



# Natural History of Hepatocellular Carcinoma and Current Treatment Options

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Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the most severe complication of chronic liver disease. The annual number of new cases worldwide is approximately 550,000, representing more than 5% of human cancers and is the third leading cause of cancer-related deaths. The stages of the malignancy as well as the severity of the underlying liver disease are essential factors in planning the therapeutic approach. Curative treatment options are represented mainly by surgery (ie, resection or transplantation), but most patients are not candidates for a curative option, and only palliative treatment could be given to these patients. Among palliative treatments, only chemoembolization has been proven to be effective, but other options are currently being investigated. Major risk factors for HCC are well known and are dependent on the geographic area. In Europe, the United States, and Japan, the main risk factors are liver cirrhosis, hepatitis B and C virus, alcohol, and tobacco; in contrast, in Africa and Asia, these factors are hepatitis B and C virus, tobacco use, and aflatoxin exposure. Cirrhosis from any cause is a predisposing factor for HCC and could be considered as a premalignant condition. The present concept of carcinogenesis in HCC is a multistage process. This article describes the natural history of HCC and discusses the various treatment options available at present.

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Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer<sup>1</sup> and the most severe complication of chronic liver disease. The annual number of new cases worldwide is approximately 550,000, representing more than 5% of human cancers and is the third leading cause of cancer-related deaths. There are large geographical differences in incidence, with high-incidence areas in Eastern Asia and Africa and low-incidence areas in Western countries. The incidence is, however, increasing in low-incidence countries and even in some high-incidence countries because of the growing incidence of hepatitis (B and C) and of obesity-related liver disease. Surveillance for HCC in patients with risk factors remains controversial but could be recommended to identify patients with small HCCs who can benefit from curative treatments. The stage of the malignancy as well as the severity of the underlying liver disease is essential factors in planning the therapeutic approach. Although several prognostic classifications have recently been validated and will

help physicians select the best therapeutic options, the overall survival remains poor, with a median survival of less than 6 months in most reported series. Curative treatment options are represented mainly by surgery (resection or transplantation), but most patients are not candidates for a curative option, and only palliative treatment could be given to these patients. Among palliative treatments, only chemoembolization has been proven to be effective, but other options are currently being investigated.

## Incidence

HCC is one of the most common cancers in men and its incidence varies widely internationally. More than 80% of the new cases come from developing countries with high seroprevalence of hepatitis B or C (HBV and HCV, respectively) virus infection. The incidence per 100,000 varies<sup>2</sup> in men from less than 10 in the United States, Europe, and Australia to 30 in Japan, Taiwan, China, and Congo; 40 to 50 in Gambia and Korea; and up to 100 per 100,000 in Mongolia. Comparable variability is also found in women. In the United States, age-adjusted incidence rates of HCC increased 2-fold between 1985 and 1998.<sup>3</sup> The same trends have been described in France and in the UK. This could be related to the

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improved survival of cirrhotic patients, and in an Italian study, for example, HCC was the main reason for death in cirrhotic patients.<sup>4</sup> In addition, the increased incidence of HCC in developed countries is caused in part by the increase of hepatitis C virus infection and of obesity and diabetes.<sup>2</sup>

## Risk Factors

Major risk factors for HCC are well known and are dependent on the geographic area. In Europe, the United States, and Japan, the main risk factors are liver cirrhosis, hepatitis B and C virus, alcohol, and tobacco; in contrast, in Africa and Asia, these factors are HBV and HCV, tobacco use, and aflatoxin exposure.

## Viral Hepatitis

Chronic infection by the hepatitis B virus is the most important risk factor for HCC in humans and the principal etiologic factor in high-risk areas like Asia and Africa. Overall, 80% of cases of HCC are related to infection with hepatitis B or C virus. Worldwide, 380 million people have HBV infection. In developed countries most HBV infections are acquired in adulthood though sexual contact, intravenous drug use, invasive medical procedures, or blood transfusions. These factors explain why, in these populations, this cancer is rare before 50 years of age. In contrast, in high-risk countries mother-to-child or child-to-child transmission of HBV is common, and HCC can be observed before a patient is 20 years of age. Chronic HBV carriers have a 20- to 100-fold greater risk of developing HCC compared with noncarriers. Among HBV antigen (HBsAg) carriers some associated factors increase the risk of HCC; these include male gender, duration of infection, age, alcohol abuse, tobacco use, aflatoxin, and coinfection with another hepatotropic virus (C or D). Other major factors are chronic inflammation (fibrosis and liver cell proliferation) and integration of HBV DNA into host-cell DNA.<sup>5</sup> Prevention of HBV infection by vaccination of newborns has been shown to reduce the incidence of HCC among Taiwanese children, with a significant and parallel decrease in HBsAg carrier rate and incidence of HCC. HBV vaccine is the first vaccine that has been shown to prevent cancer in men. Antiviral therapies which decrease liver damage could also lead to a decrease in incidence of HCC.<sup>6</sup>

