; the main diagnostic problem of MR, as other imaging techniques, is the identification and diagnosis of small lesions. The use of newer MR-contrast agents and the continuous technological advances in MR have improved the diagnostic accuracy of MR in the detection of liver lesions in cirrhotic patients. In particular, studies performed in the last years have showed that MR, enhanced with superparamagnetic iron oxide (SPIO) or dynamic gadolinium based contrast materials, has

Table 1. — Sensitivity and specificity of CT in detection of HCC

Authors	Sensitivity				Specificity
	overall	HCC > 20mm	HCC 10-20 mm	HCC < 10 mm	total
Burrel *et al.* (2003)	61%	100%	65%	10%	66%
Yao *et al.* (2001)	–	87.6%[a]	27.6%[b]		–
Hanninen *et al.* (1998)	76%	86-100%	82%	20%	–
Gambarin-Gelwan *et al.* (2000)	53%	–	–	–	94%
Lim *et al.* (2000)	71%	–	–	–	–
Shapiro *et al.* (1996)	44%	–	–	–	–
Taourel *et al.* (1995)	53%	–	–	–	–
Miller *et al.* (1994)	68%	–	–	–	81%
Rizzi *et al.* (1994)	58%	–	–	–	–

a Main lesions ; b Satellite lesions.

Table 2. — Sensitivity and specificity of MR in detection of HCC

Authors	Sensitivity				Specificity
	overall	HCC > 20mm	HCC 10-20 mm	HCC < 10 mm	total
Burrel *et al.* (2003)	76%	100%	89%	34%	75%
Barthia *et al.* (2003)	78%	91%	92%	38%	–
Llovet *et al.* (2002)	100%	–	–	–	95%
Krinsky *et al.* (2001)	55%	–	–	–	–
Ward *et al.* (2000)	81%	–	–	–	–
Peterson *et al.* (2000)	84%	–	–	–	–
Gambarin-Gelwan *et al.* (2000)	91%	–	–	–	–
Tang *et al.* (1999)	94%	–	–	–	–

improved the detection and the characterization of HCC in comparison to unenhanced MR.

In Table 2 the results of sensitivity and specificity of MR in detection of liver lesions are summarized ; the reported values obtained by different groups showed an evolution in overall ability to detect HCC, specially in smaller nodules. However, histological correlation is available in only a minority of cases, thus limiting the assessment of sensitivity (30-32).

In 2001, Krinsky *et al.* (33) found an overall sensitivity of 55% in diagnosis of HCC (compared to pathologic finding in explanted livers), with many lesions smaller than 2 cm in diameter missed by MR imaging. In 2003, in the series of Bhartia *et al.* (34), the detection of lesions of 1 to 2 cm was significantly improved using double-contrast MR imaging ; this technique revealed 12 (92%) of 13 of lesions in this size range. This detection rate compares favorably to that of Krinsky *et al.* (33) who found only 6 (50%) of 12 HCCs measuring 1-2 cm using the single-contrast imaging technique. The sensitivity of double-contrast MR imaging in the detection of subcentimeter HCC remains however disappointing (38%). In the same year, Burrel *et al.* (1) showed that MR angiography (MRA) has a high diagnostic accuracy for HCC ≤ 10 mm and was more sensitive than triphasic helical CT in nodules sized 10 to 20 mm. MRA was significanlty better than CT in the detecion of HCC (76% vs 61%), particularly for additional nodules between 10 and 20 mm (84% vs 47%). The retrospective review of MR images demonstrated that unenhanced phase is insensitive and nonspecific in the detection of HCC. This conclusion supports the results of Earls (35), who supposed that the variable signal intensities made unenhanced MR images unreliable for the characterization of HCC because of an overlap between the appareance of malignant lesions and dysplastic nodules.

MR contrast agents may contribute to differential diagnosis between HCC and dysplastic nodules ; when SPIO or gadolinium contrast agent is used alone, some overlap could be found in their enhancement characteristics, but the combination of SPIO with gadolinium enhancement provides a more rigorous approach to lesion characterization (36).

AFP and other serum markers

AFP has been considered for many years as a serum marker for HCC ; studies performed by different groups have shown discordant results about sensitivity and specificity of this protein. The level of AFP could be

normal in patients with HCC and an increased level of AFP is not specific for the diagnosis of HCC, because high levels of this marker could also be found in other conditions as chronic hepatitis, acute liver failure or cirrhosis without HCC, characterized by hepatic necrosis and liver inflammation (37). In presence of a nodule with arterial hypervascularization in a cirrhotic liver, a value over 400 ng/mL has been considered diagnostic for HCC, according to the EASL document (11). At present, a part from this issue, the role of AFP is limited to the identification of patients at risk for HCC, when its level is between 20 and 400 ng/mL. Moreover, all cases with progressive increase of AFP may be considered suspicious of HCC (8). Determination of the AFP level, associated with ultrasound examination at six month intervals, is now recommended in screening programs of cirrhotic patients.

