

## Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma

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### Abstract

**Introduction** The Asian Pacific Association for the Study of the Liver (APASL) convened an international working party on the management of hepatocellular carcinoma (HCC) in December 2008 to develop consensus recommendations.

**Methods** The working party consisted of expert hepatologist, hepatobiliary surgeon, radiologist, and oncologist from

Asian-Pacific region, who were requested to make drafts prior to the consensus meeting held at Bali, Indonesia on 4 December 2008. The quality of existing evidence and strength of recommendations were ranked from 1 (highest) to 5 (lowest) and from A (strongest) to D (weakest), respectively, according to the Oxford system of evidence-based approach for developing the consensus statements.

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**Results** Participants of the consensus meeting assessed the quality of cited studies and assigned grades to the recommendation statements. Finalized recommendations were presented at the fourth APASL single topic conference on viral-related HCC at Bali, Indonesia and approved by the participants of the conference.

**Keywords** Hepatocellular carcinoma · Consensus statements · Recommendations · Epidemiology · Diagnosis · Treatment algorithm

### Abbreviations

AASLD	American Association for Study of Liver Diseases
AFP	$\alpha$ -Fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive fraction of AFP
APASL	Asian Pacific Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
CI	Confidence interval
CEUS	Contrast-enhanced US
CSF-1	Colony-stimulating factor 1
CTAP	CT during arterial portography
CTHA	CT hepatic arteriography
DCP	Des- $\gamma$ -carboxyprothrombin
DN	Dysplastic nodule
EASL	European Association for the study of the liver
FNH	Focal nodular hyperplasia
Gd-EOB-DTPA	Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid
GPC3	Glypican-3
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HGDN	High-grade dysplastic nodules
HH	Hereditary hemochromatosis
IFN	Interferon
LAM	Lamivudine
LGDN	Low-grade dysplastic nodules
LR+	Positive likelihood ratio
MDCT	Multidetector-row CT
MTT	Molecular targeted therapy
NASH	Nonalcoholic steatohepatitis
PDGFR	Platelet-derived growth factor receptors
PIVKA-II	Prothrombin induced by vitamin K absence-II

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RCT	Randomized controlled trial
RD	Risk difference
SPIO	Superparamagnetic iron oxide
TACE	Transarterial chemoembolization
US	Ultrasonography
VEGFR	Vascular endothelial growth factor receptors

### Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of death from cancer. Approximately three-fourth of cases occur in Asian countries because of a high prevalence of chronic infection with HBV. HCC is undoubtedly a great health threat in Asian region.

The Asian Pacific Association for the Study of the Liver (APASL) convened an international working party on the management of HCC in December 2008 to develop consensus recommendations. The working party consisted of expert hepatologists, hepatobiliary surgeons, radiologists, and oncologists from Asian-Pacific region, who were requested to make drafts prior to the consensus meeting, held at Bali, Indonesia, on 4 December 2008. The consensus statements consisted of recommendations and scientific comments based on comprehensive review of the literature on each topic. The quality of existing evidence and strength of recommendations were ranked from 1 (highest) to 5 (lowest) and from A (strongest) to D (weakest), respectively, according to the Oxford system of evidence-based approach for developing the consensus statements [1]. Participants of the consensus meeting assessed the quality of cited studies and assigned grades to the recommendation statements. Finalized recommendations were presented at the fourth APASL single topic conference on viral-related HCC at Bali, Indonesia, and approved by the participants of the conference.

### Epidemiology and risk factors

#### Recommendations

Patients with cirrhosis due to HBV or HCV are at the highest risk for HCC (2a).

The incidence of HCC was significantly higher in those who were HBeAg positive or have HBV DNA with high loads ( $>10^4$  copies/mL) and older than 40 years (2a).

Coinfection with HBV and HCV may have synergistic effect on the development of HCC (2b).

Male sex, aging, and familial history are independent risk factors for HCC (2a).

Chronic and heavy alcohol intake, high body mass index (BMI  $> 25$ ) and diabetes mellitus leading to liver disease increases the risk for HCC (2b).

## Geographical distribution

The prevalence of HCC worldwide parallels that of viral hepatitis, and the majority of cases are associated with HBV and HCV. Chronic HBV infection is a leading cause of HCC in most African and Asian countries except Japan. HCV predominantly contributes to HCC in some southern European countries (e.g., Italy and Spain) and Japan.

HCC has large variation in incidence according to geographic locations [2]. High-incidence regions include sub-Saharan Africa, East Asia, and South-East Asia (i.e., China, Hong Kong, Taiwan, Korea, and Japan). The distribution of HCV-related HCC also differs among ethnic groups within the same country and among regions within the same country. In contrast, HBV-related HCC is evenly distributed, except in high aflatoxin exposure areas.

## Hepatitis B infection

Chronic infection with HBV is the strongest risk factor for HCC in Asian countries. A landmark study by Beasley et al. [3] indicated that the relative risk of HCC in these HBsAg carriers was 223 times that of the normal population. Tsukuma et al. [4] also reported that the relative risk of HBsAg was 6.9 among 917 Japanese patients with cirrhosis or chronic hepatitis.

Some authors indicated that active viral replication of HBV increases the risk of HCC in subjects with chronic HBV infection [5–9]. Yang et al. [6] reported that the incidence of HCC was significantly higher in those who were HBsAg and HBeAg positive than in those who were HBsAg positive only. Recently, this was confirmed by showing a correlation between baseline HBV DNA levels in asymptomatic adult HBsAg carriers and the risk of HCC [10–13].

Studies have now shown that HBV genotype correlates with the risk for HCC and that genotype C carries two- to threefold higher risk than genotype B in developing HCC [10, 14–19]. Other HBV variants, such as precore, basal core, and pre-S deletion mutants, may also influence the development of HCC in carriers [15, 19–25].

The impact of genetic background of patients with chronic viral hepatitis, especially those with a family history of HCC, may need further investigation.

## Hepatitis C infection

Chronic HCV infection is also strongly associated with HCC [4, 26–29]. The increased incidence of HCC in the developed world is likely to be a direct result of the HCV epidemic occurring some 20–30 years ago in the target population.

There is no clear evidence of the association between HCV genotype and HCC [30–34]. The significance of HCV viral titers in determining HCC risk needs further investigation.

## HBV and HCV coinfection, HIV coinfection with HBV or HCV

A few studies have supported the synergistic effect of HBV–HCV coinfection in the development of HCC [35–40], although the mechanism of this synergy is still unknown.

HIV coinfection in HBV or HCV patients has increased in Asia. The liver disease progresses faster in patients with HIV coinfection [41, 42].

## Cirrhosis

Cirrhosis is present in the majority of patients with HCC, especially in those with HCV infection [28]. It is unclear whether cirrhosis itself is biologically important in the hepatocarcinogenesis, or whether clonal expansion/tumor development and fibrogenesis take place concurrently.

## Male sex

Males are more likely to develop HCC than females. Male-to-female ratios are around 3 in high-risk countries [43], and they tend to be higher in patients with HBV than in those with HCV [44–46].

## Age

Age-specific incidence rates are strongly affected by the etiology of the background liver disease. Old age is an independent risk factor for HCC, especially in areas where HCV infection is endemic [2, 47]. On the other hand, the incidence rates increase after 20 years of age in countries where HBV-related carcinogenesis is dominant.

## Tobacco and alcohol intake

It is still controversial whether cigarette smoking is a risk factor for HCC [37, 48, 49]. Many authors now support the supposition that heavy alcohol intake is strongly associated with HCC [37, 49–51]. Alcohol also increases the risk for HCC in chronic hepatitis B and C [52].

## Aflatoxin

Aflatoxin exposure has been associated with HCC [53–57]. Aflatoxin is produced from fungi, which is a common contaminant in the food items such as corn, peanuts, and soy beans in areas such as Qidong, The People's Republic of China. Chen et al. [54] conducted a community-based

cohort study including 6,487 residents of the Penghu Islets in Taiwan and reported that patients with aflatoxin exposure had a high risk for HCC with an odds ratio of 5.5 as compared with those without aflatoxin exposure. It has also been shown that a synergistic effect exists between chronic HBV infection and aflatoxin exposure for hepatocarcinogenesis [53, 55, 56].

#### Metabolic factors

Recently, it has been shown that both obesity and diabetes are independent risk factors for HCC, depending on HBV and HCV infection status [58]. As both obesity and diabetes have rapidly increased in Asia, their contributions to HCC should be closely watched.

#### Family history

Family history of HCC is associated with a moderately increased risk of HCC [59–61]. In a cohort study, HBV carriers with a family history of HCC had a multivariate-adjusted rate ratio for HCC of 2.41 compared with HBV carriers without a family history of HCC. Risk of HCC increased as the number of affected relatives increased. For carriers with two or more affected relatives, the ratio increased to 5.55 [95% confidence interval (CI) 2.02–15.26] [61]. This factor needs to be incorporated into risk evaluation.

#### Hemochromatosis

Patients affected with hereditary hemochromatosis (HH), a genetic disease of iron overload, were found to lead to cirrhosis and eventually an increased risk of HCC [62–64].

## Prevention

### Prevention of HBV-related HCC

#### Recommendations

Universal hepatitis B vaccination should be implemented in the countries where HBV infection is endemic or hyperendemic (2a, A).

Interferon (IFN) therapy in adult with active hepatitis may be effective in reducing the incidence of HBV-related HCC (2b, B).

Maintained HBV suppression by oral antiviral agent(s) can reduce the risk of HCC (1b, A).

#### *HBV vaccination (primary prevention of HCC)*

About 350 million people are chronic carriers of HBV worldwide. The infection can cause acute and chronic liver diseases including cirrhosis and HCC globally. The

efficacy of universal immunization has been shown in different countries to strikingly reduce the prevalence of HBV carrier in children. A nationwide vaccination program against HBV launched in Taiwan [65, 66] has drastically reduced the HBsAg carrier rate in the younger population [67]. More important, follow-up results from the Taiwan vaccination programs have shown a significant reduction in the incidence of HCC in children. The average annual incidence of HCC in children 6–14 years of age declined from 0.70/100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and further to 0.36/100,000 between 1990 and 1994 ( $P < 0.01$ ) [68]. An 80–85% decrease of HCC in the Taiwanese adults 3–4 decades later is anticipated. The decrease of HCC after the implementation of universal vaccination against HBV not only represents a practical approach to primary prevention of a human cancer by vaccination for the first time in history but also firmly establishes HBV as the cause of HCC in human beings [69]. These data prove that preventing HBV infection leads to a reduction in HBV-related morbidity and mortality and justify advocacy for universal hepatitis B vaccination programs worldwide.

#### *Interferon therapy (secondary prevention of HCC)*

It is evident that IFN therapy reduces the risk of HCC in chronic hepatitis B with/without cirrhosis. In HBeAg-positive patients with chronic hepatitis B, several long-term follow-up studies following 4–6 months of conventional IFN therapy have shown that sustained seroclearance of HBeAg was associated with a significant increase in survival and decreased liver decompensation, especially in patients with preexisting cirrhosis [70–75]. Among these studies, there was one randomized controlled trial (RCT) that involved 101 Taiwanese men with chronic hepatitis B, 67 of whom received IFN therapy and 34 of whom received placebo [75]. During 1.1–11.5 years of follow-up after completion of therapy, the incidence of HCC in untreated patients was higher than that in IFN-treated patients (12 vs. 1.5%,  $P = 0.043$ ). The cumulative incidence of HCC was also higher in untreated patients than in treated patients ( $P = 0.013$ ). However, the beneficial effect of HCC prevention was not observed in another nonrandomized study comparing 208 Chinese patients with chronic hepatitis B who were treated with IFN against 203 untreated patients [76]. These contradictory results were due to nonrandomization, patients of younger age (median 27 vs. 32 years), patients with low or normal alanine aminotransferase (ALT) (median 46 vs. 163 U/L), and associated low response rates (22 vs. 34% at 24 months, 45 vs. 82% at 132 months) in the Hong Kong study [76] compared with the Taiwan study [71]. The beneficial effect of HCC reduction was also supported by another study of

165 HBeAg-positive patients who were treated with IFN- $\alpha$ , as reported by van Zonneveld et al. [74]. On multivariate time-dependent analysis, adjusting for baseline factors that included cirrhosis, responders were found to have a significantly lower risk of HCC than nonresponders ( $P = 0.027$ ). Because the long-term benefit of IFN therapy occurs only in patients with HBeAg loss, the actual benefit is difficult to prove when the HBeAg loss rate in untreated patients is not high enough, especially if the sample size is not big [71, 74]. Addressing these problems, a recent study comparing 233 IFN-treated patients with 233 matched, untreated controlled patients (matched for age, sex, baseline ALT, HBV DNA, and follow-up period) by Lin et al. showed a long-term significant benefit in preventing HCC development (2.7 vs. 12.5%,  $P = 0.011$ ) [77]. This study had the superiority of including more patients with appropriate disease characteristics (active hepatitis), well-matched parameters, and a longer follow-up.

A meta-analysis of 11 randomized studies comparing IFN-treated versus untreated patients with HBV-related cirrhosis showed that IFN seemingly decreased the rate of HCC [92]. The pooled estimate of the HCC preventive effect of treatment was significantly in favor of patients undergoing IFN therapy [risk difference  $-4.1$ , 95% CI  $-0.8$  to  $-7$ ,  $P < 0.013$ ]. However, these trials showed significant inconsistency if assessment did not take ethnicity of patients into account (European vs. Oriental studies). Consistent results were only observed when assessing data pooled from European reports, which did not show a preventive effect of HCC with treatment. Meta-analysis of longitudinal studies with prolonged follow-up showed no differences in the rate of HCC development between treated patients (1.9%, 95% CI 0.8–3.0) and controls (3.16%, 95% CI 1.8–4.5) [78].

In HBeAg-negative patients, Papatheodoridis et al. [72] studied a cohort of 209 IFN treated and 195 untreated patients and showed that the rate of HCC development was significantly reduced in IFN responders than in IFN nonresponders (1.8 vs. 10.5%,  $P = 0.027$ ), or in untreated patients (7.7%,  $P = 0.048$ ). Another study by Lampertico et al. [73] in 101 HBeAg-negative patients showed no difference in HCC development in responders and nonresponders. The low response rate or relatively small number of patients may be one of the reasons for failure to show significant long-term benefits of IFN therapy in HBeAg-negative patients.

#### *Lamivudine (secondary prevention of HCC)*

Lamivudine (LAM) produces marked viral suppression, reduction of hepatic necroinflammatory activity, and histologic improvement of liver fibrosis [79], as well as improved liver function even in patients with decompensation [80].

However, it is still undetermined whether LAM or other oral antiviral drugs can suppress HBV-related hepatocarcinogenesis. To date, only one RCT suggests that LAM treatment of chronic hepatitis B and advanced liver disease does reduce the incidence of HCC, but with marginal significance (hazard ratio 0.49, 95% CI 0.25–0.99,  $P = 0.047$ ) [81]. A multicenter retrospective study of 2,795 patients (657 treated with LAM, 2,138 not treated with LAM) was reported from Japan [82]. Of these, a controlled study including 377 LAM-treated patients and 377 untreated patients were selected on the basis of the propensity score. The mean follow-up period was 2.7 years in LAM-treated group and 5.3 years in the control group. In the LAM group, HCC occurred in four patients with an annual incidence rate of 0.4% per patient per year, whereas in the control group HCC occurred in 50 patients (13.3%) at a rate of 2.5% per patient per year. The cumulative HCC incidence was significantly lower in LAM group ( $P < 0.001$ ). These findings suggest that LAM effectively reduces the incidence of HCC in patients with chronic hepatitis B. Another study including 59 patients of HBeAg-positive or HBeAg-negative cirrhosis treated with long-term LAM (median 44 months, range 15–78 months) showed that the cumulative event-free (decompensation or HCC) survival rate is significantly higher ( $P = 0.001$ ) in patients with maintained virologic suppression than in those who did not have a complete virologic response or suffered a breakthrough [83]. On the basis of these studies, LAM was effective in HCC prevention in patients with chronic hepatitis B. Since drug resistance after long-term LAM therapy is likely to reverse or halt clinical benefit, long-term effects of HCC prevention after longer therapy with other antiviral agents with fewer drug resistance rates need to be studied.

#### Prevention of HCV-related HCC

##### Recommendations

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- The control of transfusion-related, iatrogenic, and illicit drug use-related viral transmission is of paramount importance (2a, A).
  - Efficient screening for HCV infection would find patients who require treatment (2b, B).
  - Interferon therapy is indicated in acute hepatitis C to prevent chronicity (1b, A).
  - Sustained virologic response to an IFN-based therapy reduces the risk of HCV-related HCC in patients with compensated chronic hepatitis C (1a, A).
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#### *Prevention of viral transmission*

It is well known that HCV infection may be transmitted, though not commonly, by mother to neonate or by sexual transmission. In Egypt, intravenous tartar emetic injection

to prevent schistosomiasis is reported to cause an endemic of HCV infection in the country [79]. In United States, the peak of HCV viral spread coincided with the peak of injecting drug abuse from 1960s to 1980s [80]. In Japan, the peak of viral spread in 1950s and 1960s accompanied the peak of paid donors' blood transfusion, which might be contaminated with HCV because of the prior amphetamine abuse and needle sharing [81]. In many countries, new acquisition of HCV infection is decreasing due to growing concern about blood-transmitted infections, especially HIV, and this trend should be further encouraged considering the absence of effective vaccination against either HCV or HIV.

#### *Screening for HCV infection*

Patients infected with HCV usually remain asymptomatic until they develop decompensation of cirrhosis or advanced HCC, when antiviral treatments are hardly effective. The Ministry of Health, Welfare, and Labor in Japan started a national screening program in 2002 for HCV (and HBV) infection among people older than 40 years, in view of the high prevalence of HCV infection in this age group. By the end of 2006, 9 million people had been screened, among whom 110,000 patients were detected to have HCV infection and 110,000 patients with HBV infection [82]. The cost-effectiveness of such programs depends on the prevalence of viral infection among the target population.

#### *Treatment of acute hepatitis C*

Although HCV is not as infectious as HBV or HIV, chronicity is established in 70–80% of patients who have acute HCV infection. After exposure to HCV, such as needlestick injury, serum HCV should be monitored. The incidence of acute hepatitis C is reported to be 1.8% after injury with an HCV-contaminated needle. IFN therapy is to be considered to prevent chronicity once acute HCV infection is confirmed. [83, 84]

#### *Treatment of chronic hepatitis C*

Nishiguchi et al. [85] showed in an RCT that IFN therapy reduced the incidence of HCC in HCV-positive patients with compensated cirrhosis. The preventive effect was stronger in patients who showed sustained virologic response than in patients who failed to attain the response [86]. Several nonrandomized cohort studies showed similar effects on the reduction of HCC development [87–89]. One nonrandomized study detected no significant difference in HCC occurrence, but the low response rate and relatively small sample size may have been responsible for these results [90]. Several meta-analyses on randomized and

nonrandomized studies on IFN therapy for patients with compensated cirrhosis concluded that the incidence of HCC was significantly reduced with therapy [91, 92].

The effect of IFN therapy on HCC incidence in non-cirrhotic patients has been evaluated in nonrandomized studies. Although some studies failed to detect significant risk reduction in treated patients, all studies agree that the risk is reduced in patients who show sustained virologic response or persistent normalization of serum ALT levels [88, 93–95]. Since the incidence of HCC among noncirrhotic patients is not high, a large-sized sample and/or a long-term observation would be required to detect the effect of antiviral therapy on HCC prevention. The fact that IFN therapy improves liver histology in sustained virologic responders may also contribute to prevention of HCC [96]. Although documentation is poor, a combination with ribavirin is likely to produce a stronger effect on HCC prevention among overall treated patients [97]. In most studies, a smaller risk reduction was found in transient responders, i.e., those who showed a temporary response during IFN administration, whereas no effects were detected in nonresponders. Since treatment has a possible effect on HCC prevention even in transient responders, long-term maintenance IFN administration may be beneficial to patients with refractory chronic hepatitis C. Several nonrandomized studies reported reduction in HCC incidence with such treatments [98, 99]. However, a large-scale RCT performed in the United States revealed no reduction in HCC even with 3.5 years of peginterferon maintenance therapy [100]. The reasons for this difference are yet to be elucidated.

#### *Viral-unrelated prevention of HCC*

##### *Recommendations*

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Prevention of HCC by elimination of aflatoxin contamination is advised (2a, B).

Prevention of HCC in patients with nonalcoholic steatohepatitis (NASH) is primarily through lifestyle modification with diet and exercise (2, B).