Chronic hepatitis C infection is one of the major causes of HCC in Japan, Europe and the United States as well as worldwide, with 170 million people infected with this virus. Acquisition later in life, usually as the result of exposure to blood products or intravenous drug abuse, may explain why HCV-associated HCC is diagnosed usually during the fifth decade of life. Other factors in such individuals which increase the risk of developing HCC include coinfection with hepatitis B virus, tobacco, genetic iron overload, alcohol abuse, male gender, diabetes, obesity, and age as well as active liver disease, fibrosis or cirrhosis, the usual consequences of longstanding (20- to 30-year) infection. Meta-analysis of interferon therapy suggests that this treatment could decrease HCC risk, mainly among those experiencing a

response. Unfortunately, vaccination is not available and prevention is based on controlling nosocomial infections and transmission by transfusion.

## Dietary Aflatoxin Exposure

This environmental carcinogen is produced by fungi contaminating corn, peanuts, soya sauce, and soya beans acts synergistically with HBV infection to amplify HCC risk. This is responsible for a specific p53 gene mutation (G to T transversion at codon 249).

## Alcohol

Alcoholic cirrhosis and alcohol abuse are responsible for 15% of HCC cases in southern Europe and for 40% in Northern Europe, where HBV and HCV carriers are low.

## Tobacco

Many epidemiologic studies have reported an association between cigarette smoking with liver cancer independent of HBV status or of alcohol abuse.

## Iron Metabolism

Iron overload in the setting of genetic hemochromatosis (HFE mutations C282Y or H63D) is associated with an increased risk of HCC and iron depletion (by phlebotomy) is effective in decreasing the risk of cirrhosis and of HCC.

## Other Factors

### Obesity and Diabetes

Epidemiological studies have shown that obesity<sup>7</sup> and diabetes are risk factors for HCC and are associated with nonalcoholic liver steatosis, which is the main cause of cryptogenic cirrhosis and which appears to have a comparable carcinogenic potential to HCV cirrhosis. Long-term use of oral contraceptives could increase the risk but further studies are needed to clarify its role.

### Cirrhosis

Cirrhosis from any cause is a predisposing factor for HCC and could be considered as a premalignant condition. Cirrhosis underlies HCC in more than 80% of cases worldwide, and in cases of HCC developing in a noncirrhotic liver almost all have chronic hepatitis. The cirrhosis per se could be the major risk factor for HCC irrespective of its etiology. The annual incidence of HCC varies among countries from less than 1 to more than 6%. The 5-year cumulative incidence of HCC in HCV-related cirrhosis is 30% in Japan, 17% in Europe and the US, and 15% in Taiwan and Singapore. In addition, it is 21% in hereditary hemochromatosis, 8% in alcoholic cirrhosis in the absence of viral infection and 4% in primary biliary cirrhosis.<sup>8</sup>

## Natural History and Prognosis

The present concept of carcinogenesis in HCC is a multistage process. Macroscopically, there is a continuum among the different nodules that could originate from a cirrhotic liver.



**Figure 1** Macroscopic image of an encapsulated HCC (courtesy of Dr. Bruno Turlin, CHRU Rennes). (Color version of figure is available online.)

Macro-regenerative nodules are common. When they are less than 5 mm in diameter, they are frequently benign or associated with a low-grade dysplasia. But these nodules might be proliferative lesions or preneoplastic foci. In the case of high-grade dysplastic nodules, usually larger than 5 mm, the risk of malignant transformation exceeds 33%. Finally, HCC may arise as unifocal disease usually circumscribed at first by a fibrotic capsule (Fig. 1) but frequently as multicentric lesions resulting from intrahepatic metastases (Fig. 2), usually tracking the portal vein or as a result of a multicentric synchronous occurrence.

