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Diagnosis of hepatocellular carcinoma

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Abstract
Hepatocellular carcinoma (HCC) is responsible for a large proportion of cancer deaths worldwide. HCC is frequently diagnosed after the development of clinical deterioration at which time survival is measured in months. Long-term survival requires detection of small tumors, often present in asymptomatic individuals, which may be more amenable to invasive therapeutic options. Surveillance of high-risk individuals for HCC is commonly performed using the serum marker alfa-fetoprotein (AFP) often in combination with ultrasonography. Various other serologic markers are currently being tested to help improve surveillance accuracy. Diagnosis of HCC often requires more sophisticated imaging modalities such as CT scan and MRI, which have multiphasic contrast enhancement capabilities. Serum AFP used alone can be helpful if levels are markedly elevated, which occurs in fewer than half of cases at time of diagnosis. Confirmation by liver biopsy can be performed under circumstances when the diagnosis of HCC remains unclear.

Introduction

Each year 500 000 to 1 million individuals are diagnosed with hepatocellular carcinoma (HCC) worldwide [1]. Incidence rates demonstrate dramatic geographic variability, ranging from <5 new cases per 100 000 persons per year in developed western countries to >100 per 100 000 persons per year in parts of south-east Asia and sub-Saharan Africa [2]. Although the United States is among regions of low incidence, a 70% increase in HCC has been observed over the past two decades, apparently related to the emergence of chronic hepatitis C [3]. The life expectancy of patients with HCC is poor, with a mean survival of 6–20 months and likely reflects the mortality/incidence ratio, which is close to 1 [4,5]. These figures have remained steady despite substantial progress in the diagnostic and therapeutic arena of HCC.

Removal of HCC by surgical means offers the best chance for possible cure. Criteria for such intervention have been refined over the last decade to optimize long-term survival in selected patients. Unfortunately $<20\%$ of patients meet the criteria for resection at time of diagnosis [6]. The focus of much research revolves around diagnostic strategies to identify early HCC, defined by size of tumor and number of lesions. Diagnostic tools commonly used include the serum tumor marker alfa-fetoprotein (AFP), radiographic imaging, and liver biopsy. No universal guidelines for diagnosis exist, partly as a result of marked differences in the diagnostic approach between Eastern and Western institutions [7]; however, common themes do emerge which allow for important distinctions and conclusions to be made.

Surveillance for HCC

Identification of early HCC which is potentially amenable to aggressive intervention and improved survival is the rationale behind screening for HCC. An effective screening program, however, requires certain criteria to be successful, including the following: a common disease with substantial mortality, an identifiable target group, acceptable tests with high sensitivity and specificity, and available treatment [8].

Surveillance of individuals at risk for HCC has been a matter of controversy for decades. Geographic variations in target populations, screening tools, and therapy complicate assessment of international literature on the effectiveness of surveillance for HCC. Many studies are limited by lead time bias. To date no substantial evidence has accumulated which improves survival benefit with surveillance of high-risk patients. As a result no universally accepted guidelines are currently available. Several large studies on surveillance do suggest benefits, however, in identifying smaller tumors with subsequent improved survival [9–11]. Bolondi *et al.* demonstrated a median survival of 30 months in patients whose HCC was detected by surveillance versus 15 months in those discovered by chance [12]. Other studies have been less convincing

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[13]. Regardless, it has become common practice among hepatologists to apply one of several surveillance methods to their high-risk patients [14].

Surveillance intervals for HCC are based on a balance between the tumor doubling time and the cost of the screening tests. Doubling time of HCC ranges from 1 to 19 months with a median of 4–6 months [15]. Most study protocols conduct screening every 6 months. The overall cost of surveillance for HCC varies according to region, population incidence, and the screening tools used. The cost of finding each tumor in high-risk individuals ranges from $11 000 to $25 000 [16]. The cost per life saved is between $2600 and $112 996. This can be compared with screening colonoscopy for colon cancer where the cost per life year saved is $25 000 and is deemed acceptable [17].

Target population for surveillance

The key to successful surveillance of HCC is defining the high-risk patient. Older age, male gender, family history of HCC, and underlying cirrhosis are repeatedly demonstrated risks factors regardless of geographic region. Hepatitis B is the most common cause of HCC in regions of high incidence [18,19]. In Taiwan, 70–90% of HCC patients are hepatitis B virus surface antigen (HBsAg)-positive compared with <25% in the United States [20]. In the Far East, many individuals are carriers of HBV, presumably because of the frequency of vertical transmission. As a result HCC tends to develop approximately one to two decades earlier than in regions of low incidence, where transmission of HBV is primarily via sexual and parenteral routes [21]. Chronic hepatitis B carriers have a 5–15-fold increased risk for HCC compared with the general population, which rises with HB e antigen positivity and cirrhosis [22,23]. Prevention of hepatitis B with universal vaccination in children has been proven to significantly reduce the incidence of HCC [24].

HCV RNA is found in the large majority of HCC patients in Japan and Spain and is on the rise in the United States. In contrast to HBV, hepatitis C virus (HCV) does not integrate into the host genome, yet chronic disease does incur a risk of developing HCC up to 24 times that of the general population [25,26]. Genotype 1b has been linked to greater risk than other genotypes, although all genotypes have been implicated in HCC [27]. Cirrhosis invariably precedes the development of HCC. In the USA, once cirrhosis due to hepatitis C is established, 1–4% of patients will develop HCC annually [28]. HCC has been shown to develop earlier and more frequently with HBV co-infection or alcohol abuse [25,29].

Cirrhosis from any cause can pose an increased risk for HCC at various levels of magnitude. Hereditary hemochromatosis carries a risk of up to 200-fold compared with the general population [30]. Cirrhosis associated with viral hepatitis generally leads to HCC more readily than non-viral-induced cirrhosis [31–33]. Primary biliary cirrhosis, autoimmune hepatitis, and Wilson disease carry less risk [34,35]. Cirrhosis, however, is not a prerequisite for HCC. As many as 30% of chronic hepatitis B patients who develop HCC are non-cirrhotic. In one study from France, 25% of patients who underwent surgical resection of HCC had either minimal or no cirrhosis [36].