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#### *Aflatoxin*

Aflatoxins are one of the most potent hepatocarcinogens and are easily acquired by human through exposure to mycotoxins. The incidence of HCC may be reduced by eliminating aflatoxin through proper food storage [78, 101]. The steady decrease in HCC incidence in affluent regions such as Singapore and Shanghai may be, in part, due to the decrease in aflatoxin contamination in the food as a result of economic development [102].

Chen et al. [54] elucidated in a community-based cohort study in Taiwan that a synergistic effect on HCC existed

between HBsAg carrier status and aflatoxin exposure. Another case–control study conducted in Sudan assessed the population-attributable risk of aflatoxin and HBV infection, jointly and separately, with respect to HCC. It demonstrated that reduction of aflatoxin contamination of foods and HBV vaccination may be useful public health strategies in HCC prevention [103].

### Coffee

Coffee has a favorable effect on liver function and liver diseases, particularly in high-risk individuals, making it a substance of interest for the prevention of HCC [104–113].

Two meta-analyses on the relationship between coffee and HCC conducted by Bravi et al. [114] and Larsson et al. [115] provided substantial evidence that there is an inverse relation between coffee and HCC. The findings from these meta-analyses indicate a reduced risk of liver cancer, among both individuals with and without a history of liver disease. Although impressive reviews are available, it is still too early in making direct recommendations regarding coffee intake.

### Vitamin K<sub>2</sub>

Vitamin K<sub>2</sub> inhibits the growth of various neoplastic cells, including hepatoma cells, by causing cell-cycle arrest and apoptosis through different proposed mechanisms [116–122].

An RCT involving the use of vitamin K<sub>2</sub> in the prevention of HCC in women with HBV- or HCV-related cirrhosis proved that there could be a possible role for this as primary preventive agent [122]. The safety, relatively low cost, and ease of use make vitamin K<sub>2</sub> a suitable candidate for clinical trials that assess the value of combination of chemoprevention or chemotherapy in at-risk patients or in patients with a confirmed diagnosis of HCC [116, 122–125].

Although short-term effects seem appealing, additional multicenter randomized controlled studies are needed to look into long-term effects of vitamin K<sub>2</sub>.

### Tobacco and alcohol intake

It is still controversial whether cigarette smoking is a risk factor for HCC [48, 49]. Many authors support the fact that heavy alcohol intake is strongly associated with HCC [49–51]. Alcohol also increases the risk for HCC in patients with chronic hepatitis B and C [102]. Therefore, abstinence of heavy alcohol drinking is probably beneficial in reducing the risk of HCC.

### NASH and HCC

Nonalcoholic steatohepatitis has been reported to affect 2–3% of the world's population, making it probably the most common liver disorder today [126]. Of these patients with NASH, 23% progress to liver cirrhosis in 10–15 years [127]. It has been observed that at the time of diagnosis, advanced fibrosis is already found in 30–40% of NASH patients, and 10–15% already have established cirrhosis. Since NASH may progress to cirrhosis (NASH being responsible for 70% of cryptogenic cirrhosis) [128], HCC development may be a part of the natural history of this disease [129]. A recent study by Chen et al. [58], which enrolled 23,820 residents in Taiwan with a 14-year follow-up, showed that extreme obesity (BMI  $\geq$  30 kg/m<sup>2</sup>) was independently associated with a fourfold risk of HCC in anti-HCV-positive subjects and a twofold risk of HCC in those without HBV or HCV after controlling for other metabolic components. Diabetes was associated with HCC in HBsAg-positive, anti-HCV-positive, or both HBsAg- and anti-HCV-negative subjects, with the highest risk in those with HCV infection [RR (multivariate-adjusted relative risk) 3.52, 95% CI 1.29–9.24] and lowest in HBV carriers (RR 2.27, 95% CI 1.10–4.66). The study also found more than 100-fold increased risk of HCC in HBV or HCV carriers with both diabetes and obesity, indicating synergistic effects of metabolic factors and hepatitis [58].

Patients who have NASH-related cirrhosis carry a substantial risk for early development of HCC and a poor prognosis because of the limited therapeutic options due to relevant comorbidity. This raises the issue of careful screening and surveillance for HCC in NASH patients who have advanced liver disease. Control of risk factors such as type II diabetes, obesity, and dyslipidemia is recommended as the first and most important approach in managing people with NAFLD and NASH and preventing development of cirrhosis and HCC [130].

Lifestyle measures such as dietary modifications based on the metabolic profile (obesity, type II diabetes, hyperlipidemia, and hypertension) and increasing physical activity in the form of aerobic exercise should be encouraged in all patients with NAFLD. There is currently a level II evidence to support the beneficial role of dietary restriction (mainly aimed at improving insulin sensitivity) and exercise in the management of NAFLD [131].

Since NAFLD and NASH are closely associated with insulin resistance, pharmacologic treatment has been targeted on insulin-sensitizing drugs. Several studies on the use of insulin-sensitizing drugs have been done. Chavez-Tapia et al. [132] conducted a systematic review of nine studies on the use of either metformin or thiazolidinediones and indicated that these drugs improve insulin resistance and liver function.

## Hemochromatosis and HCC

Hepatocellular carcinoma is long known to be associated with HH [63]. The risk for the development of HCC in patients with HH was estimated to be more than 200-fold increase in early publications [62, 133]. A subsequent Danish study also showed a 93-fold increase of HCC in HH [134]. However, the true incidence of HCC in HH may be achieved from population-based studies. Two such studies from the United States and Sweden showed a strong association of HCC and HH [64, 135]. In addition to HH, the hepatic iron overload owing to other causes, such as homozygous beta thalassemia [136] and the dietary form observed in South African blacks [137], is also associated with an increased risk of HCC. There is also evidence that marked iron overload in the setting of end-stage liver disease is also associated with HCC. However, the current data are inconclusive on the relation between mild or moderate iron overload associated with hepatitis C or alcoholic liver disease [138]. Because iron depletion by phlebotomy is safe and effective, it appears prudent to screen patients with chronic liver disease for iron overload and to institute iron depletion if iron overload is identified.

## Surveillance and diagnosis

### Surveillance

#### Recommendations

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Surveillance for HCC in high-risk populations is recommended (2a, B).

Surveillance for HCC should be performed by ultrasonography (US) and  $\alpha$ -fetoprotein (AFP) every 6 months (2a, B).

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### Rationale for surveillance

As described above, high-risk populations (e.g., cirrhosis with HBV or HCV infection) with HCC have been clearly identified by many epidemiological studies. However, the effectiveness of surveillance programs has still to be demonstrated through prospective RCTs, comparing the survival of participants with or without surveillance, though they may be susceptible to lead-time bias. To date, there is only one study that has proved the benefit of surveillance [139]. Zhang et al. [139] recruited 18,186 patients with chronic hepatitis due to HBV in China. The study revealed that surveillance with biannual AFP measurement and US reduced the mortality from HCC by 37% in spite of the fact that the compliance of scheduled tests was only 58.2%. It is desirable that this result should be validated in patients with other etiologies (e.g., chronic infection with HCV). However, it is highly

unlikely that any such randomized study could be undertaken now because the surveillance of patients with cirrhosis is widely accepted and recruiting patients to a nonscreening arm of such a study would be almost impossible.

### Who should be screened?

The efficacy of surveillance unambiguously depends on the incidence of HCC in the target population. However, because the risk of HCC in patients with chronic liver disease increases continuously with the number of risk factors, defining the population who should be screened is rather difficult. In addition, threshold for cost-effectiveness of surveillance program differs according to the economic situation of each country. Therefore, we recommend cirrhotic patients with HBV and HCV as candidates for surveillance at the present moment.

Recently, a study to better define the risk of chronic viral hepatitis by considering all important clinical and virologic features is ongoing. The results may be validated in the future [140].

### What modality should be used?

Diagnostic tests universally available to date are imaging modalities including US, CT, and MRI, and a tumor marker such as AFP. AFP is the most widely studied screening test for HCC [141–143]. However, it is known that a significant proportion of small HCCs (e.g.,  $\leq 3$  cm) do not secrete AFP to achieve a diagnostic level [142]. Furthermore, the level of AFP is elevated in patients with both HCC and chronic liver disease; thus, there is wide overlapping between the two groups [144, 145]. Most studies adopt a cutoff value of 20 ng/mL for AFP, with a sensitivity ranging from 49 to 71% and specificity from 49 to 86% in HCCs smaller than 5 cm [146–154]. Limitations in the sensitivity and specificity of AFP in surveillance of high-risk populations have led to the use of US as an additional method for the detection of HCC [142, 155–157].

Sensitivity of US is 78–90%, with 93% specificity [142, 148, 157]. In some countries such as Japan, concomitant measurement of des- $\gamma$ -carboxyprothrombin (DCP) and lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) reportedly increases the detectability of small HCC [146, 147, 149–151, 153, 154]. The use of CT or MRI with contrast media can attain a higher diagnostic accuracy than US, but their use is costly.

### Optimal interval for screening

The optimal interval of diagnostic tests in a surveillance program should be assessed from the view of cost-effectiveness because it is clear that more frequent tests can

detect HCC nodules of smaller size. Many studies have adopted an interval of 6 months between periodic diagnostic tests [155–157], although there are no randomized studies that have determined the optimal interval.

Thus, we propose periodic US and AFP measurements every 6 months as a minimum requirement. More frequent examinations, including new tumor markers such as DCP or AFP-L3 and CT/MRI, should be considered according to the medical circumstances of each country.

#### Tumor markers

##### Recommendations

$\alpha$ -Fetoprotein alone is not recommended for the diagnosis of HCC (1b, A).

Cutoff value of AFP should be set at 200 ng/mL for diagnosis (1b, A).

Simultaneous measurement of AFP and DCP provides higher sensitivity without decreasing specificity (1b, A).

Tumor makers are used in the diagnosis, prognosis, and evaluation of HCC. When a tumor marker is evaluated as a diagnostic test, its accuracy should be evaluated in terms of sensitivity, specificity, LR+, and LR+ [158]. Generally, the serum level of a tumor marker increases with the tumor size. Therefore, the range of tumor sizes should be considered in the evaluation of studies. A systematic review of studies published between 1982 and 2002 to evaluate the diagnostic accuracy of tumor markers for HCC is already available [159]. For the development of APASL consensus statement for HCC, we performed additional systematic review of studies published from 2003 to August 2008. Summary of recent studies that met the inclusion criteria is shown in Table 1 [160–169]. The results of the studies that evaluated AFP, DCP, and AFP-L3 were grossly compatible with the previous review.

#### $\alpha$ -Fetoprotein

$\alpha$ -Fetoprotein has served as a diagnostic test for HCC since the 1970s, when most patients with HCC were diagnosed at an advanced stage and with clinical symptoms [170]. A level of 500 ng/mL was considered diagnostic then. However, the usefulness of AFP as a diagnostic test in small HCCs is limited. According to this systematic review, the sensitivity, specificity, and LR+ of AFP in diagnosing HCC smaller than 5 cm in diameter ranged from 0.49 to 0.71, 0.49 to 0.86, and 1.28 to 4.03, respectively, with a cutoff value of 20 ng/mL and 0.04 to 0.31, 0.76 to 1.0, and 1.13 to 54.25, respectively, with a cutoff value of 200 ng/mL [159]. In a meta-analysis, AFP with a cutoff value of 200 ng/mL showed a better combined LR+ than with that of 20 ng/mL (5.85 vs. 2.45). The cutoff

value of AFP should be set at 200 ng/mL instead of 20 ng/mL in the diagnosis of HCC.

#### *Des- $\gamma$ -carboxyprothrombin*

Des- $\gamma$ -carboxyprothrombin, also known as prothrombin induced by vitamin K absence-II, is an abnormal prothrombin protein that is increased in the serum of HCC patients. Since the report by Liebman et al. [171], DCP has been recognized as not only a highly specific marker for HCC but also a predictor of prognosis of HCC patients [172, 173]. According to the systematic review, the sensitivity, specificity, and LR+ of DCP in HCC smaller than 5 cm in diameter ranged from 0.14 to 0.54, 0.95 to 0.99, and 6.86 to 29.7, respectively, with a cutoff value of 40 mAU/mL and 0.07 to 0.56, 0.72 to 1.0, and 3.56 to 13.0, respectively, with a cutoff value of 100 mAU/mL [159]. In the meta-analysis, DCP with a cutoff value of 40 mAU/mL showed a better combined LR+ than with that of 100 mAU/mL (12.60 vs. 4.91).

#### *Lens culinaris agglutinin-reactive fraction of AFP*

AFP-L3 is a fucosylated variant of AFP that reacts with lens culinaris agglutinin A and can differentiate an increase in AFP due to HCC from that in patients with benign liver disease [174–176]. According to the systematic review, the sensitivity, specificity, and LR+ of AFP-L3 in HCC smaller than 5 cm in diameter ranged from 0.22 to 0.33, 0.93 to 0.94, and 4.63 to 30.8, respectively, with a cutoff value of 10% and 0.21 to 0.49, 0.94 to 1.0, and 8.06 to 45.1, respectively, with a cutoff value of 15% [159]. In the meta-analysis, AFP-L3 with a cutoff value of 15% earns better combined LR+ than with a cutoff value of 10% (13.1 vs. 4.89).

#### *Glypican-3*

GPC3 is a heparan sulfate proteoglycan anchored to the plasma membrane. It has been reported that GPC3 messenger RNA levels are increased in HCC [177, 178]. To date, a lot of studies reported the usefulness of GPC3 in the differential diagnosis of HCC. However, the vast majority of reports were based on the immunohistochemical studies. Capurro et al. [164] reported sensitivity of 0.53 and specificity of 0.95 with a cutoff value of 117 ng/mL on a study of serum samples from 53 healthy individuals and 71 patients with hepatitis or HCC. More evidence is needed to recommend GPC3 in daily practice.

#### *Combination of tumor markers*

Simultaneous measurement of tumor markers improves sensitivity without decreasing specificity when they have a

**Table 1** Summary of studies on tumor markers for HCC published since 2003

Reference	Diagnostic test	Study design	Country	Patients with HCC		Control				
				<i>n</i>	Etiology	Characteristics of HCC	Modalities of diagnosis	<i>n</i>	Etiology	Characteristics of patients
Marrero et al. [160]	AFP, DCP	CC	USA	55	4% with HBV 46% with HCV 13% with ALT	NR	100% by pathology	152	7% with HBV 50% with HCV	32% with NL 34% with CH 35% with LC
Cui et al. [161]	AFP, DCP, GGTII	CC	China	120	81% with HBV 0% with HCV	26%, ≤3 cm	74% by pathology 26% by imaging	90	92% with HBV 1% with HCV	100% with LC
Wang et al. [162]	AFP, DCP	CC	China	61	46% with HBV 39% with HCV	38%, ≤2 cm 26%, 2–3 cm 36%, >3 cm	77% by pathology 23% by imaging	66	53% with HBV 42% with HCV	49% with CH 51% with LC
Sterling et al. [163]	AFP, AFP-L3	CC, CO	USA	74	100% with HCV	28%, <2 cm 68%, ≤5 cm	92% by imaging	298	100% with HCV	100% with LC
Capurro et al. [164]	AFP, GPC3	CC	Canada	34	NR	NR	NR	91	NR	58% with NL 20% with CH 22% with LC
Hippo et al. [165]	AFP, GPC3	CC	Japan	69	NR	NR	62% by pathology 38% by imaging	134	NR	28% with LC 72% with NL
Nguyen et al. [166]	AFP	CC	USA	163	100% with HCV	50%, ≤3.5 cm	53% by pathology 47% by imaging	149	100% with HCV	100% with LC
Soresi et al. [167]	AFP	CC	Italy	197	8% with HBV 75% with HCV	NR	NR	272	8% with HBV 77% with HCV	100% with LC
Arrieta et al. [168]	AFP	CC	Mexico	193	7% with HBV 30% with HCV	NR	100% by pathology	74	0% with HBV 45% with HCV	100% with LC
Paul et al. [169]	AFP	CC	India	101	NR	31%, ≤5 cm	NR	194	NR	100% with LC

AFP  $\alpha$ -fetoprotein, AFP-L3 lens culinaris agglutinin-reactive fraction of AFP, CC case-control study, CH chronic hepatitis, Co cohort study, DCP des- $\gamma$ -carboxy prothrombin, GGTII hepa-toma-specific band of serum  $\gamma$ -glutamyl transferase, HBV hepatitis B virus, HCV hepatitis C virus, LC liver cirrhosis, NL normal liver, NR not reported

weak association. Sensitivity, specificity, and LR+ of AFP and DCP in small HCCs were 0.48, 0.99, and 48 with a cutoff value of 200 ng/mL for AFP and 40 mAU/mL for DCP [179].

## Ultrasonography

### Recommendations

Ultrasonography is a screening test and not a diagnostic test for confirmation (2b, B).

Contrast-enhanced US (CEUS) is as sensitive as dynamic CT or dynamic MRI in the diagnosis of HCC (2b, B).

The evaluation of intranodular hemodynamics is important for the diagnosis of hepatic malignancies because the pathologic findings of hepatic malignancies are closely related to intranodular hemodynamics. B-mode US is useful for the screening of liver diseases but cannot demonstrate tumor vascularity. Color Doppler imaging reveals the arterial pulsating flows, such as a basket pattern flow and a “spot” pattern flow, for hepatic tumor differentiation [180, 181]. However, color Doppler US does not detect pulsatile flow in some HCCs. The reasons for this are as follows: first, color Doppler US cannot detect flows that are perpendicular to the sound field [182]. Second, the technique uses an estimate of the mean Doppler frequency shift at a particular position. On the contrary, power Doppler imaging measures the Doppler energy, which is based on the integrated power of the Doppler signal instead of its mean Doppler frequency shift. Some studies reported that power Doppler sonography was more sensitive for the depiction of blood vessels than color Doppler imaging [182, 183]. These techniques are noninvasive and inexpensive; however, they have some limitations including a low sensitivity of detecting the microflow in the nodules.

Efforts have been made to improve both sonography equipment and contrast agents to detect flow in tumors with more sensitivity [184, 185]. Sonography with an intra-arterial CO<sub>2</sub> microbubble contrast agent enables the detection of intratumoral hemodynamics. The differential diagnosis of hepatic tumors has become possible with contrast-enhanced, harmonic US based on tumor vascularity [186]. CEUS using Levovist bubbles involves the use of a nonlinear backscatter property of the resonant microbubbles produced by an intravenously administered contrast agent; it allows microflow imaging of nodules and eliminates clutter signals. However, Levovist bubbles easily collapse by ultrasound wave emission because of its fragile property. Therefore, Levovist-enhanced harmonic US images are basically obtained intermittently, and real-time images can be obtained within a short period of time at an early vascular phase and Kupffer imaging in the postvascular phase by a single sweep scan of the liver.

With the development of second-generation contrast media such as SonoVue or Sonazoid, which are made of a hard shell containing bubbles, contrast-enhanced, harmonic US has entered a new era. SonoVue and Sonazoid produce stable, nonlinear oscillations in the low-power acoustic field (i.e., low mechanical index) and supply great details of the second harmonic signals in real time. These contrast agents provide detailed perfusion features of the microvascular bed of the liver parenchyma and tumor during the vascular phase. Moreover, Kupffer imaging in the postvascular phase, which is stable for at least 3 h after injection and tolerable for multiple scanning, can be obtained in the low-power acoustic field because Sonazoid microbubbles are phagocytosed by Kupffer cells [187].

D’Onofrio et al. [188] reported that SonoVue-enhanced US detected hepatic malignancy as defects in the sinusoidal phase, with a sensitivity of 85%, specificity of 88%, positive predictive value of 92%, and negative predictive value of 77%. In our study, Sonazoid-enhanced harmonic US detected hepatic malignancy with a sensitivity of 95% (208/219), specificity of 93.3% (28/30), positive predictive value of 99% (208/210), and negative predictive value of 97.4% (38/39). These favorable results can be attributed to the characteristic features of Kupffer imaging.

Hatanaka et al. [189] reported that intranodular vascularity was detected in 99.4% of HCCs on contrast-enhanced, harmonic US. In the remaining 0.6% of HCCs, no blood signal was detected. In contrast, 98.9% of HCCs showed hyper- or isoperfusion on dynamic CT. Most of the HCCs showed HCC perfusion patterns on contrast-enhanced, harmonic US. The sensitivity and specificity of the HCC pattern were 96.6 and 94.4%, respectively. The positive and negative predictive values of this pattern were 97.7 and 91.9%, respectively.

SonoVue- or Sonazoid-enhanced harmonic US is a promising technique for the noninvasive characterization of hepatic tumors on the basis of the presence/absence of the characteristic features of each tumor type.