There are 3 components to the staging of HCC: intrahepatic staging, extrahepatic staging, and liver function. Intrahepatic staging requires precise determination of the number and size of nodules and of whether vascular invasion is present or not. Extrahepatic metastases are infrequent and only seen in advanced cases; most common locations are lymph nodes, lungs, skeleton and adrenal glands. Many staging systems have been devised but none has received universal acceptance. The Barcelona Clinic Liver Cancer (BCLC) staging<sup>9</sup> is very useful in early disease and links tumor staging with treatment strategy. The Cancer of Liver Italian Programme (CLIP) score seems to be of interest in more advanced lesions.<sup>10</sup> In the BCLC staging prognostic variables used are portal invasion, metastases, tumor morphology (size, number), Okuda classification, Child-Pugh classification, portal hypertension, serum bilirubin level, and Karnofsky Performance Status (KPS). The BCLC staging is based on natural history of HCC. The very early stage corresponds to well-compensated liver function, tumors less than 2 cm and very well-differentiated, and the pathological in situ stage (ie, no structural invasion). However, cancer invasion sometimes occurs in HCCs smaller than 2 cm. Early-stage HCC corresponds to patients with a KPS of 0, Okuda's class 1-2, Child-Pugh's class A-B and having a single nodule or 2-3 nodules less than 3 cm. Intermediate-stage patients have multinodular tumors and an excellent performance status (0). Advanced stages are reached when patient develop portal invasion, lymph node involvement, extrahepatic metastases,

and/or poor performance status (1-2). Terminal-stage patients, irrespective of tumor parameters, have a very poor performance status (>2) or are class C in Child-Pugh's classification or stage 3 in Okuda's classification. In the Barcelona experience, the 1-year survival ranged from 10% to 20% for terminal-stage patients, a 3-year survival between 20% and 40% in intermediate and advanced stages, and the 5-year survival between 50% and 70% in very early and early stages. In the CLIP classification, the pertinent variables are: tumor and liver involvement, high alpha-fetal protein (>400  $\mu\text{g/L}$ ), portal invasion, Child-Pugh classification (A, B, C). The CLIP score is then associated with a median survival ranging from 42.5 months for score 0 to 1 month for score 5-6.

The European Association for the Study of the Liver proposed a diagnostic strategy based on the following natural history.<sup>11</sup> In focal liver nodules smaller than 1 cm (malignant in less than 50% of cases), close follow-up (every 3 months) is recommended until the lesion exceeds 1 cm in size. In 1- to 2-cm nodules, fine-needle aspiration with biopsy (despite a false-negative rate of 40%) is recommended; a negative result does not rule out malignancy. In patients with cirrhosis and nodules greater than 2 cm, noninvasive criteria could be applied: HCC diagnosis is established by the concomitant finding of two imaging techniques (contrast-enhanced computed tomography, magnetic resonance imaging, and angiography) showing a hypervascularized nodule or by one positive imaging result associated with an alpha-fetal protein level higher than 400  $\mu\text{g/L}$ . In such cases a percutaneous biopsy is not mandatory.

## Current Treatment Options

Curative treatments are surgery (resection or orthotopic liver transplantation) and percutaneous treatments (radiofrequency tumor ablation or percutaneous ethanol injections). Palliative treatments are numerous but effectiveness is demonstrated only for chemoembolization and randomized controlled trials are required.



**Figure 2** Macroscopic image of a HCC associated with multiple metastatic nodules after capsule rupture (courtesy of Dr. Bruno Turlin, CHRU Rennes). (Color version of figure is available online.)