Several studies have been performed in order to identify newer markers or macromolecules as early indicators of HCC, in particular in small malignant lesions. Different groups are working to identify some genes or proteins expressed in the initial stages of hepatic carcinogenesis in human tissue or serum samples, in order to help imaging techniques in the early diagnosis of HCC. Lectin-reactive AFP, serum alpha-L-fucosidase activity, des-gamma-carboxy prothrombin, beta-catenin, Snail, E-cadherin, MMP, LYVE1 and survivin have been studied ; at present, the results obtained are not sufficient to introduce any single marker in clinical practice. The use of microarray and proteomic array technology provides an important tool for the discovery of new markers ; recently a catalytic fragment of vitronectin was identified as a new serum marker of HCC in patients with chronic liver diseases. The future development of a specific antibody against this serum protein should be important for the identification of new routine diagnostic test (38).

Therapeutic options for small hepatocellular carcinoma

At present, the available curative treatments for HCC may be summarized in three options : percutaneous techniques, surgical resection and liver transplantation. All these therapeutic treatments could improve the natural history of liver tumours and provide benefit in properly selected group of patients. In accordance with EASL recommendations, the treatment selection should consider different aspects : stage, aggressiveness and growth rate of HCC, liver function, general health of the patient and therapeutic options available in each specific center. As indicated in the Barcelona-Clinic Liver Cancer staging system (11), patients with single nodule of HCC at early stage, with compensed cirrhosis, could benefit from all curative treatments (resection, liver transplantation, percutaneous ethanol injection or radiofrequency). Each center must consider the available resources in order to select the best treatment between resection and liver transplantation in these patients ; in fact removing the liver disease together with HCC is the main advantage of liver transplantation, but the risk in these patients is tumour progression while on the waiting list. Nevertheless, the recurrence rate of HCC in patients treated with surgical resection is higher than in transplanted patients (50% at 3 years and 70% at 5 years) (39-42). Liver transplantation is considered the treatment of choice in decompensed cirrhotic patients with solitary HCC (< 5 cm) and with multinodular early malignant disease (3 nodules < 3 cm).

Percutaneous ethanol injection (PEI) is considered an alternative therapeutic option for patients with a single nodule of HCC < 3 cm in size. The ablation of neoplastic tissue with US-guided injection of ethanol is safe, relative simple and well tolerated by patients. The results of large series of cases (43-45) treated with PEI have demonstrated a complete tumor necrosis in 70-80% of HCC < 3 cm. The recurrence rate of neoplastic lesions after PEI is as frequent as surgical resection (> 50% at 3 years and > 70% at 5 years). The EASL conference recommended the use of PEI when surgical resection is precluded. In patients with decompensated liver diseases, however, liver transplantation has to be considered the treatment of choice.

Radiofrequency ablation appears to be a valid and safe procedure for treatments of small nodules of HCC ; the results of different groups showed a higher rate of complete necrosis with fewer treatment sessions compare to PEI. Livraghi obtained a total necrosis in 90% of HCC treated with RF versus 80% with PEI ; Lencioni, in 1999, presented similar results (91% vs 85%) (46-50).

According to these results RF represents now the standard technique for percutaneous ablation of HCC : PEI may still have a role for nodules < 2 cm or nodules in difficult location (perivascular, subcapsular).

These data showed that early diagnosis of malignancy and correct staging of HCC are the essential prerequisites for an effective and correct treatment of liver tumors. Surveillance and screening programs, even if imperfect, aim to improve the early diagnosis of HCC ; different potentially effective and curative treatments can be offered to cirrhotic patients with small HCC (51-52). Different outcome measures can be analyzed in order to assess the efficacy of screening in cirrhotic patients : the most important are the number and size of detected HCC, the eligibility for curative treatments (as defined by the EASL document (11)) and the reduction of disease-specific mortality related to the application of these treatments (53). According with other authors (Solmi (54), Yuen (55) and Trevisani (56)), we have demonstrated that surveillance programs significantly increased the eligibility for curative treatments in surveilled cirrhotics in comparison to outside surveillance programs (47.5% vs 31.7% $p < 0.01$) (8).

In conclusion, the critical point in the management of HCC, as other tumors, is the early diagnosis and correct staging of nodules, in order to increase the efficacy of

treatment. Future scenarios will be the improvement of targeted screening and prevention strategies for cirrhotic patients at higher risk, the introduction of treatment of borderline nodules with malignant potential and the efficient treatment allocation based on assessment of recurrence potential (OLT vs ablation/surgical resection).

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