## CT, MRI, and other imaging modalities

### Recommendations

Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test result is abnormal (1a, A).

Hallmark of HCC during CT scan or MRI is the presence of arterial enhancement, followed by washout of the tumor in the portal-venous and/or delayed phases (1b, A).

Detection and characterization of focal lesions in the liver are critical for screening patients with chronic liver disease. US is the most widely used modality for HCC screening and surveillance, largely due to its relatively low

costs and ready accessibility [190]. US as a screening test in HBsAg carriers showed a sensitivity of 71% and a specificity of 93%, but its positive predictive value is only 14% [191]. Some reports suggest the use of new techniques such as CT or MRI as promising alternative surveillance tools [192, 193]. However, CT and MRI are not appropriate surveillance tests because they are too expensive, invasive (radiation with CT or intravenous injection), and have limited availability in community setting [194]. Additional use of dynamic CT or dynamic MRI is recommended in patients undergoing HCC screening while awaiting liver transplantation because it may be associated with the greatest gain in life expectancy [195–197].

Once a screening test result is abnormal or there is a clinical suspicion of HCC, imaging is very important for the diagnosis and staging of this tumor. The most reliable diagnostic tests are triple-phase, helical CT and triple-phase, dynamic, contrast-enhanced MRI, whereas hepatic angiography or angioassisted CT [CT hepatic arteriography (CTHA) and CT during arterial portography (CTAP)] has fallen out of favor in most practice settings except in Japan [198, 199]. The evaluation of blood supply in a hepatocellular nodule is extremely important to characterize the lesion because there are sequential changes in the supplying vessels and hemodynamic state during hepatocarcinogenesis [200]. Studies based on the findings at CTAP and CTHA with pathologic correlation have shown that as the grade of malignancy within the nodules evolves, there is gradual reduction of the normal hepatic arterial and portal venous supply to the nodule followed by an increase in the abnormal arterial supply via newly formed abnormal arteries (neovascularization) [201]. The hallmark of HCC during CT scan or MRI is the presence of arterial enhancement followed by washout of the tumor in the portal-venous and/or delayed phases [202]. The presence of arterial enhancement followed by washout has a sensitivity and specificity of 90 and 95%, respectively. However, 71% of patients with HCC will have arterial enhancement and washout on more than one test, whereas the rest do not have these features and, therefore, will require liver biopsy for the diagnosis of HCC [202].

A study of systematic review on the accuracies of US, spiral CT, and MRI in diagnosing HCC in patients with chronic liver disease revealed that the pooled estimates of the 14 US studies showed a sensitivity of 60% and specificity of 97%; for the ten CT studies, sensitivity was 68% and specificity 93%; and for the nine MRI studies, sensitivity was 81% and specificity 85% [203]. The operative characteristics of CT are comparable, whereas MRI is more sensitive. The performance of CT and MRI is affected by the size of the lesions [204, 205]. Although CT and MRI are reported to have a sensitivity of 60–94.4% and 58.5–93%, respectively, in tumors larger than 1 cm, their

sensitivities for detecting tumors smaller than 1 cm are reduced by 33–45 and 33–67%, respectively [204, 206–208]. Furthermore, small, arterially enhancing nodules are common in the cirrhotic liver, and majority of these nodules are benign [209–211]. Therefore, the most important issue remains the identification of small tumors because curative treatments can be optimally applied to improve outcome [212, 213]. If left alone, these tumors can grow aggressively and invasion can occur before tumors reach the 2-cm cutoff size for small HCC [202]. Thus, every attempt, including imaging follow-up or biopsy, should be made to characterize these nodules [205].

More recently, contrast agents other than gadolinium-based contrast media have been used for imaging HCC. Superparamagnetic iron oxide (SPIO) particles used alone [214] or in conjunction with gadolinium-based contrast agents [215–217] have been shown to be highly sensitive for the detection of HCC, particularly for small tumors. The reported sensitivity of double-contrast MRI (SPIO and gadolinium) for the detection of HCC measuring 1–2 cm in diameter is 92% [215, 216]. Several studies demonstrated that SPIO-enhanced MRI is useful in differentiating small HCCs from small, arterially enhancing pseudolesion [214, 218]. When considering only studies with whole-liver explant, the highest performance was achieved using double-contrast liver MRI with both gadolinium and SPIO, with sensitivity ranging from 78 to 80%, compared with multidetector-row CT (MDCT) with 65–79%, SPIO-enhanced MRI with 66–82% and dynamic MRI with 55–95% [204]. A more recent study of MRI with explant pathologic correlation demonstrated that gadobenate dimeglumine, which is a hepatobiliary agent, enhanced MRI has a sensitivity of 80–85% and a positive predictive value of 65–66% in the detection of HCC but is of limited value for detecting and characterizing lesions smaller than 1 cm [219].

Hypovascular nodules associated with liver cirrhosis include low- or high-grade dysplastic nodules (HGDN), early HCCs, and well-differentiated HCCs [201, 220–222]. There are significant overlaps in enhancement patterns on dynamic CT or dynamic MRI and in signal intensity on T2-weighted images [200, 201, 205]. Indeed, the noninvasive diagnostic criteria based on arterial hypervascularization in contrast-enhanced imaging techniques, published by the European Association for the study of the liver (EASL), are satisfied in only 61% of small nodules in cirrhosis [223]. Furthermore, imaging of 1- to 2-cm nodules would miss the diagnosis of HCC in up to 38% of cases. More recently, when hypovascular nodules are detected by MDCT and dynamic MRI, the guidelines published by the Japan Society of Hepatology recommend the use of Sonazoid-enhanced US and SPIO-enhanced MRI [224]. When uptake by Kupffer cells is

reduced in the Kupffer phase of SPIO-enhanced MRI, malignancy should be highly suspected [214, 225, 226].

#### *Other imaging modalities*

The less invasive imaging studies including dynamic CT, MRI, and CEUS have replaced conventional angiography for the diagnosis of HCC, except during chemoembolization of tumors or embolization for ruptured HCC. CTHA and CTAP have been used for preoperative evaluation of HCC, although they are uncommonly used except in Japan [227–229]. However, the benefit of CTHA and CTAP compared with MRI for the diagnosis of HCC is not yet clear because it is more invasive than MRI and does not appear to be more accurate than MRI [230]. The role of positron emission tomography (PET) in the diagnostic and staging evaluation of HCC still remains uncertain. Several studies have suggested a role for [<sup>18</sup>F]fluorodeoxyglucose (FDG)-PET scanning for the detection of primary HCCs, tumor staging, assessing response to therapy, and for predicting prognosis [231–233]. HCCs accumulate FDG to varying degrees (only 55–65% of tumors give a positive result by PET scanning), limiting the sensitivity of PET for primary tumors [234, 235]. However, FDG-PET seems to be a useful imaging modality for identifying extrahepatic metastases, although sensitivity is limited for lesions 1 cm or smaller [231, 236].

#### Diagnostic algorithm

##### Recommendations

Typical HCC can be diagnosed by imaging regardless of the size if a typical vascular pattern, i.e., arterial enhancement with portal-venous washout, is obtained on dynamic CT, dynamic MRI, or CEUS (2b, B).

Nodular lesions show an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal-venous washout, should undergo further examinations (2b, B).

#### *Diagnostic algorithm of hypervascular HCC*

Many institutions use US for screening tumors and MDCT or dynamic MRI for subsequent examinations. When a lesion is intensely enhanced in the early arterial phase and becomes low attenuation in the equilibrium phase, it may not be problematic to diagnose the lesion as HCC, but ruling out benign hypervascular lesions, such as focal nodular hyperplasia (FNH), and arteriportal (A-P) shunt is necessary for which uptake by Kupffer cells is best detected by SPIO-enhanced MRI or Sonazoid/Levovist-enhanced US. When high SPIO-enhanced MRI

signals or a defect in the Kupffer phase of Sonazoid/Levovist-enhanced US is confirmed, the lesion is diagnosed as HCC.

When a lesion shows low attenuation in the equilibrium phase, although not intensely enhanced in the early arterial phase on MDCT, it is sometimes possible that it is a hypervascular HCC if a more sensitive tool can be used; thus, Sonazoid/Levovist-enhanced US is necessary.

Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid MRI is a choice of test that is useful to differentiate HCC (even early HCC) from DN. For hypervascular nodules, it is necessary to rule out pseudo tumors, such as A-P shunt, and benign hypervascular lesions (FNH, adenoma, or angiomyolipoma), which usually require a biopsy. It has been reported that SPIO-enhanced MRI or CEUS may omit procedures such as CTHA, CTAP, and the most sensitive tools in diagnosing HCC and biopsy because their diagnostic ability for HCC is equivalent to CTHA/CTAP [237] (Fig. 1).

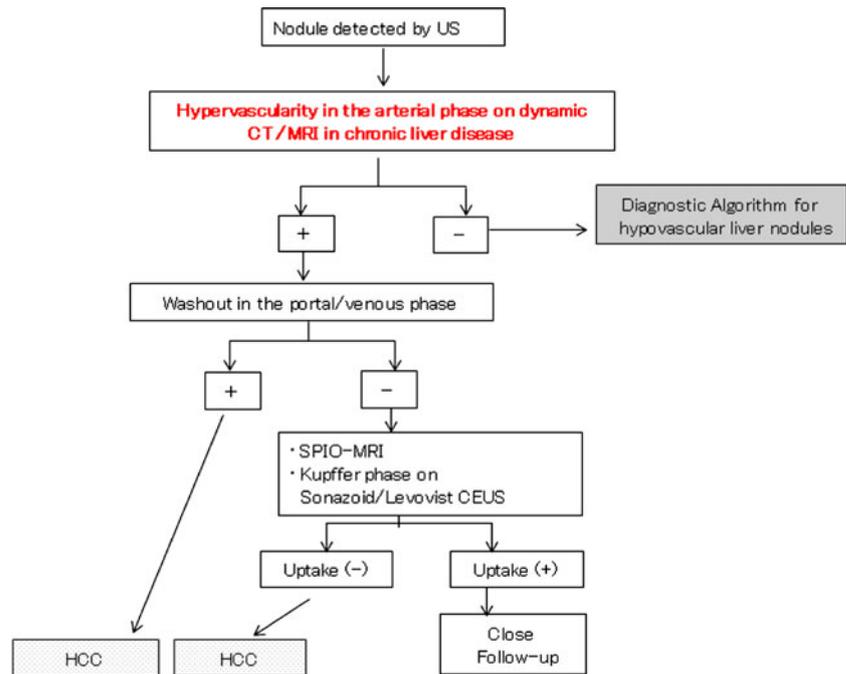
#### *Diagnostic algorithm of hypovascular HCC*

Among nodular lesions associated with liver cirrhosis, various nodules, such as low-grade dysplastic nodules (LGDN), which are considered to be precancerous lesions, HGDN, early HCC, and nodule-in-nodule liver cancer, are included as hypovascular nodules [220, 221, 238].

The most sensitive modality capable of objectively depicting the early carcinogenesis process among currently available imaging systems is (1) CTAP, followed by (2) CTHA [239, 240], (3) CEUS [241–243], and (4) SPIO-enhanced MRI [225, 244]. Portal blood flow may be maintained in some cases of DN and early HCC but reduced in other nodules, although the pathology remains because of early HCC, in which arterial blood flow has not yet increased. CTAP may detect the earliest initial change of HCC. The second earliest initial carcinogenic change is detected by CTHA or CEUS as an increase in intranodular arterial blood flow. However, both CTHA and CTAP are commonly performed in some countries only. In majority of Asia-Pacific region, CTHA and CTAP are not common diagnostic tests. Hypervascular lesions depicted as nodule-in-nodule or as entire hypervascular nodules can be interpreted as advanced cancer, although they are small.

MDCT and dynamic MRI are sensitive for the detection of arterial blood flow but are incapable of detecting arterial vascularity in some nodules depending on the acquisition timing, tumor location, and liver function; although the lesions are hypervascular on CEUS. Nodules intensely enhanced on MDCT and dynamic MRI can be assumed to already exhibit high intensity on T2-weighted MRI.

**Fig. 1** Diagnostic algorithm of hypervascular HCC



On the basis of this finding, lesions detected as hypovascular nodules by MDCT and dynamic MRI should be subjected to Sonazoid- or Levovist-enhanced US (CEUS) and/or SPIO-enhanced MRI in the diagnostic algorithm for nodules. CEUS is more sensitive for detecting arterial vascularity of target nodules than dynamic MRI [189, 243]. Thus, hypovascular nodules on dynamic CT may be diagnosed by CEUS. When uptake by Kupffer cells is reduced in the Kupffer phase of SPIO-enhanced MRI and CEUS, malignancy should be highly suspected. Although uptake is noted on SPIO-enhanced MRI, arterial blood flow may be increased in some cases on CEUS. When CTHA/CTAP is not available, such nodules should be closely followed up.

When Sonazoid or Levovist is used for CEUS, its combination with MDCT increases the accuracy of detecting intranodular arterial vascularity compared with that by a single method. Addition of the postvascular phase (Kupffer phase) allows an assumption of the degree of malignancy based on Kupffer function [189, 225, 244].

On the basis of this finding, when uptake is reduced in the Kupffer phase of SPIO-enhanced MRI or Kupffer phase of CEUS in nodules not depicted as hypervascular lesions by MDCT or dynamic MRI, the nodules should basically be regarded as HCC.

When uptake is noted on SPIO-enhanced MRI, close follow-up should be performed. When SPIO-enhanced MRI detects uptake and CEUS detects a malignant finding, i.e., increased arterial blood flow, the lesion should be regarded as malignant (Fig. 2).

## Treatment

### Liver resection and transplantation

#### Recommendations

Liver resection is a first-line curative treatment of solitary or multifocal HCC confined to the liver, anatomically respectable, and with satisfactory liver function reserve (2b, B)

Liver transplantation for HCC provides the best curative treatment of solitary HCC 5 or less cm or 3 or less tumor nodules, each 3 or less cm (Milan criteria) associated with Child-Pugh (C-P) class C cirrhosis (2b, B).

Bridge therapy using local ablation or chemoembolization may reduce dropout rate with long waiting time of more than 6 months, but there is no proven benefit in long-term survival or downstaging to allow expanded indication (2b, B).

### Liver resection

Hepatic resection has been the mainstay of curative treatment of HCC. Like surgical treatment of other cancers, surgical resection has never been compared with conservative or drug treatment in the management of HCC, but the survival data of resection from cohort studies are so compelling that it is unethical nowadays to consider such a trial. However, there is still some controversy regarding the indications for resection of HCC. HCC with diameter of less than 5 cm is regarded by some as the best candidate for resection because of increased risk of additional nodules or vascular invasion and consequently incomplete resection

with larger HCCs [245, 246]. However, it has been shown that patients with a large solitary HCC are suitable for successful resection and reasonable long-term survival results can be achieved [247, 248]. The presence of multiple tumor nodules or vascular invasion in major intrahepatic venous branches may be associated with worse prognosis; however, surgical resection is still considered the best treatment in terms of long-term survival [249, 250]. Bilobar HCC was considered a contraindication for resection, but recent studies suggest that patients with a predominant mass in one lobe and one or two small tumor nodules in the other lobe may benefit from combined resection of the predominant tumor and ablation for the contralateral nodules [251, 252]. The presence of distant metastasis, main portal vein thrombosis, or inferior vena cava thrombosis is a definite contraindication for resection.

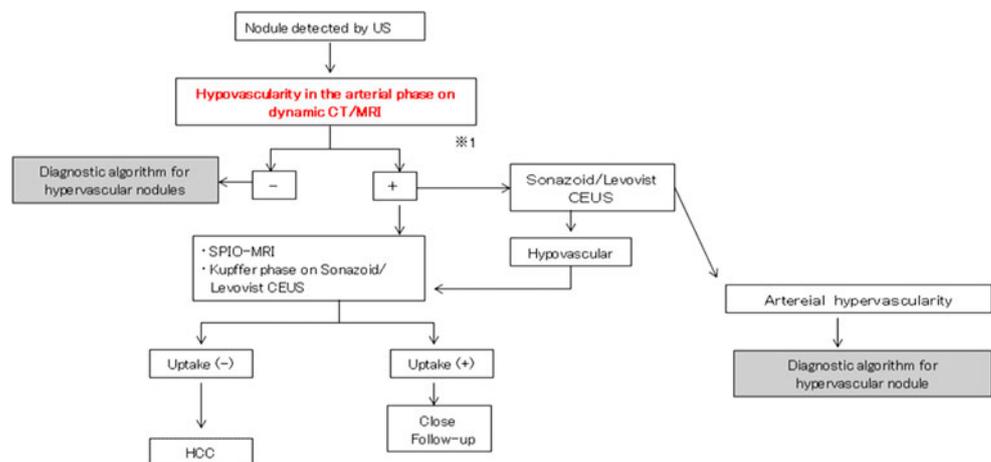
Hepatic resection for HCC is associated with a hospital mortality rate of less than 5% in major centers; however, the complication rate remains high, around 30–40% in large series [253–255]. Serious complications such as liver failure, postoperative bleeding, and bile leak occur in less than 5% of patients after hepatectomy nowadays [253–255]. However, less severe complications such as postoperative ascites, wound infection, and pneumonia remain common. Recently, laparoscopic liver resection has become popular, especially for minor resections or resection of the left lateral segment, and may reduce morbidity of liver resection [256]. However, thus far, no randomized trial comparing open and laparoscopic liver resection has been reported. The 5-year survival after resection of HCC is 35–50% in recent large cohort studies [257–259]. The long-term survival after hepatic resection depends on tumor characteristics. For small HCCs less than 5 cm in diameter, the 5-year survival rate is about 70% [260, 261]. However, recurrence occurs in 50–80% of patients at 5 years after resection, which is the main and long-term cause of deaths [262]. Despite several individual small

trials that have demonstrated potential benefit of some adjuvant therapies, evidence from such trials is weak and there is no well-proven effective adjuvant treatment to prevent recurrence so far [263]. Aggressive management of tumor recurrence by repeat resection, ablation, or transarterial chemoembolization (TACE) is currently the most practical way to prolong patient survival [263, 264].

#### Liver transplantation

Orthotopic liver transplantation is theoretically the best curative treatment of HCC patients because it involves the widest possible resection margins for cancer, removes the remnant liver at risk of malignant change, and restores hepatic function. The results of transplantation for advanced HCC have been disappointing, with a 5-year survival rate of around 20%, due to a high incidence of recurrent tumors presumably from circulating tumor cells associated with large HCCs [265]. In contrast, liver transplantation is a particularly effective treatment of patients with early HCC but advanced C-P class B or C cirrhosis when other effective treatments cannot be offered. It is now well accepted that C-P class C cirrhotic patients with solitary HCC of less than 5 cm or fewer than 3 tumor nodules each of size less than 3 cm and without radiological evidence of venous invasion or distant metastasis should be treated by transplantation [266]. These criteria, called Milan criteria, are the most widely used criteria for the inclusion of HCC patients for liver transplantation on the basis of which the 4-year survival rate of up to 75% could be achieved, with a recurrence rate lower than 15%. Although there have never been any randomized studies comparing liver transplantation to conservative management or other treatments, liver transplantation has been well accepted as treatment of choice in small HCCs associated with severe cirrhosis on the basis of the favorable survival observed in cohort studies. Recently, Yao et al. [267] suggested an expanded

**Fig. 2** Diagnostic algorithm of hypovascular HCC



criterion of solitary tumor 6.5 or less cm or three or fewer nodules with the largest lesion of 4.5 or less cm and total tumor diameter of 8 or less cm for liver transplantation. Their study showed that the long-term survival after transplantation for such patients were similar to that of liver transplantation for HCCs within the Milan criteria. Although the expanded criteria have been supported by some other studies [268], there are inadequate data in the literature to validate the long-term survival results using expanded criteria. Furthermore, it has to be noted that Yao's criteria were based on pathologic examination of explants rather than preoperative radiological imaging, which often underestimates the size of the tumor compared with measurement of tumor size in the explants. Currently, most centers worldwide still adopt Milan criteria in selection of patients for liver transplantation.

With the improvement in surgical techniques and better immunosuppressants to reduce the risk of graft rejection, the hospital mortality rate is less than 5% in major centers and the 5-year survival rate is about 60–75% [269–273]. Tumor recurrence after transplantation is lower than after resection for small HCC, and the 5-year disease-free survival rate is about 60–70%. The most important adverse prognostic factors of liver transplantation for HCC are the presence of microscopic venous invasion and histopathologic grading [272, 273]. Although the incidence of tumor recurrence is much lower after liver transplantation compared with partial hepatic resection, tumor recurrence is an important cause of long-term mortality after liver transplantation. Currently, there is no proven effective adjuvant therapy to reduce the risk of tumor recurrence.