## Surgery

Obviously, surgery could be offered only to patients without extrahepatic metastases, including lymph node involvement. Hepatic resection<sup>12</sup> is the best treatment in noncirrhotic patients who can recover from resection that preserve at least 2 segments of functional liver. In cirrhotic patients surgery could be proposed only in case of well-preserved cirrhosis and those who could tolerate resection of up to 2 segments. If a resection of more than 2 segments is necessary, a preoperative portal vein embolization to induce hypertrophy of the remnant liver would be useful. Operative mortality of resection in cirrhotic patients is currently less than 4% and the 5-year overall survival is between 30% and 50%. The main prognostic factors after resection are presence of cirrhosis, tumor size, vascular invasion, and poorly differentiated HCC. Unfortunately, postoperative recurrences are frequent. Some adjuvant treatments have been tested to decrease the frequency of these recurrences. A small randomized controlled trial from Hong Kong<sup>13</sup> evaluated the postoperative use of a single dose of <sup>131</sup>I-lipiodol after curative resection and reported promising results. Liver transplantation could simultaneously cure the tumor and the cirrhosis. Due to the severe shortage of donor livers, organ allocation to transplantation is justified only if the expected results are comparable to those of patients undergoing liver transplantation for benign disease. The Milan criteria proposed by Mazzafero and coworkers<sup>14</sup> are now widely accepted by most transplant centers: transplantation can be done in patients with a solitary nodule of 5 cm or less or patients with no more than 3 nodules less than 3 cm and no invasion of major blood vessels or lymph nodes. Using these criteria, the 4-year survival is up to 85%.

## Percutaneous Treatments

Ultrasound-guided percutaneous ethanol injection is tumoricidal in small tumors, less than 2-3 cm in diameter. This technique has many advantages: low cost, simplicity, ease of performance, minimal equipment, and good tolerability. This technique achieves response of more than 90% in small HCC (<2 cm), 60-70% in 3-cm HCC, and less than 60% if the diameter is up to 5 cm.<sup>15</sup> The use of high-volume of ethanol could improve results in patients with larger tumors. Radiofrequency ablation has been demonstrated in some studies to be more efficient than ethanol injections. This technique produces thermal injuries via an alternating electric current. These 2 techniques were compared in 2 randomized trials. In the first, radiofrequency tumor ablation gave better local control than percutaneous ethanol injection<sup>16</sup> in 102 patients. In a more recent randomized study, Lin and coworkers<sup>17</sup> have compared percutaneous ethanol injection, high-dose percutaneous ethanol injection and radiofrequency tumor ablation in HCC from 1 to 4 cm in diameter in 157 patients. Radiofrequency was better in terms of complete necrosis rate, recurrence rate, disease-free survival and overall survival. Unfortunately, the equipment is expensive but the complete necrosis could be obtained in less time than with percutaneous ethanol injection. The efficacy of radiofre-

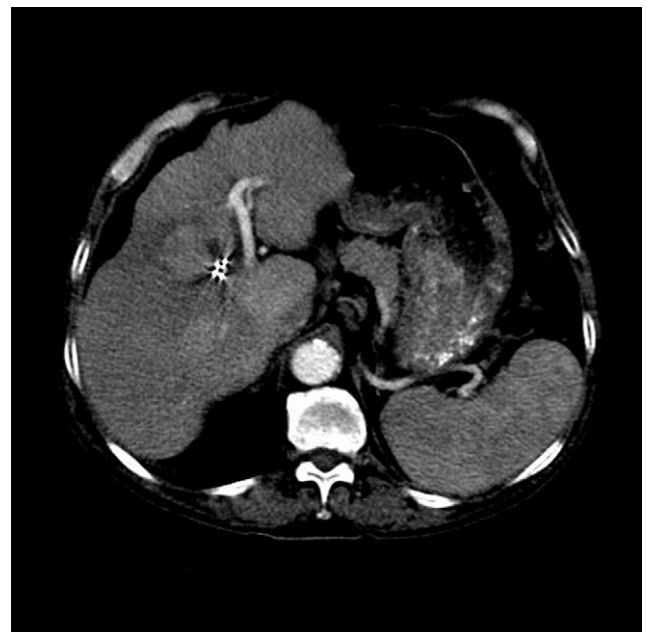
quency tumor ablation in larger tumors is more controversial.

