Surveillance protocol for early detection of HCC

For HCC detection, sensitivity of ultrasonography is higher than serum alpha fetoprotein (AFP) measurement alone, but the specificities are not markedly different. For liver cirrhosis, a combination of the two methods has been reported to increase detection rate compared with detection by ultrasonography or AFP.[3]

There is not yet clear evidence to determine the optimal interval for screening, but HCCs detected in periodic screening by AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II), AFP lectin fraction (AFP-L3) measurement, and ultrasonography are solitary and small in many cases, as compared with those detected in symptomatic patients. Thus, the Japanese Evidence-Based Clinical Practice Guidelines[3] and Consensus-Based Clinical Practice Manual[4] propose ultrasonography and tumor marker measurement every 3–4 months in the super high-risk population, and every 6 months in high-risk populations. Based on HCC doubling times, these intervals appear to be appropriate in Japan, which is different from Western Countries, where screening is done every 6–12 months.[5] At present, all three tumor markers, including AFP, PIVKA-II, and AFP-L3, are covered under the Japanese national health insurance as HCC tumor markers. Measurement of two or more tumor markers increases the sensitivity, while minimizing the specificity reduction, for small liver cancer. For patients with a very nodular background liver parenchyma because of cirrhosis or obesity, and therefore difficult to evaluate ultrasonographically, periodic imaging screening by dynamic computed tomography (CT) (MDCT) or dynamic magnetic resonance imaging (MRI) every 6–12 months is proposed by JSH,[4] which is identical to the protocol in the Japanese Evidence-Based Clinical Practice Guidelines.[3]

Result of early detection of HCC in Japan

In Japan, approximately 65% of the patients are detected at an early stage, for which curative treatment intervention is possible according to the Nationwide survey in 198 000 patients[6] (Fig. 1). This can be attributed to the establishment of a nationwide surveillance system across Japan.

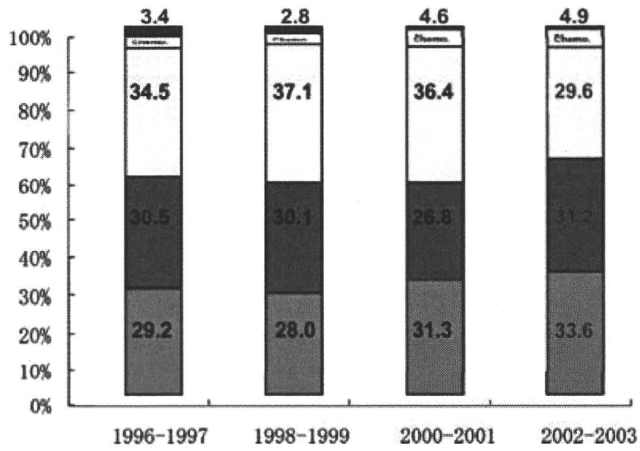

Figure 1 Treatment for newly diagnosed hepatocellular carcinoma (HCC) from 1996–2003 according to Nation-wide survey of Liver Cancer Study Group of Japan. 17th Nationwide survey clearly shows 64.8% of newly diagnosed HCCs receive potentially curative treatment such as operation or ablation. In other words, approximately 65% of HCCs are detected at early stage. ■, others; □, Chemo.; □, transcatheter arterial chemoembolization (TACE); ■, Ablation; ■, Ope.

Markers of HCC tumor biology

Alpha fetoprotein

Alpha fetoprotein is a tumor marker for HCC used worldwide. In Japan, according to the 17th Nationwide Follow-up Survey of Primary HCC by the Liver Cancer Study Group of Japan (LCSGJ),[6] most HCC patients were AFP-positive when the cutoff value was set at 15 ng/mL; however, AFP is positive in some patients with chronic hepatitis, particularly at the stage of liver cirrhosis, and in liver regeneration following necrosis. Therefore, AFP specificity is low depending on the cutoff value, and is considered inappropriate for screening HCC in the USA.[7] Accordingly, to effectively use AFP in clinical practice, it is important to recognize that sensitivity and specificity vary depending on the cutoff value.