The overall survival benefit of liver transplantation has been limited by the long waiting time for liver grafts for HCC patients. An intention-to-treat analysis has revealed a decrease in survival from 84 to 54% when the mean waiting time increased from 62 to 162 days [270]. Bridge treatments, including resection, percutaneous ablation, and TACE are commonly adopted while patients are on the waiting list to prevent tumor progression. However, the evidence for benefit of such bridge therapies is limited to retrospective case series, and it seems that bridge therapies are more likely to offer a benefit in patients with waiting time for grafts of more than 6 months [274]. Recently, live donor liver transplantation has emerged as a solution to shortage of liver grafts and is theoretically a more preferred choice for HCC patients because the waiting time is significantly reduced. However, the potential risk of donor hepatectomy (0.3–0.5% mortality) and relatively higher recipient complication (20–40%) need to be considered in offering such treatment [275]. Furthermore, live donor liver grafts are often small for size and the subsequent acute-phase injury, regeneration, and angiogenesis might increase the chance of tumor recurrence [276]. Whether

this has any clinical implication on the long-term survival of patients with live donor liver transplantation remains unclear.

Whether patients with C-P class A cirrhosis with preserved liver function and a small HCC of less than 5 cm in diameter should be treated with transplantation or resection is a controversial issue. Some authors recommended liver transplantation for small HCC even in C-P class A cirrhosis patients because of the superior, disease-free survival results after transplantation, whereas others argue that hepatic resection should be the first-line therapy for such patients because of the similar overall survival results of the two treatments and the shortage of organ donors [277]. Practically, it is difficult to perform a randomized trial comparing the two approaches, and the applicability of liver transplantation depends on local graft availability in different institutions. In centers where graft shortage is a severe problem, resection as first-line treatment followed by salvage transplantation for recurrent tumors or liver failure may be a reasonable strategy [278, 279].

## Ablation

### Recommendations

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Local ablation is an acceptable alternative to resection for small HCC (<3 cm) in C-P class A cirrhosis (2b, B).

Local ablation is a first-line treatment of unresectable, small HCC with 3 or fewer nodules in C-P class A or B cirrhosis (2b, B).

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Image-guided percutaneous ablation therapies, such as percutaneous ethanol injection [280–282], microwave coagulation [283], and radiofrequency ablation (RFA) [284–286] have been widely performed on patients with small HCC, generally for those with Child A or B cirrhosis with three or fewer tumors each 3 cm or less in diameter. They are potentially curative, minimally invasive, and easily repeatable for recurrence. Percutaneous ethanol injection was first reported in the early 1980s [280–282]. Survival rates of patients treated with percutaneous ethanol injection have been reported to be 38–60% at 5 years [287–290]. Local tumor progression rates after percutaneous ethanol injection have been reported to be 6–31% depending on the size of tumor [288, 289, 291, 292]. Percutaneous ethanol injection has been considered a safe procedure, with mortality and morbidity rates of 0–3.2% and 0–0.4%, respectively [289, 291, 293]. Percutaneous microwave coagulation, in which the cancer tissue is ablated by dielectric heat produced by microwave energy emitted from the inserted 16-gauge, bipolar-type electrode, was introduced into clinical practice in the 1990s and reported to improve local tumor control [283].

Since the introduction of RFA in the 1990s [284, 285], there has been a drastic shift from ethanol injection and

microwave coagulation to RFA [286]. RCTs proved that RFA is superior to ethanol injection in the treatment of small HCCs in terms of treatment response, recurrence, and overall survival [294–297], while some investigators reported that RFA had higher complication rates [295, 297]. An RCT demonstrated that the number of treatment sessions was fewer with RFA than with microwave coagulation [298], although the rates of complete therapeutic effect, major complications, and local tumor progression were not statistically different between the two therapies. In RFA, survival rates have been reported to be 39.9–68.5% at 5 years [299–304] and local tumor progression rates to be 2.4–16.9% [299–301, 304]. Mortality and morbidity rates of RFA have been reported to be 0.9–7.9% and 0–1.5%, respectively [300–305].

Various clinical studies, involving combination of transcatheter arterial chemoembolization followed by RFA [306] or hepatic arterial balloon occlusion during RFA [307], have been attempted to increase the ablated volume of RFA by reducing the cooling effect of the blood supply. Although the extension of necrotic area was achieved, it still remains unsettled whether these trials actually improve the prognosis or not.

There have been two RCTs to compare percutaneous ablation therapies with surgical resection. One study showed no statistical significant difference for recurrence and survival between percutaneous ethanol injection and resection [308]. Another trial showed that overall survival and disease-free survival rates were not statistically different between RFA and resection, but complications were more frequent and severe after surgery [309]. No RCTs have demonstrated that surgical resection is superior to percutaneous ablation. In nonrandomized comparative studies, hepatectomy was better than percutaneous ablation in one study [213] whereas others reported no significant difference between the two therapies [310–312]. Thus, it is difficult to conclude that surgical resection is the treatment of choice for resectable HCC.

### Transarterial chemoembolization

#### Recommendations

TACE is recommended as a first-line treatment for patients with unresectable, large/multifocal HCCs who do not have vascular invasion or extrahepatic spread (1b, A).

Selective TACE can be performed in early-stage patients in whom RFA is difficult to be performed because of tumor location or medical comorbidities (3, C).

Although the normal liver receives a dual blood supply from the hepatic artery and the portal vein, advanced HCC is supplied almost exclusively by the hepatic artery [313]. Hepatocarcinogenesis is a multistep process involving

parenchymal arterialization, sinusoidal capillarization, and development of neoangiogenesis, causing gradual change in portal to arterial blood supply [314]. The blood supply of HCCs varies according to their developmental stage and growth pattern. Although well-differentiated or early HCC is supplied by the portal vein and the hepatic artery, encapsulated nodular HCC is totally supplied by the hepatic artery [315]. This specific arterial vascular profile provides the rationale for therapeutic local chemotherapy and hepatic artery occlusion of HCCs by TACE [316]. TACE exploits the preferential hepatic arterial supply of HCC for targeted delivery of chemotherapeutic agents, usually mixed with lipiodol followed by embolization or reduction in arterial flow using various types of particles, while sparing the surrounding liver parenchyma [317]. This combination of highly concentrated chemotherapy and arterial embolization may induce highly concentrated chemotherapy and ischemic damage on the tumor, which is likely to be synergistic in producing tumor necrosis [318]. This reduction in arterial inflow causes not only ischemic necrosis within the tumors, which may increase tumor kill, but also significantly increases in tumor drug concentrations [319].

To date, multiple variations of TACE protocols remain in use throughout the world. Such variations revolve around the number and type of chemotherapeutic agents used, type of embolic materials, reliance on lipiodol, selectivity of catheter positioning, and the time interval between treatments [320]. However, a recent systematic review of cohort and randomized studies described the commonly used anticancer agents [321]. The most widely used single chemotherapeutic agent worldwide is doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), and mitomycin C (8%). Lipiodol, an iodinated ester derived from poppy-seed oil, has been found to remain more selectively in tumor nodules for few weeks to some months when injected into the hepatic artery. It is nearly always used as a vehicle to carry and localize chemotherapeutic agents inside the tumor (tumor-seeking agents) [322]. Hepatic artery obstruction is usually achieved by Gelfoam particles, but polyvinyl alcohol, starch microspheres, metallic coils, and autologous blood clots have also been used [321]. Gelfoam powder should not be used because this may cause biliary damage [323]. In a recent study, TACE performed with drug-eluting beads loaded with doxorubicin has been shown to modify the pharmacokinetics of the injected chemotherapy, thus reducing the drug-related adverse effects while maintaining the same therapeutic efficacy as TACE [324].

The procedure requires individualized protocol according to the hepatic functional reserve and tumor extent. Every effort should be made to preserve nontumorous liver parenchyma from chemoembolization. The best way to

maximize the treatment effect and to minimize procedure-related complications is to perform selective chemoembolization of all tumor feeders [325]. The dose of lipiodol and chemotherapeutic agent depends on the size and vascularity of the tumor. The end point for the mixture administration is stasis in tumor-feeding arteries or appearance of lipiodol in portal vein branches near the tumor [321, 326, 327]. In general, the end point of the TACE procedure is the visualization of the complete blockage of the tumor-feeding branch [327]. However, there is no agreement on the degree of embolization [320]. Sometimes, the development of extrahepatic collaterals supplying liver tumors prohibits effective control of the tumor by hepatic artery chemoembolization. Therefore, it is essential to check for extrahepatic collateral arterial supply to the HCC, especially when tumor is in subcapsular location or shows exophytic tumor growth [328]. When the hepatic artery and extrahepatic collaterals supply the tumor, additional chemoembolization of the extrahepatic collaterals can be tried to increase the therapeutic efficacy of TACE [329, 330].

TACE currently is considered as the mainstay of therapy for nonsurgical HCCs that are also ineligible for percutaneous ablation [320]. In 2002, two prospectively RCTs have demonstrated a significant survival benefit from TACE in selected HCC patients with preserved liver function and adequate performance status [331, 332]. A subsequent meta-analysis confirmed these findings [333]. On the basis of the results of these studies, the guidelines published by the EASL [334] and the American Association for Study of Liver Diseases [335] recommend TACE as a first-line, noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (level I). In addition, according to the guidelines published by the Japan Society of Hepatology [224], hepatectomy or TACE is recommended if there are two or three tumors of less than 3-cm diameter, and TACE or hepatic arterial infusion chemotherapy is recommended if there are more than four tumors. In addition, TACE can be performed in patients at the early stage in whom RFA cannot be performed because of tumor location (proximity to a gallbladder, biliary tree, or blood vessel) or medical comorbidities [198]. TACE is also the first-line therapy for downstaging tumors that exceed the criteria for transplantation [336–338]. Exclusion criteria in most trials are as follows: advanced liver disease (C-P class C), presence of vascular invasion or portal vein occlusion due to liver tumor, portosystemic shunt, hepatofugal blood flow, extrahepatic metastases, any contraindication to an arterial procedure (impaired clotting tests and renal failure), WHO performance stage 3 or 4, and end-stage tumorous disease (Okuda III) [339]. As the benefits of TACE procedure should not be offset by treatment-induced liver failure, patients who have liver decompensation should be

excluded. A European study revealed that only 12 of the 903 patients evaluated for HCC were suitable for TACE [332].

The main complication of TACE is the so-called postembolization syndrome. The postembolization syndrome is characterized by nausea, vomiting, abdominal pain, and fever, occurring in more than 50% of patients after the procedure [335]. Although postembolization syndrome is a self-limited condition, it is an important complication of TACE that prolongs hospitalization. The incidence of major complications has been reported to be less than 5%, including hepatic insufficiency, liver abscess, parenchymal infarction, intrahepatic aneurysm, pulmonary embolism, ischemic cholecystitis or gallbladder infarction, bone marrow depression, liver rupture, and gastric or duodenal ulceration [340]. Important predisposing factors are major portal vein obstruction, compromised hepatic functional reserve, biliary obstruction, previous biliary surgery, excessive amount of iodized oil, and nonselective embolization [341]. TACE does not induce significant liver dysfunction in patients with C-P class A or B cirrhosis despite embolization of relative proximal hepatic arteries [342]. Treatment-related mortality is less than 5% [198].

Several RCTs have focused on the impact of TACE for palliation of unresectable HCC. In two RCTs and one systematic review with meta-analysis, TACE was found to improve survival compared with supportive care in patients with unresectable HCC [331–333]. Untreated patients at an intermediate stage present a median survival of 16 months. Chemoembolization increases the median survival of these patients to 19–20 months according to RCTs and meta-analysis of pooled data, and is considered the standard of care [333, 343]. In the two RCTs, 1-, 2-, and 3-year survival rates both for Asian patients and for European patients were 57 versus 96%, 31 versus 77%, and 26 versus 47%, respectively [331, 332, 339].

TACE induces extensive tumor necrosis in more than 50% of the patients [333]. According to conventional WHO criteria, the reported rate of objective responses ranges between 16 and 60%, there being no difference between TACE and transarterial embolization [316, 333]. Less than 2% of treated patients achieve a complete response [333]. However, subsegmental TACE may increase percentage of complete necrosis compared with TACE through lobar branches of hepatic artery [326, 327]. Although there are many reports suggesting satisfactory survival rates at institutions where TACE is performed on follow-up when tumor growth is detected or the tumor marker levels increase, no RCT have compared repeated TACE at regular, short intervals of 2–3 months, with TACE repeated only when tumor growth is detected [316]. Only one retrospective study demonstrated that the group receiving regular TACE at intervals of 2 months, for at least three times, showed more common complications and

lower cumulative survival rates than group that received a TACE repeat only when tumor growth was detected.

## Systemic therapy

### Recommendations

Sorafenib is recommended for the treatment of advanced stage patients (portal vein invasion or extrahepatic spread) who are not suitable for locoregional therapy and who have C-P class A liver function (Ib, A).

Sorafenib may be used with caution in patients with C-P class B liver function (C).

Cytotoxic drugs are not routinely recommended but may be considered in highly selected patients whose general and hepatic conditions are adequate (3, C).

Recent advances in elucidating the molecular mechanisms of hepatocarcinogenesis have provided opportunities to develop molecular targeted therapy (MTT) for advanced HCC [344]. Sorafenib, an oral multikinase inhibitor, has shown survival benefit in two randomized, placebo-controlled trials [345, 346]. Several agents targeting tumor angiogenesis have also shown antitumor activity in patients with advanced HCC. Selected clinical trials of MTT for advanced HCC are summarized in Table 2.

### Sorafenib

Sorafenib inhibits the kinase activity of both wild-type B-raf ( $IC_{50} = 6$  nM) and mutant Raf<sup>V600E</sup> ( $IC_{50} = 38$  nM). In addition, sorafenib inhibits vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), c-kit, Flt-3, and RET ( $IC_{50} < 100$  nM) [347]. Therefore, both antiproliferative and antiangiogenic mechanisms may account for the antitumor effects of sorafenib.

Two randomized, placebo-controlled trials of sorafenib for the treatment of advanced HCC have been reported [345, 346]. The first trial (SHARP trial) was conducted primarily in Europe and the United States with the primary end point of overall survival. The second trial was designed originally as a bridging study to evaluate the overall efficacy and safety of sorafenib in the Asia-Pacific population. Both trials recruited HCC patients whose tumors were not eligible for or had progressed after surgery or locoregional therapy, and patients with C-P class A liver function and Eastern Cooperative Oncology Group (ECOG) performance score was 2 or less. The treatment regimen was the same (sorafenib 400 mg twice daily). Both trials were stopped early because per-protocol interim analysis indicated significant survival benefit of sorafenib over placebo.

Patients in the Asia-Pacific trial were younger, had more symptomatic disease (ECOG score = 1 or 2), and extrahepatic metastases. Despite these differences in the baseline prognostic features, the overall treatment efficacy

of sorafenib was similar between these two trials. The hazard ratios of overall survival and time to progression were 0.69 and 0.58 in the SHARP trial and 0.68 and 0.57 in the Asia-Pacific trial. Exploratory subgroup analyses of the two trials indicated that sorafenib treatment prolonged survival regardless of patients' age, performance status, and tumor burden (vascular invasion or extrahepatic spread). Time to symptomatic progression was not significantly different between patients who received sorafenib and patients who received placebo in either trial. Sorafenib is generally well tolerated. The most common drug-related adverse events included diarrhea, fatigue, hand-foot skin reaction, and rash/desquamation. These events occurred in 20–40% of patients, most of which were grade 1 or 2. The most common causes of treatment interruption or dose reduction were hand-foot skin reaction, rash, and diarrhea.

The efficacy and safety issues in patients with C-P class B cirrhosis need further clarification. A pharmacokinetic study suggested that patients with elevated bilirubin levels had lower tolerance to sorafenib treatment [348]. In the phase II trial of sorafenib for HCC, stable disease for 4 or more months was noted in 49% of patients with C-P class A cirrhosis ( $n = 98$ ) and 26% of patients with C-P class B cirrhosis ( $n = 38$ ). Patients with C-P class B cirrhosis had higher rate of elevated bilirubin (18 vs. 40%), encephalopathy (2 vs. 11%), and worsening ascites (11 vs. 18%) than patients with C-P class A cirrhosis, despite a similar incidence of all other adverse events and serious adverse events between these two groups of patients [349]. In the phase III SHARP trial, the incidence of serious hepatobiliary events was similar between the sorafenib group (11%) and the placebo group (9%). There are no clinical data for patients with C-P class C cirrhosis.

### Antiangiogenic MTT

Hepatocellular carcinoma is typically a hypervascular tumor. Many antiangiogenic MTT have been tested for the treatment of HCC. The monoclonal anti-VEGF antibody bevacizumab has been tested at a dosing schedule of 5 or 10 mg/kg every 14 days in patients with advanced HCC [350]. The objective response rate was 13% (1 complete and 5 partial response in 46 patients). The median overall survival and progression-free survival were 12.4 and 6.9 months, respectively. The results suggest that bevacizumab may have a role in the treatment of patients with advanced HCC. The most common grade 3 or 4 toxicities included hypertension (15%), bleeding (11%), and thrombosis (6%). Careful evaluation of bleeding risk, such as esophageal and gastric varices, is recommended before the use of bevacizumab or similar agents.

Sunitinib is a multitarget tyrosine kinase inhibitor that inhibits tumor angiogenesis through its inhibition of

**Table 2** Selected clinical trials of molecular targeted therapy for advanced HCC

	Treatment	Patient no.	Objective response	Median survival (months)		Level of evidence		
				OS	TTP			
Phase III trials								
Llovet et al. [345]	Sorafenib 400 mg bid	299	RR: 2.3% (7 PR) SD: 71%	10.7	$P < 0.001$	5.5	$P < 0.001$	1b
	Placebo	303	RR: 0.7% (2 PR) SD: 67%	7.9		2.8		
Cheng et al. [346]	Sorafenib 400 mg bid	150	RR: 2.7% (4 PR) SD: 55%	6.5	$P = 0.014$	2.8	$P < 0.001$	1b
	Placebo	76	RR: 1.32% (1 PR) SD: 29%	4.2		1.4		
Phase II trials								
Siegel et al. [350]	Bevacizumab 5–10 mg/kg every 2 weeks	46	RR: 13% (1 CR and 5 PR) SD: 65% (progression free at 6 months)	12.4		6.9 (PFS)		4
Zhu et al. [352]	Sunitinib 37.5 mg qd for 4 weeks, followed by 2-week rest	34	RR: 2.9% (1 PR) SD: 47%	9.9		4.0		4
Faivre et al. [353]	Sunitinib 50 mg qd for 4 weeks, followed by 2-week rest	37	RR: 2.7% (1 PR) SD: 35.1%	10.3		4.8		4
Hsu et al. [356]	Thalidomide 100 mg bid	63	RR: 6.3% (1 CR, 3 PR in 63 evaluable patients)	4.3		NA		4
Patt et al. [357]	Thalidomide 400 mg qd	32	RR: 3.2% (1 PR in 32 evaluable patients) SD: 31%	6.8		NA		4
Philip et al. [368]	Erlotinib 150 mg qd	38	RR: 9% (3 PR in 34 evaluable patients) SD: 50%	13		3.2		4
Thomas et al. [369]	Erlotinib 150 mg qd	40	RR: 0 SD: 42.5%	10.8		6.5		4
O'Dwyer et al. [370]	Gefitinib 250 mg qd	31	RR: 3.2% (1 PR) SD: 22.6%	6.5		2.8 (PFS)		4
Zhu et al. [371]	Cetuximab 400 mg/m <sup>2</sup> loading, then 250 mg/m <sup>2</sup> /week	30	RR: 0 SD: 16.7%	9.6		1.4 (PFS)		4

OS overall survival, TTP time to progression, RR response rate, SD stable disease, PR partial response, PFS progression-free survival

VEGFR and PDGFR activity [351]. Other targets of sunitinib include stem-cell factor receptor, colony-stimulating factor 1 (CSF-1), RET, and Flt-3. Two phase II trials of sunitinib for patients with advanced HCC reported a tumor stabilization rate of about 40% [352, 353]. Decreased tumor perfusion after sunitinib was demonstrated by dynamic computed tomography and magnetic resonance imaging, suggesting angiogenesis inhibition an important mechanism of its antitumor activity. Sunitinib at a daily dose of 50 mg was associated with a higher incidence of grade 3–5 toxicity, including ascites, edema, bleeding, and hepatic encephalopathy. At a daily dose of 37.5 mg, the most common toxicities included neutropenia, lymphopenia, thrombocytopenia, elevation of transaminases, fatigue, and

skin rash. A phase III, randomized trial comparing the antitumor activity of sunitinib and sorafenib is under way.