## Intra-Arterial Procedures

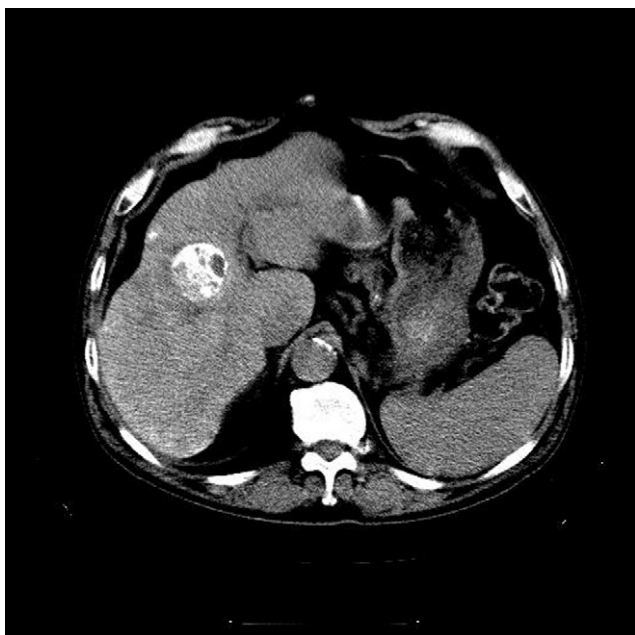
A wide spectrum of transarterial procedures has been proposed for treating HCC. The three major procedures were transarterial chemoembolization, transarterial embolization and transarterial injection of radioactive Lipiodol. These intraarterial treatments rely on the arterial hypervascularization of the tumors. Thus, obstruction of the arterial blood flow will lead to extensive necrosis. Moreover, when Lipiodol, a lipophilic contrast media, is injected into the hepatic artery of HCC patients, it concentrates in and is retained by the tumor (Figs. 3 and 4). Thus cytotoxic drugs mixed with Lipiodol achieve higher intratumoral concentration when injected into the hepatic artery and are thought to be released progressively in the lesions. Lipiodol labeled with Iodine-131 has also been used for targeted internal radiotherapy of HCC.

## Chemoembolization

Chemoembolization involves injection of a cytotoxic drug (usually CDDP, mitomycin, or doxorubicin) mixed with lipiodol followed by embolization using absorbable particles. Many nonrandomized studies have been reported showing an obvious antitumoral effect with an objective response rate ranging from 20% to 60%, with frequent severe side effects (postembolization syndrome, deterioration of liver function, liver abscesses, and some cases of massive liver necrosis and portal vein thrombosis). Seven randomized studies, including more than 500 patients, had compared trans-arterial chemoembolization with best supportive care. Two<sup>18,19</sup> of them demonstrated a survival advantage for treated patients, with



**Figure 3** Arterial phase of contrast computed tomography scan, showing centrally located hepatocellular carcinoma and metallic stent to relieve biliary compression.



**Figure 4** Same patient as in Figure 3 after intraarterial injection of  $^{131}\text{I}$ -labeled lipiodol, showing concentration of lipiodol within the tumor.

meta analysis<sup>20</sup> showing a beneficial survival effect of embolization or chemoembolization compared with conservative treatment. Currently, however, there is not consensus on the optimum chemotherapeutic agent or frequency of treatment. It is now obvious that patient selection is the key point and that the best candidates for chemoembolization are patients with well-preserved liver function (Child A), asymptomatic multi-nodular tumors involving less than 50% of the liver, and absence of vascular invasion.

### Targeted Internal Radiotherapy

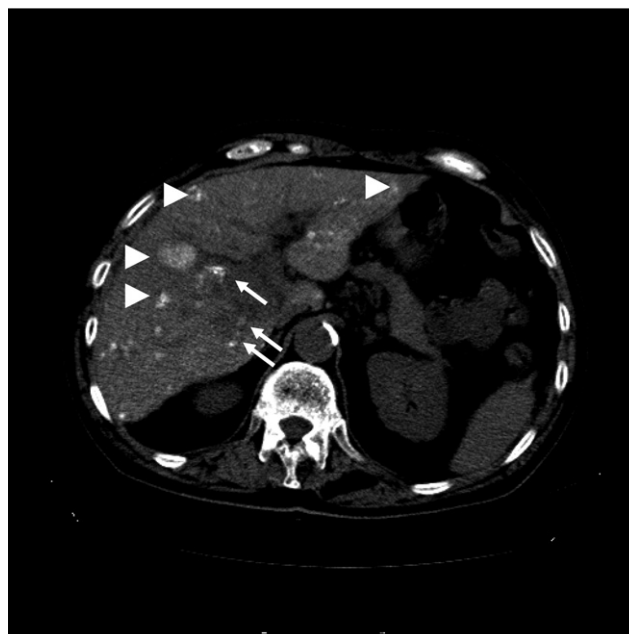
Targeted internal radiotherapy using radiolabeled lipiodol has been tested by a number of investigators. Most studies have used  $^{131}\text{I}$ -labeled lipiodol. The administered activities ranged from 740 to more than 6,000 MBq either in single or multiple treatments. The objective response rates based on tumor size ranged from 25% to 40%. In a randomized controlled study involving 142 patients,<sup>21</sup> the efficacy of this treatment was shown to be comparable to chemoembolization. In another controlled study,<sup>22</sup> including only 27 patients, this treatment yielded better survival than best supportive care in patients with portal vein thrombosis (Fig. 5). A recent phase II trial<sup>23</sup> combining intraarterial injection of  $^{131}\text{I}$ -labeled lipiodol and systemic chemotherapy showed a tolerable toxicity profile and a 47% response rate and thus warrants a phase III trial.

