US and Europe. Sonazoid consists of perfluorocarbon microbubbles that are stabilized with a surfactant (19, 20). Both SonoVue and Sonazoid are classified as second-generation contrast agents for sonography, and are strongly echogenic in a wide range of frequencies and acoustic pressures owing to the high flexibility of their shell. However, 99% of Sonazoid microbubbles are phagocytosed by Kupffer cells in the liver, whereas only 7.3% of SonoVue microbubbles are phagocytosed in this manner (23). Sonazoid microbubbles are taken up immediately after an intravenous injection and exist as microbubbles for 30 min within Kupffer cells, and hepatic parenchymal imaging reflects the distribution and function of Kupffer cells. Therefore, contrast harmonic sonography with Sonazoid can show a unique 'post-vascular image' in addition to a 'vascular image' (21–25).

In 20 patients (18 HCC; two liver metastases), these hepatic malignancies did not demonstrate intratumoral vessel images clearly after the first injection of perfluorocarbon microbubbles in the post-vascular phase. These included four patients with tumours that showed unclear defects or no defects in the post-vascular phase. In this study, all nodules were confirmed tumour enhancement on contrast-enhanced CT. By re-injection of the contrast medium in these patients, overall enhancement of the defect was seen in 16 (80%) nodules (15 HCC; one liver metastasis), and partial enhancement in four (20%) nodules (three HCC; one liver metastasis). If intratumoral vessel images could not be obtained clearly at the first injection, intratumoral perfusion into the defects could be observed after a second injection. This defect re-injection method facilitated an improvement of the visibility of these hepatic nodules on sonography. Moreover, re-injection of perfluorocarbon microbubbles might contribute to time shortening of a treatment session. Arterial finding of hepatic malignancies could be obtained by the defect re-injection method (24). Thus, a scanning programme in the early vascular phase after the first injection can be omitted in the diagnosis process.

Despite difficulties such as hepatic malignancies that could not be clearly demonstrated on B-mode sonography, contrast harmonic sonography guidance allowed satisfactory results to be achieved. Technically successful ablation was achieved in the first session in 62 (94%) of 66 patients. A complete treatment response was achieved after an average of 1.1 treatment sessions. In addition to improvement of visualization, these results might have been achieved because we had adequate time to perform RF ablation with careful targeting of the defects. During the early vascular phase, a very high skill level is required because the procedure time is too short to search for the enhanced hepatic malignancies and insert the RF electrode. For example, after a single intravenous administration of sulphur hexafluoride microbubbles (SonoVue; Bracco SpA, Milan, Italy) in human volunteers, the blood distribution $t_{1/2}$ was about 1 min and the elimination $t_{1/2}$ was approximately 6 min (30). Contrast-enhanced sonography with sulphur hexafluoride microbubbles could show vascular imaging for a longer duration than air-filled microbubbles (Levovist); nevertheless, contrast harmonic sonography with sulphur hexafluoride microbubbles for guidance of RF ablation might hasten the insertion of the RF electrode during the early vascular phase. Thus, the ability to find defect images in the post-vascular phase is one of the merits of perfluorocarbon microbubbles use.

In three patients with HCC and one with liver metastases, tumour ablation was incomplete after the first session. Despite secondary administration of perfluorocarbon microbubbles, only partial reperfusion imaging of these defects was achieved. Deep tumour location, location behind the costal bone or insufficient enhancement, that is, poor visibility of nodules would likely make a second treatment session necessary. Even if acoustic power of sonography was at a low level, the second-generation microbubbles became more broken as the sonography exposure increased in the field of the tumour (31). Enhancement of the liver parenchyma becomes weaker by prolonged sonographic exposure, and then the defects cannot be demonstrated clearly in the post-vascular phase. Therefore, it might be important to avoid an excessively long observation of the tumour on contrast harmonic sonography in RF ablation.

The principal limitation of this study was the retrospective and noncomparative design, which inherently decreases the statistical strength. Another limitation is the preliminary nature of this study with the relatively small number of patients and short follow-up time. Further prospective studies of this technique with a larger number of patients are warranted. The outcomes in this study can be attributed to the combined the effect of harmonic sonography and the contrast agent, perfluorocarbon microbubbles.

In conclusion, perfluorocarbon microbubbles could facilitate contrast harmonic sonography guidance of RF ablation by extending the time limitation, simplifying the procedure and improving detectability. RF ablation guided by perfluorocarbon microbubble-enhanced sonography could become an easier and more efficient approach to treating hepatic malignancies that are not clearly depicted on B-mode sonography.

Acknowledgement

Yasunori Minami, Kinuyo Hatanaka, Tatsuo Inoue, Satoru Hagiwara, Hobyung Chung and Kazuomi Ueshima analysed the data; Yasunori Minami and Masatoshi Kudo wrote the paper.