Lens-culinaris agglutinin-reactive fraction of alpha fetoprotein

Lens-culinaris agglutinin-reactive fraction of alpha fetoprotein (AFP-L3) fraction was developed as a tumor marker in Japan. When the cutoff value was set to 10%, the sensitivity was approximately 30% (the 17th nationwide Follow-up Survey of Primary HCC by LCSGJ). Hence its clinical usefulness as an HCC surveillance marker is not appreciated in Western countries;[8] however, AFP-L3 is widely used, mainly in Japan, as a marker representing the degree of biological malignancy of HCC. Negative conversion of this marker after treatment is meaningful, although it is only approximately 50% after curative treatments.[9] Conversely, the prognosis of cases remaining positive after treatment is poor, and the rate of distant metastases is high; the possibility of early metastasis within the liver and to other organs should be kept in mind, in such cases, which require careful follow up for early detection of recurrence or intervention (such as interferon [IFN] treatment).

Protein induced by vitamin K absence-II

The sensitivity of protein induced by vitamin K absence-II (PIVKA-II) was 59% for a cutoff value of 40 mAU/mL according to the 17th Nationwide Survey by LCSGJ. The specificity is > 95%, but the positivity rate for 3 cm or smaller HCC is low (~40%). For HCCs larger than 5 cm, the positivity rate was 97%, indicating that this marker is superior to AFP. Further, the incidence of portal tumor thrombosis is high in PIVKA-II-positive cases (annual rate: 21%), and the risk ratio relative to negative cases is reportedly 5.65.[10] Although PIVKA-II is routinely used for HCC surveillance in Japan, the 2003 Single Topical Conference of the American Association of Study of the Liver (AASLD) posi-

tioned it as a diagnostic method,[11] rather than a screening method, because of its low sensitivity nature.

Other tumor markers

In addition to the above three tumor markers, glypican-3[12] and human telomerase reverse transcriptase (hTERT)[13] are attracting attention as HCC markers. Glypican-3 is a cell membrane protein; its positivity rate in HCC patients and specificity were reported to be 40–50 and 95–100%, respectively, showing its usefulness as a tumor marker. Further, the positivity rate is particularly high in the early stage, and the sensitivity rises to more than 80% when used in combination with AFP. In the future, it seems likely that glypican-3 may be used for clinical practice, such as diagnosis and screening for HCC.

hTERT is a telomerase-containing protein that has attracted attention as a cancer marker since the late 1990s. Sensitivity at the time of blood mRNA measurement was 88%, but specificity was lower, 70%. It may be clinically applicable by setting an optimum cutoff value based on a receiver operator curve (ROC).

Newly introduced diagnostic techniques

Contrast-enhanced ultrasound with a new contrast agent, Sonazoid

Clinical significance of contrast-enhanced ultrasound

In the management of HCC, despite advances in diagnostic imaging techniques such as ultrasound (US), CT or MRI, there remain many limitations, such as screening, staging, evaluation of treatment response, treatment guidance, localization of local recurrence after radiofrequency ablation (RFA), and detection of recurrence. Among these problems, Levovist-enhanced US has made a contribution to differential diagnosis,[14,15] evaluation of malignancy grade,[16] evaluation of therapeutic response to transcatheter arterial chemoembolization (TACE),[17–19] and needle insertion guidance.[20,21] However, there are still limitations in the evaluation of the therapeutic response to RFA,[22] screening or staging.

Sonazoid (GE HealthCare, Milwaukee, WI, USA) is a newly introduced second generation ultrasound contrast agent exclusively approved in Japan in 2007. The important characteristics of Sonazoid are that it facilitates real-time imaging in blood flow images at low acoustic power and stable Kupffer phase imaging, tolerable for multiple scanning from 10 to 120 min after its injection. Sonazoid is considered to be more effective and easier to use than Levovist in vascular imaging, and allows visualization, even using non-high-end equipment, and therefore, dependence on operator's skill/equipment is decreased, which may facilitate the widespread use of contrast-enhanced US. Sonazoid-enhanced US provides very stable post-vascular phase images for up to 60–120 min,[23] which resulted in the invention of the breakthrough method, defect reperfusion imaging. Thus, sonazoid-enhanced US with defect reperfusion imaging is an innovative technology that should greatly change the daily clinical practice of HCC investigation.

Development of defect reperfusion imaging (dual phase fusion imaging)

We recently developed defect reperfusion imaging[24–26] using the properties of very stable Kupffer images and real-time fine blood flow images obtained with Sonazoid for typical HCC, which is depicted by CT but not by B mode scanning. This method is a breakthrough for accurate localization and treatment guidance.[25] Until recently, diagnosis in dynamic studies was usually based on enhancing patterns according to a time sequence or phase; however, by introducing the novel idea of dual phase imaging with the re-injection method, both Kupffer and arterial phase images are obtained at the same slice of the ultrasound plane, which is really an innovative technique. Namely, this method is performed as follows: re-injection of Sonazoid is performed into areas that show defects in the post-vascular phase.[23–26] The introduction of this method has solved several limitations in the diagnosis and treatment of HCC, such as detection of small HCCs,[27] evaluation of treatment response,[28] or needle insertion guidance. Detection rate of small HCCs by Sonazoid-enhanced US is even more sensitive than that by MDCT (Fig. 2),[27] and it seems likely that this novel technique will eventually be used worldwide.