Despite these promising results, the use of  $^{131}\text{I}$ -labeled lipiodol is limited because this isotope has a physical half-life of 8 days, emits a high-energy g-ray (364 keV, 82%), and in some jurisdictions requires a 7-day or longer hospitalization for radioprotection purposes. Rhenium-188 ( $^{188}\text{Re}$ ) has favorable characteristics for radionuclide therapy: a higher-energy b-emission that could improve response rate particu-

larly in larger tumors, a 155-keV g ray suitable for gamma camera imaging, and a relatively short physical life (17 hours), minimizing radioprotection issues. Additionally, the radionuclide is eluted from a  $^{188}\text{W}/^{188}\text{Re}$  generator, which is relatively inexpensive, has a long useful shelf-life, and provides high-yields of carrier-free  $^{188}\text{Re}$  routinely. The first clinical trials reported the use  $^{188}\text{Re}$  HDD/lipiodol. In the series reported by Sundram and coworkers,<sup>24</sup> this treatment appeared safe and well tolerated, the most frequent adverse effects consisting of mild anorexia, abdominal pain, and fever. Lambert and coworkers<sup>25</sup> have reported comparable tolerance data in a phase I study of 11 patients, but one patient experienced dyspnea and coughing, respiratory adverse events that have also been reported with the use of  $^{131}\text{I}$ -labeled lipiodol. Among these 11 patients, 1 showed a partial response and 9 had stable disease; by the conclusion of the study, however, there was clear evidence of progressive disease in 6 of the patients. Some other intra-arterial procedures have been tested, including intra-arterial injections of Yttrium-90 microspheres<sup>26</sup> and chemotherapy<sup>27</sup> but these require further study and evaluation.

### Other Palliative Therapies

Many other strategies have been tested. Estrogen blockade (with tamoxifen) was tested but in at least nine randomized trials as well as by meta-analysis failed to demonstrate any survival benefit. Other hormonal treatments (antiandrogens, somatostatin) appeared promising initially but failed to demonstrate any therapeutic advantage in subsequent, larger randomized trials any benefit. HCC is widely considered to be chemotherapy-resistant.<sup>28</sup> Systemic chemotherapy, either single-agent or combination therapies, have shown poor response rates (usually <20%) and were associated with high



**Figure 5** Multinodular hepatocellular carcinoma (arrowheads) with portal vein thrombosis retaining  $^{131}\text{I}$ -labeled lipiodol focally (arrows).

toxicity rates. Encouraging results of an initial trial with interferon have not been reproduced by others.

Targeted therapies, particularly drugs targeting the angiogenic process, are particularly promising and sorafenib, a multikinase inhibitor with activity against Raf kinase and several receptor tyrosine kinases (VEGFR, PDGFR, c-kit, FLT3 and ret) would be the future gold standard in advanced tumors.

## Conclusion

In conclusion, HCC is a common cancer with a prognosis that remains dismal despite many treatment options. Even for patients who undergo resection, the cure rate is very low. For those who are not candidates for surgery or for percutaneous procedures, only chemoembolization appears to improve survival. Other treatments need to be tested in large-scale randomized trials; these include intraarterial injection of radiolabeled Lipiodol and new systemic drugs (such as tyrosine kinase inhibitors, antivascular endothelial growth factor antibody, and antiepithelial growth factor receptor). Priorities for the future include<sup>29</sup>: a HCC clinical research network group; improvement of basic and translational research, including research to identification of the most appropriate imaging modality for assessing treatment response; and well-designed, large-scale clinical trials; including stratification of patients according to prognostic systems, quality-of-life assessment, and a placebo-negative control arm.

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