Screening tests

AFP is a serum glycoprotein that was first recognized as a marker for HCC more than 40 years ago and has since been described to detect preclinical HCC. The fetal yolk sac and fetal liver generate high levels of AFP, which decline to <10 ng/dl within 300 days of birth [37]. Serum elevations thereafter suggest underlying pathology which may be malignant. Any tumor arising from organs derived from the same endodermal lining as the hepatic diverticulum can be associated with elevations in serum AFP levels, including cancers of the stomach, pancreas, and biliary tree. Pregnancy and nonseminomatous germ-cell tumors must also be considered. Chronic hepatitis or cirrhosis raise AFP in 20% and 40% of patients, respectively, and tend to fluctuate in parallel with underlying inflammatory activity [38].

HCC can produce a range of AFP values from normal to >100 000 ng/ml [15]. Normal AFP levels are present in as many as 30% of patients at time of diagnosis and usually remain low, even with advanced HCC [39]. AFP >400–500 ng/ml is considered diagnostic for HCC, although fewer than half of patients may generate levels that high [39]. With values of that magnitude, the specificity of AFP is close to 100% but at a cost to the sensitivity which falls below 45% [40]. In a study using 20 ng/ml as the cut-off point, the sensitivity rose to 78.9%, although the specificity declined to 78.1% [41]. The positive predictive value (PPV) of AFP is low, ranging from 9% to 32% [42]. McMahon *et al.* demonstrated survival benefits in a large study using AFP alone for surveillance of HCC in chronic hepatitis B patients [9]. However, this is not considered common practice in light of the poor accuracy demonstrated in subsequent studies and in different populations [43].

Attempts to improve the accuracy of AFP have centered around the investigation of isoforms which may be specific for HCC. Human AFP is a 70-kd glycoprotein consisting of 591 amino acids and a terminal sugar side chain. Up to 11 AFP isoforms exist based on variations in the glycan terminal chain [44,45]. Microheterogenity of isoforms has been successfully identified using lectin electrophoretic techniques. Lectins are human or animal proteins that bind specifically to particular sugars. AFP specific for HCC has been shown to bind lectins lens culinaris agglutinin-A (AFP-L3), concanavalin A, and erythroagglutinating phytohemagglutinin (E-PHA) [46–48]. Taketa *et al.* found AFP-L3 to be positive in

about 35% of patients with HCC smaller than 2 cm, which may be present in serum up to 9 months before detection by imaging techniques [48]. More recently, isoelectric focusing has been investigated, which fractionates AFP into four variant bands, I–IV. AFP bands III and IV can be specific for HCC and help differentiate from AFP of cirrhosis or pregnancy [49]. One study showed a positive predictive value of 73.1% for identifying HCC using AFP band II compared with 41.5% using conventional AFP [50]. Although these techniques potentially demonstrate improved specificity for HCC, its routine use in clinical practice is restricted by high cost and assay complexity.

Des-gamma-carboxy prothombin (DCP), also called PIVKA II (protein induced by vitamin K absence), is a widely used tumor marker in Japan that was first described by Liebman *et al.* in 1984 as an abnormal form of prothombin highly specific for HCC [51]. No prospective studies have been done to follow a surveillance cohort. In western patients, specificity was described as high as 95% in one study; however, other studies have shown poor sensitivity in tumors <3 cm, which limits its clinical use [52–54]. Recent studies suggest that DCP values may be a prognostic indicator in patients with HCC [55].

Ultrasound (US) imaging is commonly applied in addition to, or in place of, AFP to help detect small hepatic tumors <3 cm. Its widespread use as a surveillance tool relates to its noninvasive nature, high availability, and low cost. In combination with AFP the PPV can be as high as 94% [43]. However, limitations exist with operator experience and when imaging obese or cirrhotic individuals. The sensitivity and positive predictive value can be as low as 35% and 15%, respectively, in some cases with cirrhosis [13,56,57]. HCC lesions typically are hypoechoic relative to surrounding tissue when under 3 cm. Larger lesions are generally hyperechoic with an infiltrative or mosaic pattern which may be surrounded by a thin hypoechoic fibrous capsule. Variation in sonographic appearance exists as a result of the presence of fat, calcium, and necrosis. CT imaging has not been well studied in the context of surveillance testing and is more commonly applied for further diagnostic purposes. A study on hepatitis C cirrhotics demonstrated CT scan imaging to have a higher sensitivity for detecting HCC than either US or AFP when used alone (88% vs 59% and 62%, respectively) [58]. Less availability and high cost limit the use of CT; however, up to 25% of hepatologists in the United States have been shown to use it on their high-risk patients in a recent survey [14]. Few data exist as regards magnetic resonance imaging (MRI) as a surveillance tool for HCC.

Diagnostic evaluation of HCC

Clinical presentation

HCC classically arises and grows in silent fashion, making its discovery challenging prior to the development of later stage disease. The various clinical presentations generally relate to the extent of hepatic reserve at time of diagnosis. Cirrhotic patients tend to have less tolerance for malignant infiltration within the liver and frequently present with nonspecific signs and symptoms of hepatic decompensation such as jaundice, hepatic encephalopathy, and anasarca. Ascites, variceal bleeding or other findings consistent with portal hypertension may indicate malignant invasion of HCC into portal structures. Abnormal laboratory values are nonspecific for chronic liver disease and may reflect effects of commonly prescribed medications for cirrhotics such as spironolactone. Noncirrhotic patients with HCC typically present in a different manner, as is commonly seen in sub-Saharan Africa and other high incidence areas. Their tumors are often allowed to grow with much less restriction. Symptoms are often related to long-standing malignancy and tumor growth including malaise, anorexia, wasting, right upper quadrant abdominal pain, and distension [4]. Physical examination may reveal an abdominal mass or hepatomegaly with hard and irregular borders that may demonstrate a vascular bruit [59]. Painless obstructive jaundice can indicate tumor encroachment onto adjacent extrahepatic biliary structures [60]. A rare catastrophic complication of HCC is tumor rupture which occurs when a large vascular tumor on the periphery of the liver outgrows its blood supply [61]. These patients present with sudden severe abdominal pain, peritoneal irritation, and hypotension. Peritoneal lavage or abdominal laparotomy can confirm the diagnosis. It is important to note that these findings and complications are not strictly confined to any patient scenario and considerable overlap does exist.