Thalidomide showed antiangiogenic properties in the early 1990s and has been tested for the treatment of various cancers [354, 355]. Several phase II studies have explored the efficacy of thalidomide as a treatment of advanced HCC [21, 356–358]. Objective response, defined as complete and partial responses, was found in approximately 5% of the patients. In addition, about 10–30% of patients had disease stabilization for more than 2–4 months after thalidomide treatment. Disease stabilization after thalidomide treatment was associated with decreased tumor vascularity [359] and decreased blood perfusion [360], suggesting that the disease-controlling effect of thalidomide is mediated at

least, in part, by its antiangiogenic effect. The most common drug-related toxicities in all the series were somnolence, constipation, dizziness, and skin rash. These adverse effects were generally manageable.

#### *Anti-EGFR MTT*

The EGFR signaling pathway may play a role in hepatocarcinogenesis [361]. Expression of transforming growth factor- $\alpha$ , an EGFR ligand, can be induced by hepatitis viral proteins and may act synergistically with viral infection in hepatocarcinogenesis [362–364]. Results of EGFR expression in HCC tumor tissues, mainly by immunohistochemistry, varied in different studies [365], and activating mutation of EGFR, the major determinant of efficacy of EGFR inhibitors in lung cancer [366], was rarely found in HCC tumor tissue [367]. Both small-molecule EGFR inhibitors and monoclonal anti-EGFR antibodies have been tested in small-scale trials for the treatment of advanced HCC, and the response rates and patient survival were not consistent among the studies [368–371]. Correlation of tumor response with expression of EGFR yielded inconclusive results [368, 369]. The most common toxicities of these inhibitors were similar, including skin rash, diarrhea, and fatigue. The therapeutic potential of EGFR inhibitors remains unclear and needs more clinical data to support their role.

#### *Cytotoxic therapy: single agent and combination*

The role of conventional cytotoxic chemotherapy is limited by its myelosuppressive toxicity, which is particularly threatening in patients with cirrhosis, hypersplenism, and cytopenia. Objective tumor response rate to single-agent cytotoxic therapies is usually less than 10%, and no survival benefit has been observed [372–376]. An earlier randomized trial comparing doxorubicin, 60–75 mg/m<sup>2</sup> every 3 weeks, with no treatment indicated a borderline improvement in overall survival (10.6 vs. 7.5 weeks) for patients who received doxorubicin [377]. However, 25% of patients died of doxorubicin-related complications, including infection and cardiotoxicity. The antitumor activity of newer cytotoxic agents, such as gemcitabine [378, 379], oxaliplatin [380], and capecitabine [381], has been modest, with single-agent tumor response rate of 10% or less (Table 2). The most common grade 3–4 toxicity was myelosuppression, which occurred in 10–40% of the patients. Combination regimens, such as cisplatin/IFN/doxorubicin/fluorouracil (PIAF), gemcitabine/oxaliplatin (GEMOX), or capecitabine/oxaliplatin (XELOX), can increase the objective response rate to approximately 20% but at the expense of increased treatment-related toxicities [382, 383]. Therefore, cytotoxic chemotherapy can be used with caution only in selected patients with advanced HCC.

#### *Future directions*

Combination therapy with MTT has been continually investigated. A randomized phase II trial of sorafenib plus doxorubicin versus doxorubicin alone reported superior median overall survival (13.7 vs. 6.5 months) and time to progression (8.6 vs. 4.8 months) in patients receiving sorafenib plus doxorubicin versus doxorubicin alone [384]. These results should be interpreted with caution because a sorafenib-alone arm was not included and high incidence of adverse events related to doxorubicin was noted. Many small-scale trials of combining MTT with cytotoxic chemotherapy have been reported [385–389]. However, the treatment efficacy in terms of tumor response rate and patient survival were similar to those reported for the cytotoxic regimens alone (Table 3) [372, 375–382]. A second approach is to combine MTT targeting different molecular pathways. Preliminary results of a phase II trial combining bevacizumab with erlotinib showed a response rate of 20% and a median overall survival of 15.5 months [390]. However, these preliminary results must be validated by larger randomized trials.

#### Treatment algorithm

In general, treatment choice for a solid tumor should be decided taking into account the probability of cure and invasiveness of the treatments. Selecting treatment options for HCC is rather complicated because one should consider the background hepatic function that significantly affects the overall survival. In addition, probability of local cure is not a good surrogate for survival in HCC because intrahepatic recurrence occurs frequently even after curative resection. Therefore, a treatment algorithm should include both tumor- and hepatic reserve-related factors and should be based on results of studies that adopted survival as the primary end point. We propose a treatment algorithm for HCC as shown in Fig. 3.

#### Tertiary prevention

##### Recommendations

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- Interferon may be effective in reducing the recurrent HBV-related HCC after curative ablation of HCC (1b, B).
  - Lamivudine may be effective in reducing the recurrent HBV-related HCC after curative ablation of HCC (2c, C).
  - Interferon-based antiviral treatments after complete removal or ablation of HCV-related HCC may reduce HCC recurrence and improve survival (1b, B).
- 

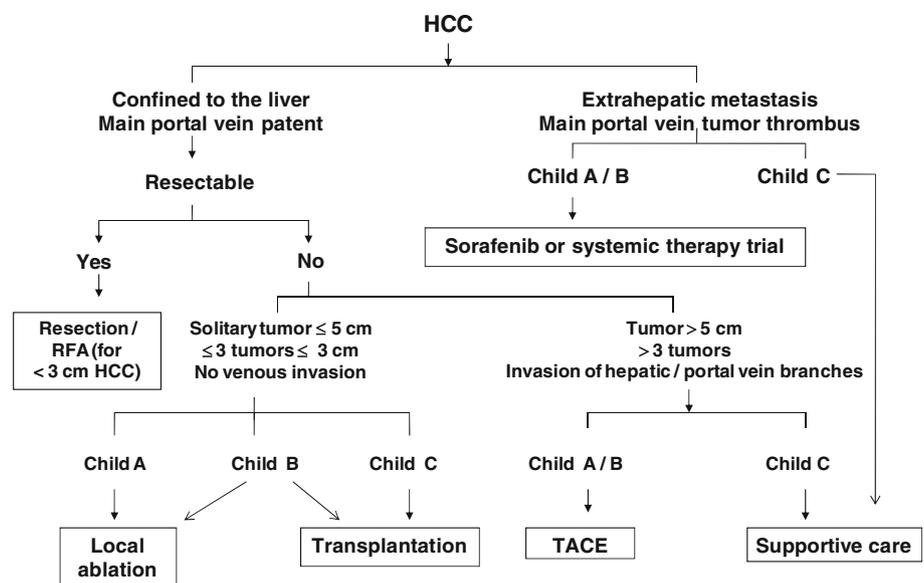
#### *Tertiary prevention for HBV-related HCC*

*Interferon* The short-term outcome of liver resection has dramatically improved over the last decade. The long-term

**Table 3** Selected clinical trials of cytotoxic therapy for advanced HCC

Treatment	Patient no.	Objective response	Median survival (months)		Level of evidence
			OS	TTP	
<b>Yeo et al. [375]</b>					
Doxorubicin 60 mg/m <sup>2</sup> on day 1, every 3 weeks	94	RR: 10.5% (9 PR) SD: 39.4%	6.8	NA	1b
Doxorubicin 40 mg/m <sup>2</sup> on day 1, every 3 weeks Cisplatin 20 mg/m <sup>2</sup> Interferon $\alpha$ -2b 5 MU/m <sup>2</sup> 5-FU 400 mg/m <sup>2</sup> , days 1–4, every 3 weeks	94	RR: 20.9% (19 PR) SD: 37.2%	8.7	NA	
<b>Gish et al. [376]</b>					
Doxorubicin 60 mg/m <sup>2</sup> on day 1, every 3 weeks	222	RR: 2.7% (6 PR) SD: NA	7.4	2.3	1b
Nolatrexed 800 mg/m <sup>2</sup> /day, days 1–3, every 3 weeks	222	RR: 0.9% (1 PR) SD: NA	5.1	2.8	
<b>Yang et al. [378]</b>					
Gemcitabine 1,250 mg/m <sup>2</sup> , days 1, 8, 15, every 4 weeks	28	RR: 17.8% (5PR) SD: 25%	4.3	2.8	4
<b>Guan et al. [379]</b>					
Gemcitabine 1,250 mg/m <sup>2</sup> , days 1, 8, every 3 weeks	48	RR: 2.1% (2 PR) SD: 43.9%	3.2	1.5	4
<b>Yen et al. [380]</b>					
Oxaliplatin 100 mg/m <sup>2</sup> every 2 weeks	36	RR: 2.8% (1 PR) SD: 47%	6	2	4
<b>Patt et al. [381]</b>					
Capecitabine 2,000 mg/m <sup>2</sup> /day, days 1–14, every 3 weeks	37	RR: 11% (1 CR, 3 PR) SD: 11%	10.1	NA	4

OS overall survival, TTP time to progression, RR response rate, SD stable disease, PR partial response

**Fig. 3** Treatment algorithm of HCC

prognosis of HCC treated by hepatectomy remains a concern because of frequent development of tumor recurrence, which is the main cause of death in addition to concomitant

hepatic decompensation. IFN has tumoricidal effect against a number of tumors including HCC. An RCT was performed to evaluate the safety and efficacy of adjuvant IFN

therapy after hepatic resection in a group of patients with predominantly HBV-related HCC [391]. The relative risk of death for IFN treatment was 0.42 (95% CI 0.17–1.05,  $P = 0.063$ ). Subset analysis showed that adjuvant IFN had no survival benefit for pTNM stage I/II tumor (5-year survival 90% in both groups,  $P = 0.917$ ) but prevented early recurrence and improved the 5-year survival of patients with stage III/IVA tumor from 24 to 68% ( $P = 0.038$ ). HCC recurrence after locoablative treatment modalities is also common. Although candidates for medical ablation usually exhibit compensated hepatic functional status, the frequent recurrence of HCC after successful ablation contributes to short-term survival. A randomized controlled study with small sample size was conducted to evaluate the effectiveness of IFN therapy in preventing HCC recurrence after successful medical ablation therapy for primary tumors [392]. The cumulative HCC recurrence rate of the patients treated with IFN-alfa and the control group was 25 and 40% at the end of 1 year and 47 and 90% at the end of 4 years, respectively ( $P = 0.0135$ ). Furthermore, this study also showed that the prevention of HCC recurrence using IFN-alfa was effective in HBV-related HCC [392].

**Lamivudine** A retrospective study was conducted to evaluate the efficacy with or without using LAM in patients following curative ablation of HBV-related HCC [393]. Cumulative recurrence rates of HCC were not significantly different between two groups ( $P = 0.622$ ). However, median C-P score at the time of HCC recurrence was significantly different in the control group ( $P = 0.005$ ). The cumulative survival rates of patients in the LAM group tended to be higher than those of patients in the control group ( $P = 0.063$ ) [393]. The outcome of LAM treatment of patients with controlled HCC in terms C-P score and survival compared with a matched, LAM-untreated cohort showed no significant difference in the cumulative incidence of HCC recurrence and survival between the two groups [394]. However, there was a significant difference in the cumulative incidence of death due to liver failure ( $P = 0.043$ ). A significant improvement in liver function was achieved by LAM treatment, even in patients with HCC. These results suggest that LAM treatment of patients with HCC may prevent death due to liver failure [394].

Recent randomized, placebo-controlled trial by Jang et al. [395] also showed that preemptive LAM therapy in patients receiving TACE significantly reduced the incidence of HBV reactivation ( $P = 0.002$ ), overall hepatitis ( $P = 0.021$ ), and severe hepatitis ( $P = 0.035$ ) due to HBV reactivation after repeat TACE. However, the prevention of HCC by preemptive LAM therapy was not shown because of advanced stage of HCC in patients receiving TACE in that trial [395]. Further prospective, randomized studies

using a larger number of patients are required to assess its role in the tertiary prevention of HCC.

#### *Tertiary prevention of HCV-related HCC*

Hepatocellular carcinoma is characterized by very frequent recurrence even after successful initial treatments, either surgical resection or medical ablation, and the risk of recurrence remains high for many years. Recurrence is particularly frequent with HCV-related HCC, and a substantial proportion of recurrence, especially in late phase, is thought to represent de novo, or multicentric, hepatocarcinogenesis [396–398]. Therefore, it could be reasonably assumed that antiviral therapy would reduce the overall incidence of recurrence by preventing de novo carcinogenesis. Indeed, several small-sized RCTs, performed in Japan or Taiwan, showed that the incidence of recurrence was reduced in HCV-related HCC by IFN therapy subsequent to initial HCC treatment [392, 399, 400].

Other RCTs, also performed in Japan and Taiwan, failed to find a significant delay in the first recurrence with IFN therapy, but the second or third recurrence was significantly reduced especially in sustained responders and the overall survival was improved [401, 402]. Another RCT in Italy did not detect effects of IFN therapy on early recurrence but late recurrence, with more than 2 years of interval, seemed to be reduced among IFN responders [403]. These data are compatible with the hypothesis that de novo carcinogenesis was prevented by successful antiviral therapy. On the other hand, two reports on long-term observation of recurrence after IFN therapy following HCC treatment [404, 405] showed that recurrence rate in IFN-treated patients increased over time, suggesting that the growth of residual microscopic tumors had been delayed by IFN (in fact, the two presumed mechanisms are not necessarily mutually exclusive). Most of these studies used IFN monotherapy and suffered from low sustained response rates because most patients had advanced fibrosis or cirrhosis. Preventive effects of IFN on HCC recurrence are yet to be reevaluated using current more efficient protocols.

Microscopic, intrahepatic residual tumors, including intrahepatic metastases, are a possible cause of HCC recurrence. Theoretically, adjuvant chemotherapy may reduce or delay such recurrence, but few chemotherapeutic agents have been shown to be effective against HCC and not a few of them may be hepatotoxic. Hasegawa et al. [406] reported an RCT using oral administration of uracil-tegafur after curative hepatic resection but found no beneficial effects on recurrence and a possible adverse effect on overall survival. In 1966, Muto et al. [407] reported that administration of polyprenic acid, an acyclic retinoid, reduced recurrence of HCC in an RCT. Updated, long-term

data were subsequently published [408], postulating that the eradication of premalignant or latent malignant clones is the mechanism of action. The effect is, however, yet to be confirmed in a large-scale RCT. Vitamin K<sub>2</sub> was reported to inhibit HCC development among female patients with cirrhosis, who had received the vitamin for the prevention of osteoporosis [122]. A small RCT suggested that vitamin K<sub>2</sub> was effective in suppressing HCC recurrence and may improve survival [124]. However, subsequent, large-scale RCT met with an early termination because of lacking evidence of effects.

#### *Viral-unrelated tertiary prevention of HCC*

**Vitamin K<sub>2</sub>** Apart from its use as a primary preventive agent for HCC, the use of vitamin K<sub>2</sub> as secondary preventive agent has also been investigated. Otsuka et al. [123] examined the biological effects of extrinsic supplementation of vitamin K<sub>2</sub> in HCC cells in vitro and in vivo. Administration of vitamin K<sub>2</sub> to nude mice inoculated with liver tumor cells reduced both tumor growth and weight loss. It was concluded that, similar to an acyclic retinoid, vitamin K<sub>2</sub> may be a promising therapeutic means for the management of HCC.

A pilot study by Mizuta et al. [124] on HCC patients who had undergone either percutaneous local ablation or surgery suggested that menatetrenone, a vitamin K<sub>2</sub> analogue, may have a suppressive effect on the recurrence of HCC and a beneficial effect on survival.

However, a later study (albeit smaller) by Hotta et al. [125] demonstrated that vitamin K<sub>2</sub> may not be as useful for the prevention of HCC recurrence as for primary prevention.

**Sho-saiko-to** Sho-saiko-to (SST or TJ9), a traditional (Chinese) herbal medicine, was demonstrated to improve liver function tests in patients with chronic active hepatitis in a multicenter, cross-over RCT by Hirayama et al. [409]. A later prospective, randomized (albeit nonblind) study by Oka et al. [410] could elucidate the use of TJ-9 in preventing the development of HCC in patients with cirrhosis, particularly in patients without HBsAg. Successive studies continued to confirm that TJ-9 could protect experimental liver injury caused by D-galactosamine and liver fibrosis by inhibition of lipid peroxide formation in liver cells [411, 412].

**Juzen-taiho-to (TJ-48)** A recently published study on Juzen-taiho-to, a traditional (Japanese) herbal formulation similar to Sho-saiko-to, presented new information on its anticancer effect in humans [413]. In this study, the administration of TJ-48 improved intrahepatic, recurrence-free survival after surgical treatment of HCC and its

protective effects were probably due to reduction in oxidant and cytokine production by Kupffer cells.

#### References

1. Centre for Evidence-Based Medicine. Levels of evidence 2001 [cited 1 Dec 2008]. <http://www.cebm.net/index.aspx?o=1025>
2. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, vol. VIII. Lyon: IARC Scientific; 2002. Publication No.: 155
3. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. *Lancet* 1981;2:1129–1133
4. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993; 328:1797–1801
5. Chen CJ, Liang KY, Chang AS, Chang YC, Lu SN, Liaw YF, et al. Effects of hepatitis B virus, alcohol drinking, cigarette smoking and familial tendency on hepatocellular carcinoma. *Hepatology* 1991;13:398–406
6. 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;347:168–174
7. Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, et al. Additive effect modification of hepatitis B surface antigen and e antigen on the development of hepatocellular carcinoma. *Br J Cancer* 1996;73:1498–1502
8. Lu SN, Lin TM, Chen CJ, Chen JS, Liaw YF, Chang WY, et al. A case-control study of primary hepatocellular carcinoma in Taiwan. *Cancer* 1988;62:2051–2055
9. Lin TM, Chen CJ, Lu SN, Chang AS, Chang YC, Hsu ST, et al. Hepatitis B virus e antigen and primary hepatocellular carcinoma. *Anticancer Res* 1991;11:2063–2065
10. Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005;97:265–272
11. Chan HL, Tse CH, Mo F, Koh J, Wong VW, Wong GL, et al. High viral load and hepatitis B virus subgenotype Ce are associated with increased risk of hepatocellular carcinoma. *J Clin Oncol* 2008;26:177–182
12. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65–73
13. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006;101:1797–1803
14. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Chung H, et al. Evaluation of posttreatment response of hepatocellular carcinoma with contrast-enhanced coded phase-inversion harmonic US: comparison with dynamic CT. *Radiology* 2001; 221:721–730
15. Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100:1134–1143
16. Yuen MF, Sablon E, Yuan HJ, Wong DK, Hui CK, Wong BC, et al. Significance of hepatitis B genotype in acute exacerbation, HBsAg seroconversion, cirrhosis-related complications, and hepatocellular carcinoma. *Hepatology* 2003;37:562–567

17. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000;118:554–559
18. Sumi H, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, et al. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. *Hepatology* 2003;37:19–26
19. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, et al. A case–control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. *Hepatology* 2001;33:218–223
20. Fang ZL, Yang J, Ge X, Zhuang H, Gong J, Li R, et al. Core promoter mutations (A(1762)T and G(1764)A) and viral genotype in chronic hepatitis B and hepatocellular carcinoma in Guangxi, China. *J Med Virol* 2002;68:33–40
21. Chiou HE, Wang TE, Wang YY, Liu HW. Efficacy and safety of thalidomide in patients with hepatocellular carcinoma. *World J Gastroenterol* 2006;12:6955–6960
22. Chen BF, Liu CJ, Jow GM, Chen PJ, Kao JH, Chen DS. High prevalence and mapping of pre-S deletion in hepatitis B virus carriers with progressive liver diseases. *Gastroenterology* 2006;130:1153–1168
23. Chen CH, Hung CH, Lee CM, Hu TH, Wang JH, Wang JC, et al. Pre-S deletion and complex mutations of hepatitis B virus related to advanced liver disease in HBeAg-negative patients. *Gastroenterology* 2007;133:1466–1474
24. Chou YC, Yu MW, Wu CF, Yang SY, Lin CL, Liu CJ, et al. Temporal relationship between hepatitis B virus enhancer II/basal core promoter sequence variation and risk of hepatocellular carcinoma. *Gut* 2008;57:91–97
25. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003;124:327–334
26. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463–472
27. Tradati F, Colombo M, Mannucci PM, Rumi MG, De Fazio C, Gamba G, et al. A prospective multicenter study of hepatocellular carcinoma in Italian hemophiliacs with chronic hepatitis C. The Study Group of the Association of Italian Hemophilia Centers. *Blood* 1998;91:1173–1177
28. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995;21:650–655
29. Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, et al. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. *Am J Epidemiol* 2003;157:674–682
30. Serfaty L, Aumaitre H, Chazouilleres O, Bonnard AM, Rosmorduc O, Poupon RE, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998;27:1435–1440
31. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. *Hepatology* 1998;28:1687–1695
32. Fattovich G, Ribero ML, Pantalena M, Diodati G, Almasio P, Nevens F, et al. Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in Europe. *J Viral Hepat* 2001;8:206–216
33. 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;25:754–758
34. Bruno S, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007;46:1350–1356
35. Chuang WL, Chang WY, Lu SN, Su WP, Lin ZY, Chen SC, et al. The role of hepatitis B and C viruses in hepatocellular carcinoma in a hepatitis B endemic area. A case–control study. *Cancer* 1992;69:2052–2054
36. Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. *Cancer* 1999;85:2132–2137
37. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. *J Gastroenterol Hepatol* 1997;12:S294–S308
38. Yu MC, Tong MJ, Coursaget P, Ross RK, Govindarajan S, Henderson BE. Prevalence of hepatitis B and C viral markers in black and white patients with hepatocellular carcinoma in the United States. *J Natl Cancer Inst* 1990;82:1038–1041
39. Tagger A, Donato F, Ribero ML, Chiesa R, Portera G, Gelatti U, et al. Case–control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. *Int J Cancer* 1999;81:695–699
40. Kaklamani E, Trichopoulos D, Tzonou A, Zavitsanos X, Kountantaki Y, Hatzakis A, et al. Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. *JAMA* 1991;265:1974–1976
41. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002;360:1921–1926
42. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US–Canadian multicenter study. *J Hepatol* 2007;47:527–537
43. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108
44. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology* 1995;22:1027–1033
45. Lee CM, Lu SN, Changchien CS, Yeh CT, Hsu TT, Tang JH, et al. Age, gender, and local geographic variations of viral etiology of hepatocellular carcinoma in a hyperendemic area for hepatitis B virus infection. *Cancer* 1999;86:1143–1150
46. Lu SN, Su WW, Yang SS, Chang TT, Cheng KS, Wu JC, et al. Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan. *Int J Cancer* 2006;119:1946–1952
47. Yoshida H, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, et al. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. *Gut* 2004;53:425–430
48. Yu MC, Tong MJ, Govindarajan S, Henderson BE. Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. *J Natl Cancer Inst* 1991;83:1820–1826
49. Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case–control study in Fukuoka, Japan. *Int J Cancer* 1992;51:509–514
50. Mohamed AE, Kew MC, Groeneveld HT. Alcohol consumption as a risk factor for hepatocellular carcinoma in urban southern African blacks. *Int J Cancer* 1992;51:537–541

51. Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. *Am J Epidemiol* 2002;155:323–331
52. Chiesa R, Donato F, Tagger A, Favret M, Ribero ML, Nardi G, et al. Etiology of hepatocellular carcinoma in Italian patients with and without cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2000;9:213–216
53. Wang JS, Huang T, Su J, Liang F, Wei Z, Liang Y, et al. Hepatocellular carcinoma and aflatoxin exposure in Zhuqing Village, Fusui County, People's Republic of China. *Cancer Epidemiol Biomarkers Prev* 2001;10:143–46
54. Chen CJ, Wang LY, Lu SN, Wu MH, You SL, Zhang YJ, et al. Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. *Hepatology* 1996;24:38–42
55. Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. *Cancer Epidemiol Biomarkers Prev* 1994;3:3–10
56. Ross RK, Yuan JM, Yu MC, Wogan GN, Qian GS, Tu JT, et al. Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. *Lancet* 1992;339:943–946
57. Wang LY, Hatch M, Chen CJ, Levin B, You SL, Lu SN, et al. Aflatoxin exposure and risk of hepatocellular carcinoma in Taiwan. *Int J Cancer* 1996;67:620–625
58. Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. *Gastroenterology* 2008;135:111–121
59. London WT, Evans AA, McGlynn K, Buetow K, An P, Gao L, et al. Viral, host and environmental risk factors for hepatocellular carcinoma: a prospective study in Haimen City, China. *Intervirology* 1995;38:155–161
60. Evans AA, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. *Cancer Epidemiol Biomarkers Prev* 2002;11:369–76
61. Yu MW, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, et al. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. *J Natl Cancer Inst* 2000;92:1159–1164
62. Bradbear RA, Bain C, Siskind V, Schofield FD, Webb S, Axelsen EM, et al. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. *J Natl Cancer Inst* 1985;75:81–84
63. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985;313:1256–1262
64. Elmberg M, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003;125:1733–1741
65. Chen DS, Hsu NH, Sung JL, Hsu TC, Hsu ST, Kuo YT, et al. A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. *JAMA* 1987;257:2597–2603
66. Hsu HM, Chen DS, Chuang CH, Lu JC, Jwo DM, Lee CC, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface antigen-carrier mothers. *JAMA* 1988;260:2231–2235
67. Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996;276:906–908
68. Chang MH, Shau WY, Chen CJ, Wu TC, Kong MS, Liang DC, et al. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. *JAMA* 2000;284:3040–3042
69. Kao JH, Chen DS. Recent updates in hepatitis vaccination and the prevention of hepatocellular carcinoma. *Int J Cancer* 2002;97:269–271
70. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med* 1996;334:1422–1427
71. Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999;29:971–975
72. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon- $\alpha$  treated and untreated patients with HBeAg-negative chronic hepatitis B. *J Hepatol* 2001;34:306–313
73. Lampertico P, Del Ninno E, Vigano M, Romeo R, Donato MF, Sablon E, et al. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. *Hepatology* 2003;37:756–763
74. van Zonneveld M, Honkoop P, Hansen BE, Niesters HG, Murad SD, de Man RA, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology* 2004;39:804–810
75. Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology* 1997;113:1660–1667
76. Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. *Hepatology* 2001;34:139–145
77. Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. *J Hepatol* 2007;46:45–52
78. Craxi A, Camma C. Prevention of hepatocellular carcinoma. *Clin Liver Dis* 2005;9:329–346
79. Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. *Hepatology* 2006;43:915–922
80. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. *Gastroenterology* 2004;127:1372–1380
81. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. *Oncology* 2002;62(Suppl 1):8–17
82. Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. *Intervirology* 2006;49:7–17
83. Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. *Lancet* 1991;338:914–915
84. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001;345:1452–1457
85. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon- $\alpha$  on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. *Lancet* 1995;346:1051–1055
86. Nishiguchi S, Shiomi S, Nakatani S, Takeda T, Fukuda K, Tamori A, et al. Prevention of hepatocellular carcinoma in patients

- with chronic active hepatitis C and cirrhosis. *Lancet* 2001; 357:196–197
87. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. *J Hepatol* 1996; 24:141–147
  88. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: a national surveillance program of cirrhotic and non-cirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. *Inhibition of Hepatocarcinogenesis by Interferon Therapy*. *Ann Intern Med* 1999;131:174–181
  89. Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005;142:105–114
  90. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, et al. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. European Concerted Action on Viral Hepatitis (EUROHEP). *J Hepatol* 1997;27:201–205
  91. Papatheodoridis GV, Papadimitropoulos VC, Hadziyannis SJ. Effect of interferon therapy on the development of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a meta-analysis. *Aliment Pharmacol Ther* 2001; 15:689–698
  92. Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. *J Hepatol* 2001;34:593–602
  93. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. *Ann Intern Med* 1998; 129:94–99
  94. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; 29:1124–1130
  95. Shindo M, Ken A, Okuno T. Varying incidence of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C responding differently to interferon therapy. *Cancer* 1999; 85:1943–1950
  96. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. *Ann Intern Med* 2000;132:517–524
  97. Yu ML, Lin SM, Chuang WL, Dai CY, Wang JH, Lu SN, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. *Antivir Ther* 2006;11:985–994
  98. Saito Y, Saito H, Tada S, Nakamoto N, Horikawa H, Kurita S, et al. Effect of long-term interferon therapy for refractory chronic hepatitis c: preventive effect on hepatocarcinogenesis. *Hepatogastroenterology* 2005;52:1491–1496
  99. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, et al. Prolonged-interferon therapy reduces hepatocarcinogenesis in aged-patients with chronic hepatitis C. *J Med Virol* 2007; 79:1095–1102
  100. Lok AS, Seeff LB, Morgan TR, Di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis c-related advanced liver disease. *Gastroenterology* [Epub 2008]
  101. Wogan GN. Aflatoxins as risk factors for hepatocellular carcinoma in humans. *Cancer Res* 1992;52:2114s–2118s
  102. Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* 2004;127:S72–S78
  103. Omer RE, Kuijsten A, Kadaru AM, Kok FJ, Idris MO, El Khidir IM, et al. Population-attributable risk of dietary aflatoxins and hepatitis B virus infection with respect to hepatocellular carcinoma. *Nutr Cancer* 2004;48:15–21
  104. La Vecchia C. Coffee, liver enzymes, cirrhosis and liver cancer. *J Hepatol* 2005;42:444–446
  105. Adami HO, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekblom A, et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. *Int J Cancer* 1992;51:898–902
  106. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. *Int J Cancer* 2000;85:498–502
  107. La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. *Eur J Cancer Prev* 1998;7:315–320
  108. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee consumption and serum aminotransferases in middle-aged Japanese men. *J Clin Epidemiol* 2001;54:823–829
  109. Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tatara K. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. *Eur J Epidemiol* 2000;16:419–423
  110. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2005;128:24–32
  111. Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. *Am J Epidemiol* 1997;146:1019–1024
  112. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee drinking and serum gamma-glutamyltransferase: an extended study of Self-Defense Officials of Japan. *Ann Epidemiol* 1999;9:325–331
  113. Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, et al. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. *Int J Epidemiol* 1998;27:438–443
  114. Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* 2007;46:430–435
  115. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology* 2007;132:1740–1745
  116. Tamori A, Habu D, Shiomi S, Kubo S, Nishiguchi S. Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma. *Hepatol Res* 2007;37(Suppl 2):S303–S307
  117. Sakai I, Hashimoto S, Yoda M, Hida T, Ohsawa S, Nakajo S, et al. Novel role of vitamin K2: a potent inducer of differentiation of various human myeloid leukemia cell lines. *Biochem Biophys Res Commun* 1994;205:1305–1310
  118. Miyakawa T, Kajiwara Y, Shirahata A, Okamoto K, Itoh H, Ohsato K. Vitamin K contents in liver tissue of hepatocellular carcinoma patients. *Jpn J Cancer Res* 2000;91:68–74
  119. Carr BI, Wang Z, Kar S, Wang M. Prothrombin inhibits hepatocyte DNA synthesis (DNA-S) and expression of the  $\alpha 5$  integrin gene. *Proc AACR* 1995;36:266
  120. Kar S, Carr BI. Growth inhibition and protein tyrosine phosphorylation in MCF 7 breast cancer cells by a novel K vitamin. *J Cell Physiol* 2000;185:386–393
  121. Varnum BC, Young C, Elliott G, Garcia A, Bartley TD, Fridell YW, et al. Axl receptor tyrosine kinase stimulated by the

- vitamin K-dependent protein encoded by growth-arrest-specific gene 6. *Nature* 1995;373:623–626
122. Habu D, Shiomi S, Tamori A, Takeda T, Tanaka T, Kubo S, et al. Role of vitamin K2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. *JAMA* 2004;292:358–361
  123. Otsuka M, Kato N, Shao RX, Hoshida Y, Ijichi H, Koike Y, et al. Vitamin K2 inhibits the growth and invasiveness of hepatocellular carcinoma cells via protein kinase A activation. *Hepatology* 2004;40:243–251
  124. Mizuta T, Ozaki I, Eguchi Y, Yasutake T, Kawazoe S, Fujimoto K, et al. The effect of menatetrenone, a vitamin K2 analog, on disease recurrence and survival in patients with hepatocellular carcinoma after curative treatment: a pilot study. *Cancer* 2006; 106:867–872
  125. Hotta N, Ayada M, Sato K, Ishikawa T, Okumura A, Matsumoto E, et al. Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma. *Hepatogastroenterology* 2007;54:2073–2077
  126. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994;107:1103–1109
  127. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;116: 1413–1419
  128. >Caldwell SH, Oelsner DH, Iezzoni JC, Hespeneheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. *Hepatology* 1999; 29:664–669
  129. Cuadrado A, Orive A, Garcia-Suarez C, Dominguez A, Fernandez-Escalante JC, Crespo J, et al. Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. *Obes Surg* 2005; 15:442–446
  130. Wang RT, Koretz RL, Yee HF Jr. Is weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. *Am J Med* 2003;115:554–559
  131. Chan HL, de Silva HJ, Leung NW, Lim SG, Farrell GC. How should we manage patients with non-alcoholic fatty liver disease in 2007? *J Gastroenterol Hepatol* 2007;22:801–808
  132. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Sanchez-Avila F, Montano-Reyes MA, Uribe M. Insulin sensitizers in treatment of nonalcoholic fatty liver disease: systematic review. *World J Gastroenterol* 2006;12:7826–7831
  133. Strohmeyer G, Niederau C, Stremmel W. Survival and causes of death in hemochromatosis. Observations in 163 patients. *Ann N Y Acad Sci* 1988;526:245–257
  134. Hsing AW, McLaughlin JK, Olsen JH, Mellekjar L, Wacholder S, Fraumeni JF Jr. Cancer risk following primary hemochromatosis: a population-based cohort study in Denmark. *Int J Cancer* 1995;60:160–162
  135. Yang Q, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of multiple-cause mortality data. *Ann Intern Med* 1998;129:946–953
  136. Borgna-Pignatti C, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A, et al. Hepatocellular carcinoma in the thalassaemia syndromes. *Br J Haematol* 2004;124:114–117
  137. Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Pateron AC, Rouault TA, et al. Dietary iron overload as a risk factor for hepatocellular carcinoma in black Africans. *Hepatology* 1998;27:1563–1566
  138. Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. *Gastroenterology* 2004;127:S79–S86
  139. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004;130:417–422
  140. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009;50:80–88
  141. McMahon BJ, Bulkow L, Harpster A, 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;32:842–846
  142. 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;22:432–438
  143. Lok AS, Lai CL. alpha-Fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection: role in the early detection of hepatocellular carcinoma. *Hepatology* 1989;9:110–115
  144. Bloomer JR, Waldmann TA, McIntire KR, Klatskin G. Alpha-fetoprotein in non-neoplastic hepatic disorders. *JAMA* 1975; 233:38–41
  145. Alpert E, Feller ER. Alpha-fetoprotein (AFP) in benign liver disease. Evidence that normal liver regeneration does not induce AFP synthesis. *Gastroenterology* 1978;74:856–858
  146. Ikoma J, Kaito M, Ishihara T, Nakagawa N, Kamei A, Fujita N, et al. Early diagnosis of hepatocellular carcinoma using a sensitive assay for serum des-gamma-carboxy prothrombin: a prospective study. *Hepatogastroenterology* 2002;49:235–238
  147. Kasahara A, Hayashi N, Fusamoto H, Kawada Y, Imai Y, Yamamoto H, et al. Clinical evaluation of plasma des-gamma-carboxy prothrombin as a marker protein of hepatocellular carcinoma in patients with tumors of various sizes. *Dig Dis Sci* 1993;38:2170–6
  148. Maringhini A, Cottone M, Sciarrino E, Marceno MP, La Seta F, Fusco G, et al. Ultrasonography and alpha-fetoprotein in diagnosis of hepatocellular carcinoma in cirrhosis. *Dig Dis Sci* 1988; 33:47–51
  149. Mita Y, Aoyagi Y, Yanagi M, Suda T, Suzuki Y, Asakura H. The usefulness of determining des-gamma-carboxy prothrombin by sensitive enzyme immunoassay in the early diagnosis of patients with hepatocellular carcinoma. *Cancer* 1998;82:1643–1648
  150. Nomura F, Ishijima M, Horikoshi A, Nakai T, Ohnishi K. Determination of serum des-gamma-carboxy prothrombin levels in patients with small-sized hepatocellular carcinoma: comparison of the conventional enzyme immunoassay and two modified methods. *Am J Gastroenterol* 1996;91:1380–1383
  151. Nomura F, Ishijima M, Kuwa K, Tanaka N, Nakai T, Ohnishi K. Serum des-gamma-carboxy prothrombin levels determined by a new generation of sensitive immunoassays in patients with small-sized hepatocellular carcinoma. *Am J Gastroenterol* 1999;94:650–654
  152. Oka H, Saito A, Ito K, Kumada T, Satomura S, Kasugai H, et al. Multicenter prospective analysis of newly diagnosed hepatocellular carcinoma with respect to the percentage of Lens culinaris agglutinin-reactive alpha-fetoprotein. *J Gastroenterol Hepatol* 2001;16:1378–1383
  153. Suehiro T, Sugimachi K, Matsumata T, Itasaka H, Taketomi A, Maeda T. Protein induced by vitamin K absence or antagonist II as a prognostic marker in hepatocellular carcinoma. Comparison with alpha-fetoprotein. *Cancer* 1994;73:2464–2471
  154. Tanabe Y, Ohnishi K, Nomura F, Iida S. Plasma abnormal prothrombin levels in patients with small hepatocellular carcinoma. *Am J Gastroenterol* 1988;83:1386–1389