MRI using a new contrast agent, Gd-EOB-DTPA in the diagnosis of early HCC

Hepatocellular carcinoma is known to show multistep progression from the hyperplastic nodule to early HCC and finally to moderately/poorly differentiated HCC (Fig. 3). It is important to differentiate between premalignant nodules and early HCC. The imaging diagnosis of HCC by CT/MRI has been made by dynamic acquisition (hemodynamic diagnosis) using extracellular contrast medium, such as iodine contrast agent or gadolinium-diethylene-triamine-pentaacetic acid (GD-DTPA). HCC is supplied solely from arterial, not portal blood flow. Super paramagnetic iron oxide (SPIO) is specifically taken up by Kupffer cells and has been used as a liver-specific contrast agent for MRI since 1997; Kupffer cells are not present in overt HCC.

A newly introduced contrast agent, Gd-EthOxyBenzl-DTPA (Gd-EOB-DTPA), approved in 2008 in Japan, is a hepatocyte-specific MRI contrast medium with a different mechanism, using both dynamic and Kupffer cell imaging. This new contrast medium is useful to diagnose cases that would have been difficult using previous techniques such as dynamic MRI or SPIO-MRI. Gd-EOB-DTPA consists of the extracellular contrast medium, Gd-DTPA, and the lipid-soluble EOB group. Acquisition of both water and lipid solubility increases cell membrane permeability and the agent is therefore taken up by hepatocytes. Although the mechanism for hepatocellular uptake has not been fully clarified, it may involve organic anion transporting polypeptide (OATP1)[29] (Fig. 4). Recently, it was reported that uptake of Gd-DTPA-EOB is regulated by OATP1B3 in humans.[30] For excretion into bile, the active transport out of hepatocytes is by multidrug resistant protein (MRP2) system[31] (Fig. 4). Active transport is indicated by the high biliary excretion rate (~50%) of Gd-EOPB-DTPA. Imaging diagnosis of HCC can be made within 10–20 min after Gd-EOB-DTPA injection.

Typical HCCs show high intensity of Gd-EOB-DTPA in the arterial-dominant phase and low intensity in the portal-dominant