Extrahepatic manifestations of HCC are well described and may relate either to distant metastases or paraneoplastic phenomena. Advanced HCC can metastasize to any organ system via hematogenous or lymphatic routes, and most commonly spreads to bone, lung, and abdominal viscera [62]. Bone pain or other complications relating to metastasis may be the initial presenting sign of HCC. Paraneoplastic manifestations occur rarely in HCC and include hypoglycemia, hypocalcemia, polycythemia, and feminization syndrome [63]. Watery diarrhea has been shown to be significantly more common with cirrhosis and HCC than with cirrhosis alone and can be an initial presenting symptom. Increased production of intestinal secretory substances, such as gastrin and vasoactive intestinal peptide (VIP), has been suggested as a possible cause [64,65]. Various cutaneous features are well described in HCC including the Leser-Trelat sign, dermatomyositis, pemphigus foliaceus, and pityriasis rotunda, but are not necessarily specific for the disease [66]. Porphyria cutanea tarda (PCT) is frequently associated with chronic hepatitis C. Several studies have linked its presentation to a higher risk of developing HCC [67].

Routine surveillance of high-risk patients has made the discovery of asymptomatic HCC more common. These individuals whose tumors are identified prior to the development of hepatic decompensation or other complications described above, are more likely to be better candidates for aggressive interventions proven to prolong survival.

AFP in diagnosis of HCC

AFP has been shown to correlate with tumor size and volume at time of diagnosis. A study from Thailand found that HCC patients with AFP >400 ng/ml tend to have greater size, bilobar involvement, portal vein thrombosis, and decreased survival [68]. When left untreated, AFP-producing tumors continue to increase over time, coinciding with progression of disease. Poorly differentiated tumors with more aggressive features can be seen more often in patients with high levels of AFP. Prognosis has been shown to be reduced when AFP levels are >1000 ng/ml, but exceptions do exist [69]. Tumors with normal AFP levels at time of diagnosis tend to remain so throughout their course even with advanced disease. Inconsistencies in tumor AFP levels reflect variables associated with its synthesis in HCC and pose a challenge in making systematic assumptions on tumor characteristics based on AFP level alone.

Monitoring AFP levels can be helpful in the diagnosis of recurrent disease, although this is largely restricted to patients with AFP-producing tumors. Successful removal of tumor by surgical means is usually followed by an immediate fall in AFP levels to normal values, as the half-life is 3.4–5 days [38]. Persistently elevated levels may indicate residual disease or incomplete resection, yet exceptions have been noted. Similarly, normalized AFP levels do not exclude the possibility of remaining disease [70–72]. A gradual rise in AFP is frequently consistent with disease recurrence. AFP levels are also shown to mirror tumor responsiveness to nonsurgical therapies for HCC such as chemotherapy [73]. In one study, patients whose AFP remained low in response to chemotherapy had a survival advantage compared with those with either transient AFP fall or no response at all [74].

Diagnostic imaging

Imaging plays a key role in the diagnosis of HCC. Advances in imaging technology over the past two decades have contributed to better characterization of hepatic lesions with a wider array of options. Regardless, detection of small tumors continues to be difficult, particularly in cirrhotic individuals whose parenchymal architecture is abnormal. Differentiating HCC from benign lesions commonly seen in cirrhosis or from secondary malignancies remains a challenge.

Ultrasound

Ultrasound (US) imaging has largely been replaced in diagnosis by CT scan and MRI as a diagnostic instrument of choice as a result of low sensitivity and positive predictive value with coexisting cirrhosis. The recent addition of sonographic contrast agents such as intra-arterial carbon dioxide and helium shows promise in improving accuracy [75–77]. However, application of duplex and color Doppler sonography can be particularly useful in the assessment of intrahepatic vascular flow. HCC lesions typically display fine branching patterns of increased vascularity with greater flow velocity than metastatic lesions or hemangiomas [78,79]. Doppler evaluation of the portal vein can help differentiate bland thrombus from tumor invasion. Malignant portal invasion commonly produces wave forms demonstrating arterial flow. The power Doppler is thought to be three to five times more sensitive in depicting tumor vascularity than color Doppler by eliminating angle dependence [80–82].

CT scan

CT evaluation of patients with suspected HCC should be done using multiphasic contrast imaging of the liver. Following rapid intravenous infusion of contrast, imaging is conducted at various time intervals corresponding to the phase of contrast enhancement. Triphasic scanning denotes hepatic imaging performed before contrast, during arterial and venous phases. HCC tumors derive blood flow predominantly from the hepatic artery and tend to enhance during the arterial phase or 2–40 seconds after contrast infusion. The surrounding hepatic parenchyma obtains 75–80% of its blood flow through the portal vein and is best demonstrated 50–90 seconds after infusion of contrast during the portal phase. Arterial phase enhancement can increase HCC tumor detection by 10% [83,84]. HCC typically appears heterogeneous on CT, which may reflect intratumoral fibrous stranding (mosaic sign), fatty metamorphosis, necrosis, or calcifications [85,86]. The presence of satellite nodules in close proximity to the lesion is often characteristic. Fibrous structures within or encapsulating the lesion strongly retain contrast and enhance readily on delayed imaging (3–10 min after infusion) [87].