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Hepatol Int (2010) 4:439–474
DOI 10.1007/s12072-010-9165-7

GUIDELINES

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

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Received: 11 February 2009 / Accepted: 9 December 2009 / Published online: 18 March 2010

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

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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-alfa, 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 non-responders (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
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).

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 noncirrhotic 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
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).

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_2

Vitamin K_2 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_2 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_2 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_2.

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^2) 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
Surveillance for HCC in high-risk populations is recommended (2a, B).
Surveillance for HCC should be performed by ultrasonography (US) and α-fetoprotein (AFP) every 6 months (2a, B).

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-γ-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
α-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.

α-Fetoprotein

α-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-γ-carboxyprothrombin

Des-γ-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		
				n	Etiology	Characteristics of HCC	Modalities of diagnosis	*n*	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 α-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *CC* case–control study, *CH* chronic hepatitis, *Co* cohort study, *DCP* des-γ-carboxy prothrombin, *GGTII* hepatoma-specific band of serum γ-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_2 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 (neoangiogenesis) [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 [^{18}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 arterioportal (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.

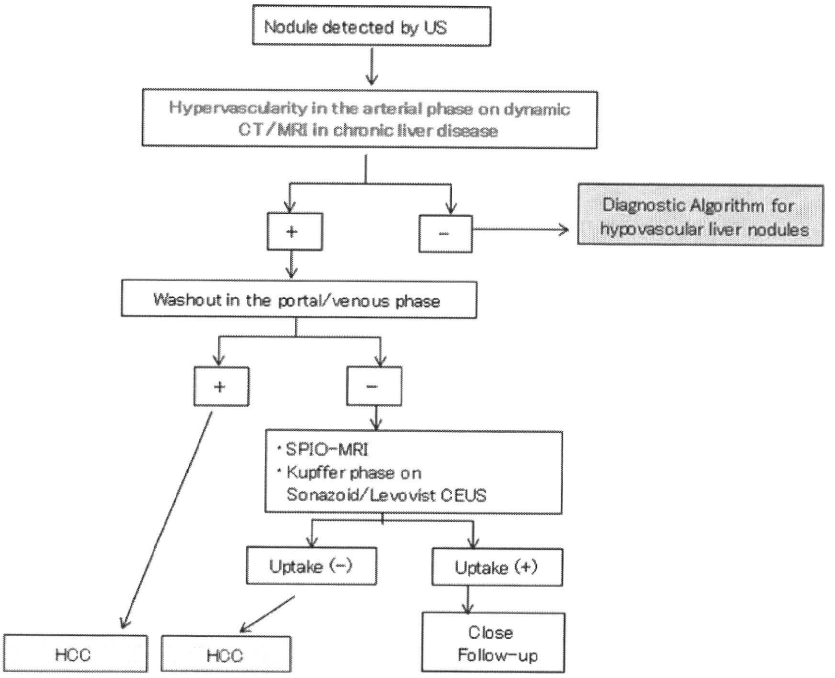

Fig. 1 Diagnostic algorithm of hypervascular HCC

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 CT or 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

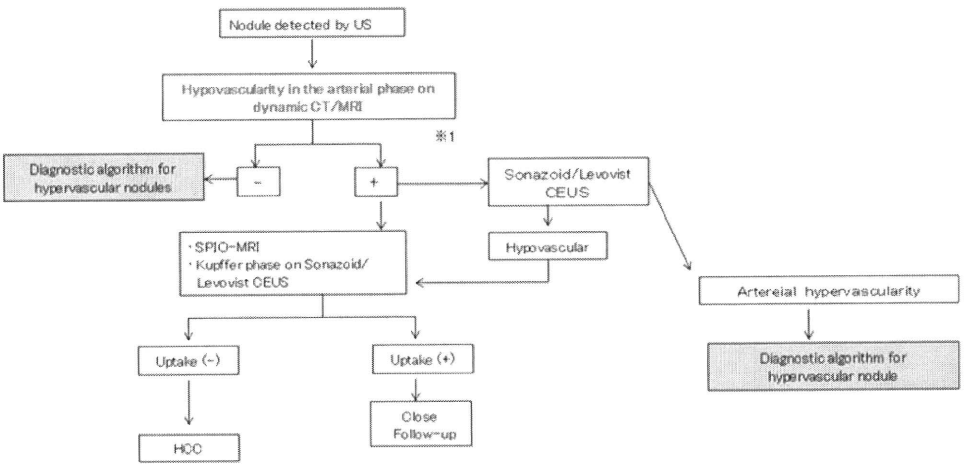

Fig. 2 Diagnostic algorithm of hypovascular HCC

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
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).

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