155. Gebo KA, Chander G, Jenckes MW, Ghanem KG, Herlong HF, Torbenson MS, et al. Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. *Hepatology* 2002;36:S84–S92
156. Cottone M, Turri M, Caltagirone M, Parisi P, Orlando A, Fiorentino G, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alpha-fetoprotein. *J Hepatol* 1994;21:1029–1034
157. Pateron D, Ganne N, Trinchet JC, Arousseau 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
158. Irwig L, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, et al. Guidelines for meta-analyses evaluating diagnostic tests. *Ann Intern Med* 1994;120:667–676
159. Tateishi R, Yoshida H, Matsuyama Y, Mine N, Kondo Y, Omata M. Diagnostic accuracy of tumor markers for hepatocellular carcinoma: a systematic review. *Hepatol Int* 2008;2:17–30
160. Marrero JA, Su GL, Wei W, Emick D, Conjeevaram HS, Fontana RJ, et al. Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in American patients. *Hepatology* 2003;37:1114–1121
161. Cui R, He J, Zhang F, Wang B, Ding H, Shen H, et al. Diagnostic value of protein induced by vitamin K absence (PIVKAI) and hepatoma-specific band of serum gamma-glutamyl transferase (GGTII) as hepatocellular carcinoma markers complementary to alpha-fetoprotein. *Br J Cancer* 2003;88:1878–1882
162. Wang CS, Lin CL, Lee HC, Chen KY, Chiang MF, Chen HS, et al. Usefulness of serum des-gamma-carboxy prothrombin in detection of hepatocellular carcinoma. *World J Gastroenterol* 2005;11:6115–6119
163. Sterling RK, Jeffers L, Gordon F, Sherman M, Venook AP, Reddy KR, et al. Clinical utility of AFP-L 3% measurement in North American patients with HCV-related cirrhosis. *Am J Gastroenterol* 2007;102:2196–2205
164. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, et al. Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. *Gastroenterology* 2003;125:89–97
165. Hippo Y, Watanabe K, Watanabe A, Midorikawa Y, Yamamoto S, Ihara S, et al. Identification of soluble NH<sub>2</sub>-terminal fragment of glypican-3 as a serological marker for early-stage hepatocellular carcinoma. *Cancer Res* 2004;64:2418–2423
166. Nguyen MH, Garcia RT, Simpson PW, Wright TL, Keeffe EB. Racial differences in effectiveness of alpha-fetoprotein for diagnosis of hepatocellular carcinoma in hepatitis C virus cirrhosis. *Hepatology* 2002;36:410–417
167. Soresi M, Magliarisi C, Campagna P, Leto G, Bonfissuto G, Riili A, et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. *Anticancer Res* 2003;23:1747–1753
168. Arrieta O, Cacho B, Morales-Espinosa D, Ruelas-Villavicencio A, Flores-Estrada D, Hernandez-Pedro N. The progressive elevation of alpha fetoprotein for the diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. *BMC Cancer* 2007; 7:28
169. Paul SB, Gulati MS, Sreenivas V, Madan K, Gupta AK, Mukhopadhyay S. Evaluating patients with cirrhosis for hepatocellular carcinoma: value of clinical symptomatology, imaging and alpha-fetoprotein. *Oncology* 2007;72(Suppl 1):117–123
170. Kew MC. Alpha-fetoprotein. In Read AE, editor. *Modern Trends in Gastroenterology*, vol. 5. London: Butterworths; 1975. p 91
171. 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;310:1427–1431
172. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yet al. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 2001;91:561–569
173. Imamura H, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, et al. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. *Br J Surg* 1999;86:1032–1038
174. Sato Y, Nakata K, Kato Y, Shima M, Ishii N, Koji T, et al. Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. *N Engl J Med* 1993;328:1802–1806
175. 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;53:5419–5423
176. Aoyagi Y, Isemura M, Yosizawa Z, Suzuki Y, Sekine C, Ono T, et al. Fucosylation of serum alpha-fetoprotein in patients with primary hepatocellular carcinoma. *Biochim Biophys Acta* 1985;830:217–223
177. Hsu HC, Cheng W, Lai PL. Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution. *Cancer Res* 1997;57:5179–5184
178. Zhu ZW, Friess H, Wang L, Abou-Shady M, Zimmermann A, Lander AD, et al. Enhanced glypican-3 expression differentiates the majority of hepatocellular carcinomas from benign hepatic disorders. *Gut* 2001;48:558–564
179. Sassa T, Kumada T, Nakano S, Uematsu T. Clinical utility of simultaneous measurement of serum high-sensitivity des-gamma-carboxy prothrombin and Lens culinaris agglutinin A-reactive alpha-fetoprotein in patients with small hepatocellular carcinoma. *Eur J Gastroenterol Hepatol* 1999;11:1387–1392
180. Tanaka S, Kitamura T, Fujita M, Nakanishi K, Okuda S. Color Doppler flow imaging of liver tumors. *AJR Am J Roentgenol* 1990;154:509–514
181. Tanaka S, Kitamura T, Fujita M, Kasugai H, Inoue A, Ishiguro S. Small hepatocellular carcinoma: differentiation from adenomatous hyperplastic nodule with color Doppler flow imaging. *Radiology* 1992;182:161–165
182. Rubin JM, Bude RO, Carson PL, Bree RL, Adler RS. Power Doppler US: a potentially useful alternative to mean frequency-based color Doppler US. *Radiology* 1994;190:853–856
183. Koito K, Namieno T, Morita K. Differential diagnosis of small hepatocellular carcinoma and adenomatous hyperplasia with power Doppler sonography. *AJR Am J Roentgenol* 1998;170:157–161
184. Fujimoto M, Moriyasu F, Nishikawa K, Nada T, Okuma M. Color Doppler sonography of hepatic tumors with a galactose-based contrast agent: correlation with angiographic findings. *AJR Am J Roentgenol* 1994;163:1099–1104
185. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K. Hepatocellular carcinoma: depiction of tumor parenchymal flow with intermittent harmonic power Doppler US during the early arterial phase in dual-display mode. *Radiology* 2001;220:349–356
186. Kudo M, Tomita S, Tochio H, Mimura J, Okabe Y, Kashida H, et al. Sonography with intraarterial infusion of carbon dioxide microbubbles (sonographic angiography): value in differential diagnosis of hepatic tumors. *AJR Am J Roentgenol* 1992; 158:65–74
187. Yanagisawa K, Moriyasu F, Miyahara T, Yuki M, Iijima H. Phagocytosis of ultrasound contrast agent microbubbles by Kupffer cells. *Ultrasound Med Biol* 2007;33:318–325
188. D'Onofrio M, Martone E, Faccioli N, Zamboni G, Malago R, Mucelli RP. Focal liver lesions: sinusoidal phase of CEUS. *Abdom Imaging* 2006;31:529–536

189. Hatanaka K, Kudo M, Minami Y, Ueda T, Tatsumi C, Kitai S, et al. Differential diagnosis of hepatic tumors: value of contrast-enhanced harmonic sonography using the newly developed contrast agent, Sonazoid. *Intervirol* 2008;51(Suppl 1):61–9
190. 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;94:2224–2229
191. Collier J, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998;27:273–278
192. Kobayashi K, Sugimoto T, Makino H, Kumagai M, Unoura M, Tanaka N, et al. Screening methods for early detection of hepatocellular carcinoma. *Hepatology* 1985;5:1100–1105
193. Federle MP. Use of radiologic techniques to screen for hepatocellular carcinoma. *J Clin Gastroenterol* 2002;35:S92–S100
194. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–1236
195. Saab S, Ly D, Nieto J, Kanwal F, Lu D, Raman S, et al. Hepatocellular carcinoma screening in patients waiting for liver transplantation: a decision analytic model. *Liver Transpl* 2003;9:672–681
196. Burrell M, Llovet JM, Ayuso C, Iglesias C, Sala M, Miquel R, et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. *Hepatology* 2003;38:1034–1042
197. Van Thiel DH, Yong S, Li SD, Kennedy M, Brems J. The development of de novo hepatocellular carcinoma in patients on a liver transplant list: frequency, size, and assessment of current screening methods. *Liver Transpl* 2004;10:631–637
198. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology* 2008;134:1752–1763
199. Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol* 2003;98:679–690
200. Kim TK, Jang HJ, Wilson SR. Imaging diagnosis of hepatocellular carcinoma with differentiation from other pathology. *Clin Liver Dis* 2005;9:253–279
201. Matsui O. Imaging of multistep human hepatocarcinogenesis by CT during intra-arterial contrast injection. *Intervirol* 2004;47:271–276
202. Marrero JA, Hussain HK, Nghiem HV, Umar R, Fontana RJ, Lok AS. Improving the prediction of hepatocellular carcinoma in cirrhotic patients with an arterially-enhancing liver mass. *Liver Transpl* 2005;11:281–289
203. Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 2006;101:513–523
204. Kim SH, Choi BI, Lee JY, Kim SJ, So YH, Eun HW. Diagnostic accuracy of multi-/single-detector row CT and contrast-enhanced MRI in the detection of hepatocellular carcinomas meeting the Milan criteria before liver transplantation. *Intervirol* 2008;51(Suppl 1):52–60
205. Willatt JM, Hussain HK, Adusumilli S, Marrero JA. MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies. *Radiology* 2008;247:311–330
206. Ebara M, Ohto M, Watanabe Y, Kimura K, Saisho H, Tsuchiya Y, et al. Diagnosis of small hepatocellular carcinoma: correlation of MR imaging and tumor histologic studies. *Radiology* 1986;159:371–377
207. Rode A, Bancel B, Douek P, Chevallier M, Vilgrain V, Picaud G, et al. Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. *J Comput Assist Tomogr* 2001;25:327–336
208. Krinsky GA, Lee VS, Theise ND, Weinreb 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;219:445–454
209. Baron RL, Peterson MS. From the RSNA refresher courses: screening the cirrhotic liver for hepatocellular carcinoma with CT and MR imaging: opportunities and pitfalls. *Radiographics* 2001;21:S117–S132
210. Holland AE, Hecht EM, Hahn WY, Kim DC, Babb JS, Lee VS, et al. Importance of small ( $\leq 20$ -mm) enhancing lesions seen only during the hepatic arterial phase at MR imaging of the cirrhotic liver: evaluation and comparison with whole explanted liver. *Radiology* 2005;237:938–944
211. 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;180:1007–1014
212. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907–1917
213. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000;32:1224–1229
214. Kim YK, Kwak HS, Kim CS, Chung GH, Han YM, Lee JM. Hepatocellular carcinoma in patients with chronic liver disease: comparison of SPIO-enhanced MR imaging and 16-detector row CT. *Radiology* 2006;238:531–541
215. Bhartia B, Ward J, Guthrie JA, Robinson PJ. Hepatocellular carcinoma in cirrhotic livers: double-contrast thin-section MR imaging with pathologic correlation of explanted tissue. *AJR Am J Roentgenol* 2003;180:577–584
216. Ward J, Guthrie JA, Scott DJ, Atchley J, Wilson D, Davies MH, et al. Hepatocellular carcinoma in the cirrhotic liver: double-contrast MR imaging for diagnosis. *Radiology* 2000;216:154–162
217. Yoo HJ, Lee JM, Lee MW, Kim SJ, Lee JY, Han JK, et al. Hepatocellular carcinoma in cirrhotic liver: double-contrast-enhanced, high-resolution 3.0T-MR imaging with pathologic correlation. *Invest Radiol* 2008;43:538–546
218. Mori K, Yoshioka H, Itai Y, Okamoto Y, Mori H, Takahashi N, et al. Arterioportal shunts in cirrhotic patients: evaluation of the difference between tumorous and nontumorous arterioportal shunts on MR imaging with superparamagnetic iron oxide. *AJR Am J Roentgenol* 2000;175:1659–1664
219. Choi SH, Lee JM, Yu NC, Suh KS, Jang JJ, Kim SH, et al. Hepatocellular carcinoma in liver transplantation candidates: detection with gadobenate dimeglumine-enhanced MRI. *AJR Am J Roentgenol* 2008;191:529–536
220. Sakamoto M, Hirohashi S, Shimozato Y. Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. *Hum Pathol* 1991;22:172–178
221. Sakamoto M, Hirohashi S. Natural history and prognosis of adenomatous hyperplasia and early hepatocellular carcinoma: multi-institutional analysis of 53 nodules followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or percutaneous ethanol injection. *Jpn J Clin Oncol* 1998;28:604–608
222. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. *Liver Transpl* 2004;10:S3–S8
223. Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, et al. Characterization of small nodules in cirrhosis by

- assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. *Hepatology* 2005;42:27–34
224. Kudo M, Okanoue T. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. *Oncology* 2007;72(Suppl 1):2–15
  225. Imai Y, Murakami T, Yoshida S, Nishikawa M, Ohsawa M, Tokunaga K, et al. Superparamagnetic iron oxide-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading. *Hepatology* 2000;32:205–212
  226. Lim JH, Choi D, Cho SK, Kim SH, Lee WJ, Lim HK, et al. Conspicuity of hepatocellular nodular lesions in cirrhotic livers at ferumoxides-enhanced MR imaging: importance of Kupffer cell number. *Radiology* 2001;220:669–676
  227. Heiken JP, Weyman PJ, Lee JK, Balfe DM, Picus D, Brunt EM, et al. Detection of focal hepatic masses: prospective evaluation with CT, delayed CT, CT during arterial portography, and MR imaging. *Radiology* 1989;171:47–51
  228. Kanematsu M, Hoshi H, Imaeda T, Murakami T, Inaba Y, Yokoyama R, et al. Detection and characterization of hepatic tumors: value of combined helical CT hepatic arteriography and CT during arterial portography. *AJR Am J Roentgenol* 1997;168:1193–1198
  229. Kanematsu M, Hoshi H, Murakami T, Inaba Y, Kim T, Yamada T, et al. Detection of hepatocellular carcinoma in patients with cirrhosis: MR imaging versus angiographically assisted helical CT. *AJR Am J Roentgenol* 1997;169:1507–1515
  230. Choi D, Kim S, Lim J, Lee W, Jang H, Lee S, et al. Preoperative detection of hepatocellular carcinoma: ferumoxides-enhanced MR imaging versus combined helical CT during arterial portography and CT hepatic arteriography. *AJR Am J Roentgenol* 2001;176:475–482
  231. Yoon KT, Kim JK, Kim do Y, Ahn SH, Lee JD, Yun M, et al. Role of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastasis in pretreatment staging of hepatocellular carcinoma. *Oncology* 2007;72(Suppl 1):104–110
  232. Yang SH, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, et al. The role of (18)F-FDG-PET imaging for the selection of liver transplantation candidates among hepatocellular carcinoma patients. *Liver Transpl* 2006;12:1655–1660
  233. Shiomi S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. *Am J Gastroenterol* 2001;96:1877–1880
  234. Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolverson MK, Solomon H, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol* 2000;32:792–797
  235. Trojan J, Schroeder O, Raedle J, Baum RP, Herrmann G, Jacobi V, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. *Am J Gastroenterol* 1999;94:3314–3319
  236. Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, et al. <sup>18</sup>F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. *J Gastroenterol* 2004;39:961–968
  237. Tanimoto A, Wakabayashi G, Shinmoto H, Nakatsuka S, Okuda S, Kuribayashi S. Superparamagnetic iron oxide-enhanced MR imaging for focal hepatic lesions: a comparison with CT during arteriography plus CT during hepatic arteriography. *J Gastroenterol* 2005;40:371–380
  238. Kojiro M. Pathology of hepatocellular carcinoma. In Okuda K, Tabor E, editors. *Liver Cancer*. New York: Churchill Livingstone; 1997. p. 165–187
  239. Tajima T, Honda H, Taguchi K, Asayama Y, Kuroiwa T, Yoshimitsu K, et al. Sequential hemodynamic change in hepatocellular carcinoma and dysplastic nodules: CT angiography and pathologic correlation. *AJR Am J Roentgenol* 2002;178:885–897
  240. Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M. Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. *Radiology* 2002;225:143–149
  241. Kudo M. Imaging diagnosis of hepatocellular carcinoma and premalignant/borderline lesions. *Semin Liver Dis* 1999;19:297–309
  242. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K. Contrast-enhanced subtraction harmonic sonography for evaluating treatment response in patients with hepatocellular carcinoma. *AJR Am J Roentgenol* 2001;176:661–666
  243. Wen YL, Kudo M, Zheng RQ, Ding H, Zhou P, Minami Y, et al. Characterization of hepatic tumors: value of contrast-enhanced coded phase-inversion harmonic angio. *AJR Am J Roentgenol* 2004;182:1019–1026
  244. Asahina Y, Izumi N, Uchihara M, Noguchi O, Ueda K, Inoue K, et al. Assessment of Kupffer cells by ferumoxides-enhanced MR imaging is beneficial for diagnosis of hepatocellular carcinoma: comparison of pathological diagnosis and perfusion patterns assessed by CT hepatic arteriography and CT arteriography. *Hepatol Res* 2003;27:196–204
  245. Akriviadis EA, Llovet JM, Efromidis SC, Shouval D, Canelo R, Ringe B, et al. Hepatocellular carcinoma. *Br J Surg* 1998;85:1319–1331
  246. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002;35:519–524
  247. Regimbeau JM, Farges O, Shen BY, Sauvaget A, Belghiti J. Is surgery for large hepatocellular carcinoma justified? *J Hepatol* 1999;31:1062–1068
  248. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg* 2002;194:592–602
  249. Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Ann Surg Oncol* 2005;12:364–373
  250. Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery* 2005;137:403–410
  251. Liu CL, Fan ST, Lo CM, Ng IO, Poon RT, Wong J. Hepatic resection for bilobar hepatocellular carcinoma: is it justified? *Arch Surg* 2003;138:100–104
  252. Choi D, Lim HK, Joh JW, Kim SJ, Kim MJ, Rhim H, et al. Combined hepatectomy and radiofrequency ablation for multifocal hepatocellular carcinomas: long-term follow-up results and prognostic factors. *Ann Surg Oncol* 2007;14:3510–3518
  253. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. *Arch Surg* 1999;134:984–992
  254. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 2004;240:698–708 (discussion 708–710)
  255. Asiyabola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? *J Gastrointest Surg* 2008;12:842–851

256. Polignano FM, Quyn AJ, de Figueiredo RS, Henderson NA, Kulli C, Tait IS. Laparoscopic versus open liver segmentectomy: prospective, case-matched, intention-to-treat analysis of clinical outcomes and cost effectiveness. *Surg Endosc* 2008;22:2564–2570
257. Grazi GL, Ercolani G, Pierangeli F, Del Gaudio M, Cescon M, Cavallari A, et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg* 2001;234:71–78
258. Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, et al. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001;234:63–70
259. Capussotti L, Muratore A, Amisano M, Polastri R, Bouzari H, Massucco P. Liver resection for hepatocellular carcinoma on cirrhosis: analysis of mortality, morbidity and survival—a European single center experience. *Eur J Surg Oncol* 2005;31:986–993
260. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. *Ann Surg* 2007;245:51–58
261. Ishii H, Furuse J, Kinoshita T, Konishi M, Nakagohri T, Takahashi S, et al. Hepatectomy for hepatocellular carcinoma patients who meet the Milan criteria. *Hepatogastroenterology* 2008;55:621–626
262. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg* 2000;231:544–551
263. Yamazaki S, Takayama T. Surgical treatment of hepatocellular carcinoma: evidence-based outcomes. *World J Gastroenterol* 2008;14:685–692
264. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. *Ann Surg* 1999;229:216–222
265. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery* 1991;110:726–734 (discussion 734–735)
266. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693–699
267. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;33:1394–1403
268. Fernandez JA, Robles R, Marin C, Sanchez-Bueno F, Ramirez P, Pons JA, et al. Can we expand the indications for liver transplantation among hepatocellular carcinoma patients with increased tumor size? *Transplant Proc* 2003;35:1818–1820
269. Otto G, Heuschen U, Hofmann WJ, Krumm G, Hinz U, Herfarth C. Survival and recurrence after liver transplantation versus liver resection for hepatocellular carcinoma: a retrospective analysis. *Ann Surg* 1998;227:424–432
270. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;30:1434–1440
271. Figueras J, Ibanez L, Ramos E, Jaurrieta E, Ortiz-de-Urbina J, Pardo F, et al. Selection criteria for liver transplantation in early-stage hepatocellular carcinoma with cirrhosis: results of a multicenter study. *Liver Transpl* 2001;7:877–883
272. Jonas S, Bechstein WO, Steinmuller T, Herrmann M, Radke C, Berg T, et al. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001;33:1080–1086
273. Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. *Ann Surg* 1998;228:479–490
274. Belghiti J, Carr BI, Greig PD, Lencioni R, Poon RT. Treatment before liver transplantation for HCC. *Ann Surg Oncol* 2008;15:993–1000
275. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med* 2002;346:1074–1082
276. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2004;127:S277–S282
277. Poon RT. Optimal initial treatment for early hepatocellular carcinoma in patients with preserved liver function: transplantation or resection? *Ann Surg Oncol* 2007;14:541–547
278. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002;235:373–382
279. Belghiti J, Cortes A, Abdalla EK, Regimbeau JM, Prakash K, Durand F, et al. Resection prior to liver transplantation for hepatocellular carcinoma. *Ann Surg* 2003;238:885–892 (discussion 892–893)
280. Sugiura N, Takara K, Ohto M, Okuda K, Hirokawa N. Percutaneous intratumoral injection of ethanol under ultrasound imaging for treatment of small hepatocellular carcinoma. *Acta Hepatol Jpn* 1983;24:920
281. Livraghi T, Festi D, Monti F, Salmi A, Vettori C. US-guided percutaneous alcohol injection of small hepatic and abdominal tumors. *Radiology* 1986;161:309–312
282. Shiina S, Yasuda H, Muto H, Tagawa K, Unuma T, Ibukuro K, et al. Percutaneous ethanol injection in the treatment of liver neoplasms. *AJR Am J Roentgenol* 1987;149:949–952
283. Seki T, Wakabayashi M, Nakagawa T, Itho T, Shiro T, Kunieda K, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994;74:817–825
284. Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, et al. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am* 1995;1:73–81
285. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999;210:655–661
286. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology* 2002;62(Suppl 1):64–68
287. Shiina S, Tagawa K, Niwa Y, Unuma T, Komatsu Y, Yoshiura K, et al. Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. *AJR Am J Roentgenol* 1993;160:1023–1028
288. Ebara M, Okabe S, Kita K, Sugiura N, Fukuda H, Yoshikawa M, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005;43:458–464
289. Sung YM, Choi D, Lim HK, Lee WJ, Kim SH, Kim MJ, et al. Long-term results of percutaneous ethanol injection for the treatment of hepatocellular carcinoma in Korea. *Korean J Radiol* 2006;7:187–192
290. Ikai I, Arii S, Okazaki M, Okita K, Omata M, Kojiro M, et al. Report of the 17th nationwide follow-up survey of primary liver cancer in Japan. *Hepatol Res* 2007;37:676–691

291. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* 1995;197:101–108
292. Ishii H, Okada S, Nose H, Okusaka T, Yoshimori M, Takayama T, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer* 1996;77:1792–1796
293. Di Stasi M, Buscarini L, Livraghi T, Giorgio A, Salmi A, De Sio I, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. *Scand J Gastroenterol* 1997;32:1168–1173
294. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003;228:235–240
295. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma  $\leq 4$  cm. *Gastroenterology* 2004;127:1714–1723
296. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. *Gastroenterology* 2005;129:122–130
297. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. *Gut* 2005;54:1151–1156
298. Shibata T, Iimuro Y, Yamamoto Y, Maetani Y, Ametani F, Itoh K, et al. Small hepatocellular carcinoma: comparison of radiofrequency ablation and percutaneous microwave coagulation therapy. *Radiology* 2002;223:331–337
299. Machi J, Bueno RS, Wong LL. Long-term follow-up outcome of patients undergoing radiofrequency ablation for unresectable hepatocellular carcinoma. *World J Surg* 2005;29:1364–1373
300. Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, et al. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. *Radiology* 2005;234:961–967
301. Tateishi R, Shiina S, Teratani T, Obi S, Sato S, Koike Y, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer* 2005;103:1201–1209
302. Cabassa P, Donato F, Simeone F, Grazioli L, Romanini L. Radiofrequency ablation of hepatocellular carcinoma: long-term experience with expandable needle electrodes. *AJR Am J Roentgenol* 2006;186:S316–S321
303. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 2008;47:82–89
304. Yan K, Chen MH, Yang W, Wang YB, Gao W, Hao CY, et al. Radiofrequency ablation of hepatocellular carcinoma: long-term outcome and prognostic factors. *Eur J Radiol* 2008;67:336–347
305. Kasugai H, Osaki Y, Oka H, Kudo M, Seki T. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: an analysis of 3,891 ablations in 2,614 patients. *Oncology* 2007;72(Suppl 1):72–75
306. Cheng BQ, Jia CQ, Liu CT, Fan W, Wang QL, Zhang ZL, et al. Chemoembolization combined with radiofrequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial. *JAMA* 2008;299:1669–1677
307. Kobayashi M, Ikeda K, Kawamura Y, Hosaka T, Sezaki H, Yatsuji H, et al. Randomized controlled trial for the efficacy of hepatic arterial occlusion during radiofrequency ablation for small hepatocellular carcinoma—direct ablative effects and a long-term outcome. *Liver Int* 2007;27:353–359
308. Huang GT, Lee PH, Tsang YM, Lai MY, Yang PM, Hu RH, et al. Percutaneous ethanol injection versus surgical resection for the treatment of small hepatocellular carcinoma: a prospective study. *Ann Surg* 2005;242:36–42
309. Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243:321–328
310. Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, et al. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. *Hepatology* 1993;18:1121–1126
311. Livraghi T, Bolondi L, Buscarini L, Cottone M, Mazziotti A, Morabito A, et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. *J Hepatol* 1995;22:522–526
312. Ryu M, Shimamura Y, Kinoshita T, Konishi M, Kawano N, Iwasaki M, et al. Therapeutic results of resection, transcatheter arterial embolization and percutaneous transhepatic ethanol injection in 3225 patients with hepatocellular carcinoma: a retrospective multicenter study. *Jpn J Clin Oncol* 1997;27:251–257
313. Nakashima T, Kojiro M. Pathologic characteristics of hepatocellular carcinoma. *Semin Liver Dis* 1986;6:259–266
314. Park YN, Yang CP, Fernandez GJ, Cubukcu O, Thung SN, Theise ND. Neoangiogenesis and sinusoidal “capillarization” in dysplastic nodules of the liver. *Am J Surg Pathol* 1998;22:656–662
315. Goseki N, Nosaka T, Endo M, Koike M. Nourishment of hepatocellular carcinoma cells through the portal blood flow with and without transcatheter arterial embolization. *Cancer* 1995;76:736–742
316. Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. *Gastroenterology* 2004;127:S179–S188
317. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983;148:397–401
318. Ramsey DE, Kernagis LY, Soulen MC, Geschwind JF. Chemoembolization of hepatocellular carcinoma. *J Vasc Interv Radiol* 2002;13:S211–S221
319. Kruskal JB, Hlatky L, Hahnfeldt P, Teramoto K, Stokes KR, Clouse ME. In vivo and in vitro analysis of the effectiveness of doxorubicin combined with temporary arterial occlusion in liver tumors. *J Vasc Interv Radiol* 1993;4:741–747
320. Liapi E, Geschwind JF. Transcatheter and ablative therapeutic approaches for solid malignancies. *J Clin Oncol* 2007;25:978–986
321. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007;30:6–25
322. Vogl TJ, Naguib NN, Nour-Eldin NE, Rao P, Emami AH, Zangos S, et al. Review on transarterial chemoembolization in hepatocellular carcinoma: palliative, combined, neoadjuvant, bridging, and symptomatic indications. *Eur J Radiol* 2009;72:505–516
323. Makuuchi M, Sukigara M, Mori T, Kobayashi J, Yamazaki S, Hasegawa H, et al. Bile duct necrosis: complication of transcatheter hepatic arterial embolization. *Radiology* 1985;156:331–334
324. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007;46:474–481

325. Iwamoto S, Sanefuji H, Okuda K. Angiographic subsegmentectomy for the treatment of patients with small hepatocellular carcinoma. *Cancer* 2003;97:1051–1056
326. Matsui O, Kadoya M, Yoshikawa J, Gabata T, Arai K, Demachi H, et al. Small hepatocellular carcinoma: treatment with subsegmental transcatheter arterial embolization. *Radiology* 1993; 188:79–83
327. Miyayama S, Matsui O, Yamashiro M, Ryu Y, Kaito K, Ozaki K, et al. Ultrasensitive transcatheter arterial chemoembolization with a 2-F tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. *J Vasc Interv Radiol* 2007;18:365–376
328. Nakai M, Sato M, Kawai N, Minamiguchi H, Masuda M, Tanihata H, et al. Hepatocellular carcinoma: involvement of the internal mammary artery. *Radiology* 2001;219:147–152
329. Chung JW, Kim HC, Yoon JH, Lee HS, Jae HJ, Lee W, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma: prevalence and causative factors of extrahepatic collateral arteries in 479 patients. *Korean J Radiol* 2006;7:257–266
330. Miyayama S, Matsui O, Taki K, Minami T, Ryu Y, Ito C, et al. Extrahepatic blood supply to hepatocellular carcinoma: angiographic demonstration and transcatheter arterial chemoembolization. *Cardiovasc Intervent Radiol* 2006;29:39–48
331. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164–1171
332. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:1734–1739
333. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;37:429–442
334. Bruix J, Sherman M, Llovet 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;35:421–430
335. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208–1236
336. Yao FY, Hirose R, LaBerge JM, Davern TJ III, Bass NM, Kerlan RK Jr, et al. A prospective study on downstaging of hepatocellular carcinoma prior to liver transplantation. *Liver Transpl* 2005;11:1505–1514
337. Hanje AJ, Yao FY. Current approach to down-staging of hepatocellular carcinoma prior to liver transplantation. *Curr Opin Organ Transplant* 2008;13:234–240
338. Yao FY, Kerlan RK Jr, Hirose R, Davern TJ III, Bass NM, Feng S, et al. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008;48:819–827
339. Staunton M, Dodd JD, McCormick PA, Malone DE. Finding evidence-based answers to practical questions in radiology: which patients with inoperable hepatocellular carcinoma will survive longer after transarterial chemoembolization? *Radiology* 2005;237:404–413
340. Chan AO, Yuen MF, Hui CK, Tso WK, Lai CL. A prospective study regarding the complications of transcatheter intraarterial lipiodol chemoembolization in patients with hepatocellular carcinoma. *Cancer* 2002;94:1747–1752
341. Chung JW, Park JH, Han JK, Choi BI, Han MC, Lee HS, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology* 1996;198: 33–40
342. Caturelli E, Siena DA, Fusilli S, Villani MR, Schiavone G, Nardella M, et al. Transcatheter arterial chemoembolization for hepatocellular carcinoma in patients with cirrhosis: evaluation of damage to nontumorous liver tissue-long-term prospective study. *Radiology* 2000;215:123–128
343. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008;48(Suppl 1):S20–S37
344. Llovet JM, Bruix J. Molecular targeted therapies in hepatocellular carcinoma. *Hepatology* 2008;48:1312–1327
345. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390
346. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25–34
347. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: a multi-kinase inhibitor for treating cancer. *Nat Rev Drug Discov* 2006;5:835–844
348. Miller AA, Murry DJ, Owzar K, Hollis DR, Abou-Alfa GK, Desai A, et al. Pharmacokinetic (PK) and phase I study of sorafenib (S) for solid tumors and hematologic malignancies in patients with hepatic or renal dysfunction (HD or RD): CALGB 60301. *J Clin Oncol* 2007;25:3538 (abstract)
349. Abou-Alfa GK, Amadori D, Santoro A, Figer JDG A, Lathia C, Voliotis D, et al. Is sorafenib (S) safe and effective in patients (pts) with hepatocellular carcinoma (HCC) and Child-Pugh B (CPB) cirrhosis? *J Clin Oncol* 2008;26:4518 (abstract)
350. Siegel AB, Cohen EI, Ocean A, Lehrer D, Goldenberg A, Knox JJ, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. *J Clin Oncol* 2008;26:2992–2998
351. Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884–896
352. Zhu AX, Sahani DV, di Tomaso E, Duda DG, Catalano OA, Ancukiewicz M, et al. Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): insights from a multidisciplinary phase II study. *J Clin Oncol* 2008;26:4521 (abstract)
353. Faivre SJ, Raymond E, Douillard J, Boucher E, Lim HY, Kim JS, et al. Assessment of safety and drug-induced tumor necrosis with sunitinib in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2007;25:3546 (abstract)
354. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994;91:4082–4085
355. Kruse FE, Joussen AM, Rohrschneider K, Becker MD, Volcker HE. Thalidomide inhibits corneal angiogenesis induced by vascular endothelial growth factor. *Graefes Arch Clin Exp Ophthalmol* 1998;236:461–466
356. Hsu C, Chen CN, Chen LT, Wu CY, Yang PM, Lai MY, et al. Low-dose thalidomide treatment for advanced hepatocellular carcinoma. *Oncology* 2003;65:242–249
357. Patt YZ, Hassan MM, Lozano RD, Nooka AK, Schnirer II, Zeldis JB, et al. Thalidomide in the treatment of patients with hepatocellular carcinoma: a phase II trial. *Cancer* 2005;103:749–755
358. Lin AY, Brophy N, Fisher GA, So S, Biggs C, Yock TI, et al. Phase II study of thalidomide in patients with unresectable hepatocellular carcinoma. *Cancer* 2005;103:119–125
359. Hsu C, Chen CN, Chen LT, Wu CY, Hsieh FJ, Cheng AL. Effect of thalidomide in hepatocellular carcinoma: assessment with

- power Doppler US and analysis of circulating angiogenic factors. *Radiology* 2005;235:509–516
360. Wang J, Chen LT, Tsang YM, Liu TW, Shih TT. Dynamic contrast-enhanced MRI analysis of perfusion changes in advanced hepatocellular carcinoma treated with an antiangiogenic agent: a preliminary study. *AJR Am J Roentgenol* 2004;183:713–719
  361. Breuhahn K, Longerich T, Schirmacher P. Dysregulation of growth factor signaling in human hepatocellular carcinoma. *Oncogene* 2006;25:3787–3800
  362. Ono M, Morisawa K, Nie J, Ota K, Taniguchi T, Saibara T, et al. Transactivation of transforming growth factor alpha gene by hepatitis B virus preS1. *Cancer Res* 1998;58:1813–1816
  363. Sato Y, Kato J, Takimoto R, Takada K, Kawano Y, Miyanishi K, et al. Hepatitis C virus core protein promotes proliferation of human hepatoma cells through enhancement of transforming growth factor alpha expression via activation of nuclear factor-kappaB. *Gut* 2006;55:1801–1808
  364. Jakubczak JL, Chisari FV, Merlino G. Synergy between transforming growth factor alpha and hepatitis B virus surface antigen in hepatocellular proliferation and carcinogenesis. *Cancer Res* 1997;57:3606–3611
  365. Kiss A, Wang NJ, Xie JP, Thorgeirsson SS. Analysis of transforming growth factor (TGF)-alpha/epidermal growth factor receptor, hepatocyte growth factor/c-met, TGF-beta receptor type II, and p53 expression in human hepatocellular carcinomas. *Clin Cancer Res* 1997;3:1059–1066
  366. Yang CH. EGFR tyrosine kinase inhibitors for the treatment of NSCLC in East Asia: present and future. *Lung Cancer* 2008;60(Suppl 2):S23–S30
  367. Su MC, Lien HC, Jeng YM. Absence of epidermal growth factor receptor exon 18–21 mutation in hepatocellular carcinoma. *Cancer Lett* 2005;224:117–121
  368. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol* 2005;23:6657–6663
  369. Thomas MB, Chadha R, Glover K, Wang X, Morris J, Brown T, et al. Phase 2 study of erlotinib in patients with unresectable hepatocellular carcinoma. *Cancer* 2007;110:1059–1067
  370. O'Dwyer PJ, Giantonio BJ, Levy DE, Kauh JS, Fitzgerald DB, Benson AB. Gefitinib in advanced unresectable hepatocellular carcinoma: results from the Eastern Cooperative Oncology Group's Study E1203. *J Clin Oncol* 2006;24:4143 (abstract)
  371. Zhu AX, Stuart K, Blaszkowsky LS, Muzikansky A, Reitberg DP, Clark JW, et al. Phase 2 study of cetuximab in patients with advanced hepatocellular carcinoma. *Cancer* 2007;110:581–589
  372. Hsu C, Cheng JC, Cheng AL. Recent advances in non-surgical treatment for advanced hepatocellular carcinoma. *J Formos Med Assoc* 2004;103:483–495
  373. Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? *Oncologist* 2006;11:790–800
  374. Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma—an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006;23:1535–1547
  375. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005;97:1532–1538
  376. Gish RG, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, et al. Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007;25:3069–3075
  377. Lai CL, Wu PC, Chan GC, Lok AS, Lin HJ. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer* 1988;62:479–483
  378. Yang TS, Lin YC, Chen JS, Wang HM, Wang CH. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer* 2000;89:750–756
  379. Guan Z, Wang Y, Maoleekoonpaioj S, Chen Z, Kim WS, Ratanatharathorn V, et al. Prospective randomised phase II study of gemcitabine at standard or fixed dose rate schedule in unresectable hepatocellular carcinoma. *Br J Cancer* 2003;89:1865–1869
  380. Yen Y, Lim DW, Chung V, Morgan RJ, Leong LA, Shibata SI, et al. Phase II study of oxaliplatin in patients with unresectable, metastatic, or recurrent hepatocellular cancer: a California Cancer Consortium Trial. *Am J Clin Oncol* 2008;31:317–322
  381. Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer* 2004;101:578–586
  382. Louafi S, Boige V, Ducreux M, Bonyhay L, Mansoubakht T, de Baere T, et al. Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. *Cancer* 2007;109:1384–1390
  383. Boige V, Raoul JL, Pignon JP, Bouche O, Blanc JF, Dahan L, et al. Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03–03 trial. *Br J Cancer* 2007;97:862–867
  384. Abou-Alfa GK, Johnson P, Knox J, Lacava J, Leung T, Mori A, et al. Preliminary results from a phase II, randomized, double-blind study of sorafenib plus doxorubicin versus placebo plus doxorubicin in patients with advanced hepatocellular carcinoma. In Proceedings of the 14th European cancer conference of the European Cancer Organisation (ECCO). Barcelona: ECCO; 2007. pp 23–27 (abstract no.: 3500)
  385. Zhu AX, Blaszkowsky LS, Ryan DP, Clark JW, Muzikansky A, Horgan K, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:1898–1903
  386. Sun W, Haller DG, Mykulowycz K, Rosen M, Soulen M, Capparo M, et al. Combination of capecitabine, oxaliplatin with bevacizumab in treatment of advanced hepatocellular carcinoma (HCC): a phase II study. *J Clin Oncol* 2007;25:4547 (abstract)
  387. Asnacios A, Fartoux L, Romano O, Tesmoingt C, Louafi SS, Mansoubakht T, et al. Gemcitabine plus oxaliplatin (GEMOX) combined with cetuximab in patients with progressive advanced stage hepatocellular carcinoma: results of a multicenter phase 2 study. *Cancer* 2008;112:2733–2739
  388. O'Neil BH, Bernard SA, Goldberg RM, Moore DT, Garcia R, Marroquin C, et al. Phase II study of oxaliplatin, capecitabine, and cetuximab in advanced hepatocellular carcinoma. *J Clin Oncol* 2008;26(Suppl):4604 (abstract)
  389. Hsu CH, Yang T, Hsu C, Toh H, Epstein R, Hsiao L, et al. Phase II study of bevacizumab (A) plus capecitabine (X) in patients (pts) with advanced/metastatic hepatocellular carcinoma (HCC): final report. *J Clin Oncol* 2008;26(Suppl):4603 (abstr)
  390. Thomas MB, Chadha R, Iwasaki M, Glover K, Abruzzese JL. The combination of bevacizumab (B) and erlotinib (E) shows significant biological activity in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2007;25(Suppl):4567 (abstract)
  391. Lo CM, Liu CL, Chan SC, Lam CM, Poon RT, Ng IO, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. *Ann Surg* 2007;245:831–842
  392. Lin SM, Lin CJ, Hsu CW, Tai DI, Sheen IS, Lin DY, et al. Prospective randomized controlled study of interferon-alpha in

- preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. *Cancer* 2004;100:376–382
393. Kuzuya T, Katano Y, Kumada T, Toyoda H, Nakano I, Hirooka Y, et al. Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. *J Gastroenterol Hepatol* 2007;22:1929–1935
  394. Piao CY, Fujioka S, Iwasaki Y, Fujio K, Kaneyoshi T, Araki Y, et al. Lamivudine treatment in patients with HBV-related hepatocellular carcinoma—using an untreated, matched control cohort. *Acta Med Okayama* 2005;59:217–224
  395. Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology* 2006;43:233–240
  396. Kumada T, Nakano S, Takeda I, Sugiyama K, Osada T, Kiriyama S, et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. *Hepatology* 1997;25:87–92
  397. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer* 2000;89:500–507
  398. Sakon M, Umeshita K, Nagano H, Eguchi H, Kishimoto S, Miyamoto A, et al. Clinical significance of hepatic resection in hepatocellular carcinoma: analysis by disease-free survival curves. *Arch Surg* 2000;135:1456–1459
  399. Ikeda K, Arase Y, Saitoh S, Kobayashi M, Suzuki Y, Suzuki F, et al. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor—a prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000;32:228–232
  400. Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Yamazaki O, et al. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001;134:963–967
  401. Shiratori Y, Shiina S, Teratani T, Imamura M, Obi S, Sato S, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003;138:299–306
  402. Hung CH, Lee CM, Wang JH, Tung HD, Chen CH, Lu SN. Antiviral therapy after non-surgical tumor ablation in patients with hepatocellular carcinoma associated with hepatitis C virus. *J Gastroenterol Hepatol* 2005;20:1553–1559
  403. Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006;44:1543–1554
  404. Sakaguchi Y, Kudo M, Fukunaga T, Minami Y, Chung H, Kawasaki T. Low-dose, long-term, intermittent interferon-alpha-2b therapy after radical treatment by radiofrequency ablation delays clinical recurrence in patients with hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005;48:64–70
  405. Nishiguchi S, Tamori A, Kubo S. Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005;48:71–75
  406. Hasegawa K, Takayama T, Ijichi M, Matsuyama Y, Imamura H, Sano K, et al. Uracil-tegafur as an adjuvant for hepatocellular carcinoma: a randomized trial. *Hepatology* 2006;44:891–895
  407. Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, et al. Prevention of second primary tumors by an acyclic retinoid, polyphenolic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. *N Engl J Med* 1996;334:1561–1567
  408. Takai K, Okuno M, Yasuda I, Matsushima-Nishiwaki R, Uematsu T, Tsurumi H, et al. Prevention of second primary tumors by an acyclic retinoid in patients with hepatocellular carcinoma. Updated analysis of the long-term follow-up data. *Intervirology* 2005;48:39–45
  409. Hirayama C, Okumura M, Tanikawa K, Yano M, Mizuta M, Ogawa N. A multicenter randomized controlled clinical trial of Shosaiko-to in chronic active hepatitis. *Gastroenterol Jpn* 1989;24:715–719
  410. Oka H, Yamamoto S, Kuroki T, Harihara S, Marumo T, Kim SR, et al. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer* 1995;76:743–749
  411. Shimizu I, Ma YR, Mizobuchi Y, Liu F, Miura T, Nakai Y, et al. Effects of Sho-saiko-to, a Japanese herbal medicine, on hepatic fibrosis in rats. *Hepatology* 1999;29:149–160
  412. Shiota G, Maeta Y, Mukoyama T, Yanagidani A, Udagawa A, Oyama K, et al. Effects of Sho-Saiko-to on hepatocarcinogenesis and 8-hydroxy-2'-deoxyguanosine formation. *Hepatology* 2002;35:1125–1133
  413. Tsuchiya M, Kono H, Matsuda M, Fujii H, Rusyn I. Protective effect of Juzen-taiho-to on hepatocarcinogenesis is mediated through the inhibition of Kupffer cell-induced oxidative stress. *Int J Cancer* 2008;123:2503–2511