Brancatelli *et al.* describe hepatic lesions which can mimic HCC on CT imaging including regenerating nodules, hemangiomas, focal fat, dysplastic nodules, and peliosis [88]. The accuracy increases with greater imaging speed, which allows faster administration of contrast media, thereby dramatically improving contrast enhancement [89]. The added speed and flexibility of multidetector CT (MDCT) allows high quality, thin-section imaging with three-dimensional capabilities [90]. CT arteriography is a more invasive yet effective option to improve accuracy as a result of higher quantity of contrast administered at a faster rate. In a large population-based study, Oliver *et al.* reported

a 66% increase in detection of HCC foci compared with triphasic CT scanning [91]. However, the invasive and costly nature of this approach tends to restrict its use. CT arteriography and portography appear to be used more often in the Far East to define hepatic vasculature before surgical intervention.

MRI

MRI uses similar concepts to those applied to CT imaging when evaluating hepatic lesions suspicious for HCC. Recent advances in MR technology allow images to be obtained within the time frame of one breath hold. T1- and T2-weighted sequence images of HCC lesions vary considerably but typically appear hypointense and hyperintense, respectively. Focal hemorrhage, fatty change, or tumor accumulation of copper and glycogen contribute to this inconsistency. MRI sensitivity is lowest when evaluating tumors <2 cm in diameter [92]. Dynamic gadolinium contrast imaging enhances arterial blood supply during the early phase, which improves characterization of HCC tumors. The sensitivity and specificity are similar to those of multiphasic CT scan imaging. The addition of superparamagnetic iron oxide contrast has been investigated to improve accuracy, particularly with T2-weighted sequencing [89,93]. Superparamagnetic iron oxide comprises tissue-specific MRI contrast agent particles taken up by Kupffer cells in the liver. The combination of superparamagnetic iron oxide-enhanced and gadolinium chelate-enhanced dynamic MRI produces results comparable to those of CT hepatic arteriography [94]. MRI has become the diagnostic imaging mode of choice for HCC at many institutions worldwide.

Angiography

Angiography has been used as a diagnostic tool for HCC because of its highly vascular nature; however, the detection of tumors has been disappointing, particularly when <2 cm in diameter. At present angiography is more often used to define hepatic anatomy before resection or as guidance for transarterial chemoembolization therapy.

Evaluation for extrahepatic spread

Radiographic imaging for extrahepatic metastasis is routinely performed on patients with early disease in order to confirm proper staging prior to surgical intervention. No guidelines exist and protocols differ among centers and regions. At our institution, patients undergo CT scan of the chest, abdomen, and pelvis; nuclear bone scan; and positron emission tomography (PET). Patients who qualify for nonsurgical procedures (transarterial chemoembolization, radiofrequency ablation, chemotherapy) may benefit from further imaging which may potentially spare patients from unnecessary intervention. With more advanced stage HCC, full body imaging may not be necessary unless there is clinical suspicion of spread.

PET scan has limited use as a diagnostic tool for HCC. PET nuclear imaging relies on radiolabeled glucose (F-18 FDG), which incorporates into neoplastic cells demonstrating increased metabolic activity. Well or moderately differentiated HCC tumors that metastasize may not generate a high level of metabolism requirements compared to that of surrounding tissues. A recent study by Liangpunsakul *et al*. showed that PET did not reveal abnormal hepatic lesions which were identified on CT scan and later proven HCC on explant [95]. The high cost of PET also limits its frequent use.

Liver biopsy

Diagnostic evaluation of hepatic lesions with liver biopsy has been practiced for over half a century. When performed at specialized centers, liver biopsy offers a safe and effective means to confirm suspicious lesions for HCC. Cytologic and histologic samples can be obtained by percutaneous fine-needle aspiration (FNA) and needle core biopsy, respectively, under US or CT guidance. The diagnostic accuracy of liver biopsy is greater when both FNA and core biopsy techniques are used simultaneously than when either is used alone. The sensitivity and specificity are superior to any other diagnostic test, at 96% and 95%, respectively [96]. An on-site pathologist can provide immediate interpretations of cytologic cell blocks to assure proper placement of the biopsy needle. Open surgical biopsy procedures may sometimes be performed when suspected HCC lesions cannot be accurately located by radiographic methods.

Microscopic features of HCC include elevated nuclear to cytoplasmic ratio, trabecular architecture, atypical naked nuclei, and peripheral endothelial wrapping [97]. Histologic appearance ranges from nearly normal-appearing hepatocytes in well differentiated tumors to the largely anaplastic multinucleate giant cells characteristic of poorly differentiated HCC [98]. Distinguishing well differentiated HCC from benign hepatic masses such as adenoma or focal nodular hyperplasia may be difficult. The most recognizable premalignant histological finding is dysplasia.

Liver biopsy need not be performed under circumstances in which the diagnosis of HCC is certain after clinical, laboratory, and radiographic evaluation. Confirmation of HCC with liver biopsy plays a larger role in various other emerging scenarios. One such scenario is prior to orthotopic liver transplantation or hepatic resection. Routine surveillance programs are more frequently identifying tumors in younger asymptomatic patients with smaller lesions and better hepatic reserve. Many of these patients are eligible for surgical interventions which can significantly improve survival [99]. Without preoperative confirmation of HCC by liver biopsy several studies have shown that

the rate of false-positive diagnosis can be substantial in patients with small tumors [76,100,101]. In the United States, the number of HCC patients transplanted has increased substantially over the past decade, particularly with the implementation of the MELD transplant allocation system. Hayashi *et al*. recently demonstrated that the false-positive rate can be as high as 33% after histological examination of the explant [102]. This risk of subjecting patients with small hepatic lesions to unnecessary surgical intervention can be limited by performing liver biopsy. The accuracy of liver biopsy in diagnosing lesions <2 cm in diameter is 95.6% [103]. Complications associated with liver biopsy are rare and can be diminished by using a one stick approach, such as the coaxial technique. Mortality rates are between 0.006% and 0.3%, with risk of serious hemorrhage or infection <1% [104]. Liver biopsy should be avoided when platelet counts are $<50\,000$ per mm^3 or the international normalizing ratio (INR) is >2.

The potential for spread of tumor from the biopsy needle track is of great concern and fuels much of the controversy surrounding the need for liver biopsy. Although several studies show rates as high as 5%, the majority of large studies indicate that the risk is closer to 1% [105–108]. At our institution, not one case has been identified after a recent review of all liver biopsies done over a 5-year period. Furthermore, follow-up studies of cases in which needle tract metastasis were excised indicate that the long-term survival of transplant or resected patients was not affected [106,109,110].

Another common scenario in which the liver biopsy can be useful is in the patient whose suspicious lesion does not necessarily meet the characteristic radiographic or laboratory features of HCC. For example, the patient with an AFP <400 ng/ml with a lesion which fully demonstrates arterial enhancement on multiphasic CT imaging. AFP <400 ng/ml can be present in as many as 60% of patients at presentation, while HCC tumor with fatty change or necrosis can impede characteristic radiographic arterial enhancement. Many patients fit this "gray zone" and confirmation of the diagnosis is important, especially as some will go on to have interventions such as radiofrequency ablation, transarterial chemoembolization, or chemotherapy.

Summary

The diagnosis of HCC poses many challenges which can vary among different regions and centers. AFP and US imaging are most often used every 6 months for surveillance purposes in high-risk individuals. In the presence of a rising AFP or suspicion of underlying malignancy, surveillance intervals should be shortened and more sensitive imaging techniques such as multiphasic CT scan or MRI can be applied. The intensity of diagnostic work-up should be individualized and tailored according to each patient's potential to tolerate aggressive therapeutic interventions. Liver biopsy can confirm diagnosis when necessary or rule out other lesions that may mimic HCC. Several diagnostic strategies have been proposed, many of which are center- and region-specific. The European Association for the Study of the Liver (EASL), for example, has listed standard criteria for diagnosis of HCC that incorporate both invasive and noninvasive measures [111]. Noninvasive criteria include two imaging techniques, both demonstrating a focal lesion >2 cm in diameter with features of arterial hypervascularization, or a single radiologic study with these features combined with a serum AFP level of >400 ng/ml. Use of this and other criteria can be very helpful, but the lack of evidence-based studies should preclude their strict use in diagnosis of HCC. Further research studies continue to focus on developing ways to improve diagnostic tools and strategies with the aim of identifying earlier stages of HCC.

References

[1] Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.
[2] Pal S, Pande GK. Current status of surgery and transplantation in the management of hepatocellular carcinoma: an overview. J Hepatobiliary Pancreat Surg 2001;8:323–36.
[3] El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999; 340:745–50.
[4] Schafer DF, Sorrell MF. Hepatocellular carcinoma. Lancet 1999;353:1253–7.
[5] Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. Hepatology 1998;28:751–5.
[6] Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. Semin Liver Dis 1999;19:311–22.
[7] Torzilli G, Belghiti J, Makuuchi M. Differences and similarities in the approach to hepatocellular carcinoma between Eastern and Western institutions. Liver Transpl 2004; 10(2 Suppl 1):S1–S2.
[8] Prorok PC. Epidemiologic approach for cancer screening. Problems in design and analysis of trials. Am J Pediatr Hematol Oncol 1992;14:117–28.
[9] McMahon BJ, Bulkow L, Harpster AL, Snowball M, Lanier A, Sacco F, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000;32(4 Pt 1):842–6.
[10] Mima S, Sekiya C, Kanagawa H, Kohyama H, Gotoh R, Mizuo H, et al. Mass screening for hepatocellular carcinoma: experience in Hokkaido, Japan. J Gastroenterol Hepatol 1994;9:361–5.
[11] Tong MJ, Blatt LM, Kao VW. Surveillance for hepatocellular carcinoma in patients with chronic viral hepatitis in the United States of America. J Gastroenterol Hepatol 2001;16:553–9.
[12] 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.
[13] Pateron D, Ganne N, Trinchet JC, Aurousseau MH, Mal F, Meicler C, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. J Hepatol 1994;20:65–71.
[14] Chalasani N, Said A, Ness R, Hoen H, Lumeng L. Screening for hepatocellular carcinoma in patients with cirrhosis in the

United States: results of a national survey. Am J Gastroenterol 1999;94:2224–9.
[15] Koteish A, Thuluvath PJ. Screening for hepatocellular carcinoma. J Vasc Interv Radiol 2002;13(9 Pt 2):S185–S190.
[16] Di Bisceglie AM, Carithers RL Jr, Gores GJ. Hepatocellular carcinoma. Hepatology 1998;28:1161–5.
[17] Lieberman DA. Cost-effectiveness model for colon cancer screening. Gastroenterology 1995;109:1781–90.
[18] Bailey MA, Brunt EM. Hepatocellular carcinoma: predisposing conditions and precursor lesions. Gastroenterol Clin North Am 2002;31:641–62.
[19] McMahon BJ. Hepatocellular carcinoma and viral hepatitis. In: Wilson RA, editor. Viral hepatitis: diagnosis, treatment, prevention. New York: Marcel Dekker; 1997. p 315–30.
[20] Hillebrand DJ, Sandowski SA. Hepatobiliary disease. Hepatocellular carcinoma. Clin Fam Pract 2000;2:79–97.
[21] Bosch FX. Global epidemiology of hepatocellular carcinoma. In: Okuda K, Tabor E, editors Liver cancer. New York: Churchill Livingstone; 1997. p 13–28.
[22] Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. Cancer 1988;61:1942–56.
[23] Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–74.
[24] Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997; 336:1855–9.
[25] Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998;75:347–54.
[26] Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–31.
[27] Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, et al. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology 1997;25:754–8.
[28] National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology 1997;26(3 Suppl 1):2S–10S.
[29] Miyakawa H, Sato C, Tazawa J, Izumi N, Hatton K, Ebata A, et al. A prospective study on hepatocellular carcinoma in liver cirrhosis: respective roles of alcohol and hepatitis C virus infection. Alcohol Alcohol 1994; 29(Suppl 1):75–9.
[30] Stal P. Iron as a hepatotoxin. Dig Dis Sci 1995;13:205–22.
[31] Kato Y, Nakata K, Omagari K, Furukawa R, Kusumoto Y, Mori I, et al. Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. Cancer 1994;74:2234–8.
[32] Benvegnu L, Fattovich G, Noventa F, Tremolada F, Chemello L, Ceccetto A, et al. Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis. A prospective study. Cancer 1994;74:2442–8.
[33] Zaman SN, Melia WM, Johnson RD, Portmann BC, Johnson PJ, Williams R. Risk factors in development of hepatocellular carcinoma in cirrhosis: prospective study of 613 patients. Lancet 1985;1:1357–60.
[34] Melia WM, Johnson PJ, Neuberger J, Zaman S, Portmann BC, Williams R. Hepatocellular carcinoma in primary biliary cirrhosis: detection by alpha-fetoprotein estimation. Gastroenterology 1984;87:660–3.
[35] Ryder SD, Koskinas J, Rizzi PM, McFarlane IG, Portmann BC, Naoumov NV, et al. Hepatocellular carcinoma complicating autoimmune hepatitis: role of hepatitis C virus. Hepatology 1995;22:718–22.
[36] Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F, et al. Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000;32:200–4.
[37] Kashyap R, Join A, Nalesnik M, Carr B, Barnes J, Vargas HE, et al. Clinical significance of elevated alpha-fetoprotein in adults and children. Dig Dis Sci 2001;46:1709–13.
[38] Johnson PJ. The role of serum alpha-fetoprotein estimation in the diagnosis and management of hepatocellular carcinoma. Clin Liver Dis 2001;5:145–59.
[39] Colombo M. Screening for cancer in viral hepatitis. Clin Liver Dis 2001;5:109–22.
[40] Gupta S, Bent S, Kohlwes J. Test characteristics of alpha-fetoprotein for detecting hepatocellular carcinoma in patients with hepatitis C. A systematic review and critical analysis. Ann Intern Med 2003;139:46–50.
[41] Taketa K. Alpha-fetoprotein. J Med Technol 1989;33:1380.
[42] Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology 2002; 122:1609–19.
[43] Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995; 22:432–8.
[44] Johnson PJ, Poon TC, Hjelm NM, Ho CS, Ho SK, Welby C, et al. Glycan composition of serum alpha-fetoprotein in patients with hepatocellular carcinoma and non-seminomatous germ cell tumour. Br J Cancer 1999;81:1188–95.
[45] Shimizu K, Katoh H, Yamashita F, Tanaka F, Tanaka M, Tanikawa K, et al. Comparison of carbohydrate structures of serum alpha-fetoprotein by sequential glycosidase digestion and lectin affinity electrophoresis. Clin Chim Acta 1996;254:23–40.
[46] Aoyagi Y, Suzuki Y, Isemura M, Nomoto M, Sekine C, Igarashi K, et al. The fucosylation index of alpha-fetoprotein and its usefulness in the early diagnosis of hepatocellular carcinoma. Cancer 1988;61:769–74.
[47] Saitoh S, Ikeda K, Koida I, Suzuki Y, Kobayashi M, Tsubota A, et al. Diagnosis of hepatocellular carcinoma by concanavalin A affinity electrophoresis of serum alpha-fetoprotein. Cancer 1995;76:1139–44.
[48] Taketa K, Endo Y, Sekiya C, Tanikawa K, Koji T, Taga H, et al. A collaborative study for the evaluation of lectin-reactive alpha-fetoproteins in early detection of hepatocellular carcinoma. Cancer Res 1993;53:5419–23.
[49] Burditt LJ, Johnson MM, Johnson PJ, Williams R. Detection of hepatocellular carcinoma-specific alpha-fetoprotein by isoelectric focusing. Cancer 1994;74:25–9.
[50] Johnson PJ, Leung N, Cheng P, Welby C, Leung WT, Lau WY, et al. 'Hepatoma-specific' alphafetoprotein may permit preclinical diagnosis of malignant change in patients with chronic liver disease. Br J Cancer 1997;75:236–40.
[51] Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med 1984;310:1427–31.
[52] Marrero JA, Su GL, Wei W, Emick D, Conjeevaram HS, Fontana RL, et al. Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in American patients. Hepatology 2003;37:1114–21.
[53] Weitz IC, Liebman HA. Des-gamma-carboxy (abnormal) prothrombin and hepatocellular carcinoma: a critical review. Hepatology 1993;18:990–7.
[54] Tanabe Y, Ohnishi K, Nomura F, Iida S. Plasma abnormal prothrombin levels in patients with small hepatocellular carcinoma. Am J Gastroenterol 1988;83:1386–9.
[55] Nagaoka S, Yatsuhashi H, Hamada H, Yano K, Matsumoto T, Daikoku M, et al. The des-gamma-carboxy prothrombin index is a new prognostic indicator for hepatocellular carcinoma. Cancer 2003;98:2671–7.

[56] Murakami T, Mochizuki K, Nakamura H. Imaging evaluation of the cirrhotic liver. Semin Liver Dis 2001;21:213–24.
[57] Takayasu K, Moriyami N, Muramatsu Y, Makuuchi M, Hosegawa H, Okazaki N, et al. The diagnosis of small hepatocellular carcinomas: efficacy of various imaging procedures in 100 patients. AJR Am J Roentgenol 1990;155:49–54.
[58] Chalasani N, Horlander JC Sr, Said A, Hoen H, Kopecky KK, Stockberger SM Jr, et al. Screening for hepatocellular carcinoma in patients with advanced cirrhosis. Am J Gastroenterol 1999;94:2988–93.
[59] Di Bisceglie AM. Epidemiology and clinical presentation of hepatocellular carcinoma. J Vasc Interv Radiol 2002;13(9 Pt 2):S169–S171.
[60] Murata K, Shiraki K, Kawakita T, Yamamoto N, Okano H, Sakai T, et al. Hepatocellular carcinoma presenting with obstructive jaundice: a clinicopathological study of eight patients. Hepatogastroenterology 2003;50:2057–60.
[61] Chen ZY, Qi QH, Dong ZL. Etiology and management of hemorrhage in spontaneous liver rupture: a case report of 70 cases. World J Gastroenterol 2002;8:1063–6.
[62] Si MS. Prevalence of metastasis in hepatocellular carcinoma: risk factors and impact on survival. Am Surg 2003;69:879.
[63] Luo JC. Clinical characteristics and prognosis of hepatocellular carcinoma patients with paraneoplastic syndromes. Hepatogastroenterology 2002;49:1315.
[64] Bruix J, Castells A, Calvet X, Feu F, Bru C, Sole M, et al. Diarrhea as a presenting symptom of hepatocellular carcinoma. Dig Dis Sci 1990;35:681–5.
[65] Steiner E, Velt P, Gutierrez O, Schwartz S, Chey W. Hepatocellular carcinoma presenting with intractable diarrhea. A radiologic-pathologic correlation. Arch Surg 1986; 121:849–51.
[66] Ackerman D. Cutaneous metastasis from hepatocellular carcinoma. Int J Dermatol 2001;40:782.
[67] Fracanzani AL. Liver cancer risk is increased in patients with porphyria cutanea tarda in comparison to matched control patients with chronic liver disease. J Hepatol 2001;35:498.
[68] Tangkijvanich P, Anukulkamkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. J Clin Gastroenterol 2000;31:302–8.
[69] Hanazaki K, Kajikawa S, Koide N, Adachi W, Amano J. Prognostic factors after hepatic resection for hepatocellular carcinoma with hepatitis C viral infection: univariate and multivariate analysis. Am J Gastroenterol 2001; 96:1243–50.
[70] Andorno E, Salizzoni M, Schieroni R, De Hemptinne B. Role of serum alpha-fetoprotein in pre- and post-orthotopic liver transplantation (OLT) for malignant disease. J Nucl Med Allied Sci 1989;33(3 Suppl):132–4.
[71] Johnson PJ, Williams R. Serum alpha-fetoprotein estimations and doubling time in hepatocellular carcinoma: influence of therapy and possible value in early detection. J Natl Cancer Inst 1980;64:1329–32.
[72] Urabe T, Hayashi S, Terasaki S, Terada M, Matsushita E, Kaneko S, et al. [An assessment of therapeutic effect of hepatocellular carcinoma by the serial changes in serum AFP value]. Nippon Shokakibyo Gakkai Zasshi 1990;87:100–8 [in Japanese].
[73] Johnson PJ, Williams R, Thomas H, Sherlock S, Murray-Lyon IM. Induction of remission in hepatocellular carcinoma with doxorubicin. Lancet 1978;1:1006–9.
[74] McIntire KR, Vogel CL, Primack A, Waldmann TA, Kyalwazi SK. Effect of surgical and chemotherapeutic treatment on alpha-fetoprotein levels in patients with hepatocellular carcinoma. Cancer 1976;37:677–83.
[75] Choi BI, Kim AY, Lee JY, Kim KW, Lee KH, Kim TK, et al. Hepatocellular carcinoma: contrast enhancement with Levovist. J Ultrasound Med 2002;21:77–84.
[76] Kubo S, Kinashita H, Hirohashi K, Tsukamoto T, Shuto T. Preoperative localization of hepatomas by sonography with microbubbles of carbon dioxide. AJR Am J Roentgenol 1994;163:1405–6.
[77] Nishiharu T, Yamashita Y, Arakawa A, Sumi S, Mitsuzaki K, Matsukawa T, et al. Sonographic comparison of intraarterial CO_2 and helium microbubbles for detection of hepatocellular carcinoma: preliminary observations. Radiology 1998; 206:767–71.
[78] Reinhold C, Hammers L, Taylor CR, Quedens-Case CL, Holland CK, Taylor KJ. Characterization of focal hepatic lesions with duplex sonography: findings in 198 patients. AJR Am J Roentgenol 1995;164:1131–5.
[79] Tanaka S, Kitamura T, Fujita M, Nakanishi K, Okuda S. Color Doppler flow imaging of liver tumors. AJR Am J Roentgenol 1990;154:509–14.
[80] Koito K, Namieno T, Morita K. Differential diagnosis of small hepatocellular carcinoma and adenomatous hyperplasia with power Doppler sonography. AJR Am J Roentgenol 1998;170:157–61.
[81] Choi BI, Kim TK, Han JK, Chung JW, Park JH, Han MC. Power versus conventional color Doppler sonography: comparison in the depiction of vasculature in liver tumors. Radiology 1996;200:55–8.
[82] Lencioni R, Pinto F, Armilotta M, Bartolozzi C. Assessment of tumor vascularity in hepatocellular carcinoma: comparison of power Doppler US and color Doppler US. Radiology 1996;201:353–8.
[83] Oliver JH 3rd, Baron RL, Federle MP, Rockette HE Jr. Detecting hepatocellular carcinoma: value of unenhanced or arterial phase CT imaging or both used in conjunction with conventional portal venous phase contrast-enhanced CT imaging. AJR Am J Roentgenol 1996;167:71–7.
[84] Baron RL, Oliver JH 3rd, Dodd GD 3rd, Nalesnik M, Holbert BL, Carr B. Hepatocellular carcinoma: evaluation with biphasic, contrast-enhanced, helical CT. Radiology 1996;199:505–11.
[85] Stevens WR, Gulino SP, Batts KP, Stephens DH, Johnson CD. Mosaic pattern of hepatocellular carcinoma: histologic basis for a characteristic CT appearance. J Comput Assist Tomogr 1996;20:337–42.
[86] Stevens WR, Johnson CD, Stephens DH, Batts KP. CT findings in hepatocellular carcinoma: correlation of tumor characteristics with causative factors, tumor size, and histologic tumor grade. Radiology 1994;191:531–7.
[87] Yoshikawa J, Matsui O, Kadoya M, Gabata T, Arai K, Takashima T. Delayed enhancement of fibrotic areas in hepatic masses: CT-pathologic correlation. J Comput Assist Tomogr 1992;16:206–11.
[88] Brancatelli G, Baron RL, Peterson MS, Marsh W. Helical CT screening for hepatocellular carcinoma in patients with cirrhosis: frequency and causes of false-positive interpretation. AJR Am J Roentgenol 2003;180:1007–14.
[89] Choi BI. The current status of imaging diagnosis of hepatocellular carcinoma. Liver Transpl 2004;10(2 Suppl 1): S20–S25.
[90] Szklaruk J, Silverman PM, Charnsangavej C. Imaging in the diagnosis, staging, treatment, and surveillance of hepatocellular carcinoma. AJR Am J Roentgenol 2003; 180:441–54.
[91] Oliver JH, Baron RL, Carr BI. CT imaging of hepatocellular carcinoma:CT-arteriography versus trophasic helical contrast CT. Radiology 1997;205:144.
[92] Krinsky GA, Lee VS, Theise ND, Weinraub JC, Rofsky NM, Diflo T, et al. Hepatocellular carcinoma and dysplastic nodules in patients with cirrhosis: prospective diagnosis with MR imaging and explantation correlation. Radiology 2001;219:445–54.
[93] Sadek AG, Mitchell DG, Siegelman ES, Outwater EK, Mateucci T, Hann HW. Early hepatocellular carcinoma

that develops within macroregenerative nodules: growth rate depicted at serial MR imaging. Radiology 1995;195: 753–6.

[94] Yu JS, Kim MJ. Hepatocellular carcinoma: contrast-enhanced MRI. Abdom Imaging 2002;27:157–67.

[95] Liangpunsakul S, Agarwal D, Horlander JC, Kieff B, Chalasani N. Positron emission tomography for detecting occult hepatocellular carcinoma in hepatitis C cirrhotic awaiting liver transplantation. Transplant Proc 2003;35:2995–7.

[96] Borzio M, Borzio F, Macchi R, Croce AM, Bruno S, Ferrari A, et al. The evaluation of fine-needle procedures for the diagnosis of focal liver lesions in cirrhosis. J Hepatol 1994;20:117–21.

[97] Pitman MB. Fine needle aspiration biopsy of the liver. Principal diagnostic challenges. Clin Lab Med 1998; 18:483–506, vi.

[98] Robbins S, Kumar V. Basic pathology. 4th ed. Philadelphia: WB Saunders; 1987. p 598.

[99] Inoue K, Takayama T, Higaki T, Watanabe Y, Makuuchi M. Clinical significance of early hepatocellular carcinoma. Liver Transpl 2004;10(2 Suppl 1):S16–S19.

[100] Fornari F, Filice C, Rapaccini JL, Caturelli E, Cavanna L, Civardi G, et al. Small (< or = 3 cm) hepatic lesions. Results of sonographically guided fine-needle biopsy in 385 patients. Dig Dis Sci 1994;39:2267–75.

[101] 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.

[102] Hayashi PH, Trotter JF, Forman L, Kugelmas M, Steinberg T, Russ P, et al. Impact of pretransplant diagnosis of hepatocellular carcinoma on cadaveric liver allocation in the era of MELD. Liver Transpl 2004;10:42–8.

[103] Caturelli E, Ghittoni G, Roselli P, De Palo M, Anti M. Fine needle biopsy of focal liver lesions: the hepatologist's point of view. Liver Transpl 2004;10(2 Suppl 1):S26–S29.

[104] Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.

[105] Huang GT, Sheu JC, Yang PM, Lee HS, Wang TH, Chen DS. Ultrasound-guided cutting biopsy for the diagnosis of hepatocellular carcinoma – a study based on 420 patients. J Hepatol 1996;25:334–8.

[106] Durand F, Regimbeau GM, Belghiti J, Sauvanet A, Vilgrain V, Terris B, et al. Assessment of the benefits and risks of percutaneous biopsy before surgical resection of hepatocellular carcinoma. J Hepatol 2001;35:254–8.

[107] Kim SH, Lim HK, Lee WJ, Cho JM, Jang HJ. Needle-tract implantation in hepatocellular carcinoma: frequency and CT findings after biopsy with a 19.5-gauge automated biopsy gun. Abdom Imaging 2000;25:246–50.

[108] Ohlsson B, Nilsson J, Strenram U, Akerman M, Tranberg KG. Percutaneous fine-needle aspiration cytology in the diagnosis and management of liver tumours. Br J Surg 2002;89:757–62.

[109] Chapoutot C, Perney P, Fabre D, Taourel P, Bruel JM, Larrey D, et al. [Needle-tract seeding after ultrasound-guided puncture of hepatocellular carcinoma. A study of 150 patients]. Gastroenterol Clin Biol 1999;23:552–6 [in French].

[110] Yamada N, Shinzawa H, Ukai K, Wakabayashi H, Togashi H, Takahashi T, et al. Subcutaneous seeding of small hepatocellular carcinoma after fine needle aspiration biopsy. J Gastroenterol Hepatol 1993;8:195–8.

[111] Bruix J, Sherman M, Lloret JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–30.