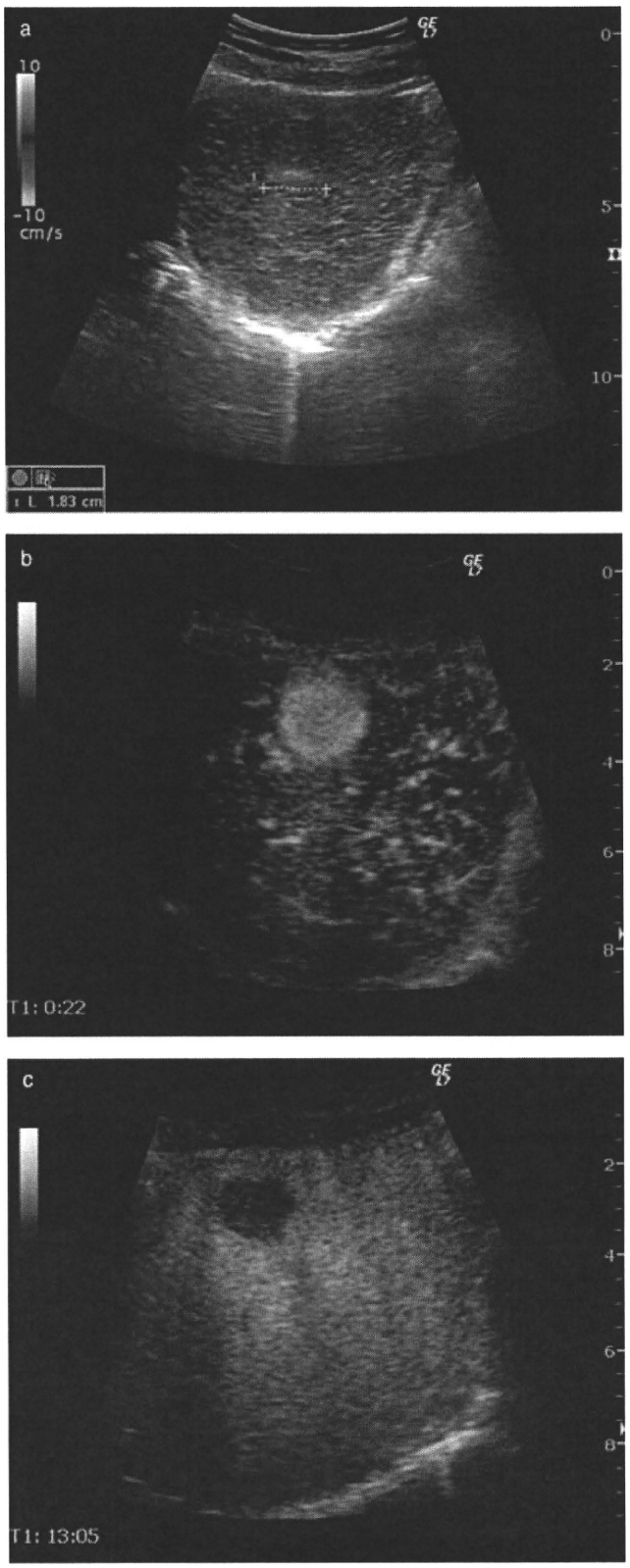

Figure 2 A case of hepatocellular carcinoma (HCC) demonstrated by Sonazoid-enhanced ultrasound. (a) B-mode image shows ill-defined isoechoic nodule measuring 1.83 cm in size. (b) Sonazoid-enhance ultrasound (US) clearly demonstrates this nodule as a hypervascular tumor. (c) Kupffer phase image shows this nodule as a clear defect, suggesting typical HCC.

phase and thereafter. In the arterial-dominant phase, Gd-EOB-DTPA is not taken up by normal hepatocytes, and thus, HCC nodules are intensely stained in the arterial dominant phase. In the portal-dominant phase and thereafter, Gd-EOB-DTPA is gradually taken up by normal hepatocytes, increasing the clear contrast between normal liver parenchyma and HCC nodules (Fig. 5).[29,32] After 20 min, the liver/tumor contrast is as high as or superior to that in CT during arterial portography (CTAP) except for approximately 5% of overt HCC cases, which show high or iso-intense on hepatocyte phase image (Table 1). Hepatocyte phase image of Gd-EOB-DTPA MRI is speculated to be regulated by the balance of OATP1B3 and MRP2 expression (Table 1).

In well-differentiated early HCC, some nodules may not be completely shown as defective areas on CTAP, but Gd-EOB-DTPA uptake is apparently lower than that in the surrounding normal liver parenchyma, being imaged as a low-intensity nodule. Well-differentiated early HCCs having Kupffer cells with enhanced SPIO uptake and receiving portal blood flow on CTAP have been difficult to characterize by SPIO-MRI or CTAP. However, they can be imaged clearly as hypointense nodules using Gd-EOB-DTPA hepatocyte phase MRI in many early HCC cases due to differences in the biological characteristics. This indicates that this new contrast agent may lead to a breakthrough in the diagnosis of early HCC (Table 2) (Fig. 6),[32,33] which has been clinically difficult and difficult even by pathological diagnosis in biopsy samples. It could be that this technique may be the most sensitive tool for detection of the phenotypic change of early hepatocarcinogenesis, much more sensitive than CTAP, computed tomography hepatic arteriography (CTHA), or SPIO-MRI (Fig. 7).

There are two reasons why pathological diagnosis of early HCC is sometimes difficult using biopsy: (i) possibility of sampling error; and (ii) stromal invasion, an important clue of pathological diagnosis of early HCCs,[34] can occasionally not be found in the biopsy sample compared with the resected specimen. Recently, a consensus on pathological diagnosis of early HCC has been established between 'East and West'.[34] Diagnosis of early HCC by Gd-EOB-DTPA-MRI may be the most comparable tool with that by expert liver specialized pathologist compared with pre-existing imaging modalities according to multicenter trials (Table 2). Accuracy in diagnosing early HCC is as high as 93%, which is much better than CTAP (Table 2). If so, this will change the diagnostic algorithm by introducing Gd-EOB-DTPA MRI in hypervascular and hypovascular liver nodules[4] (Figs 8,9).

Value of an integrated staging system

Various staging systems have been proposed for HCC and are used in the different regions, such as: (i) Okuda stage; (ii) Barcelona Clinic Liver Cancer (BCLC) stage;[35,36] (iii) Cancer of Liver Italian Program (CLIP) score;[37] (iv) Japan Integrated Staging (JIS)

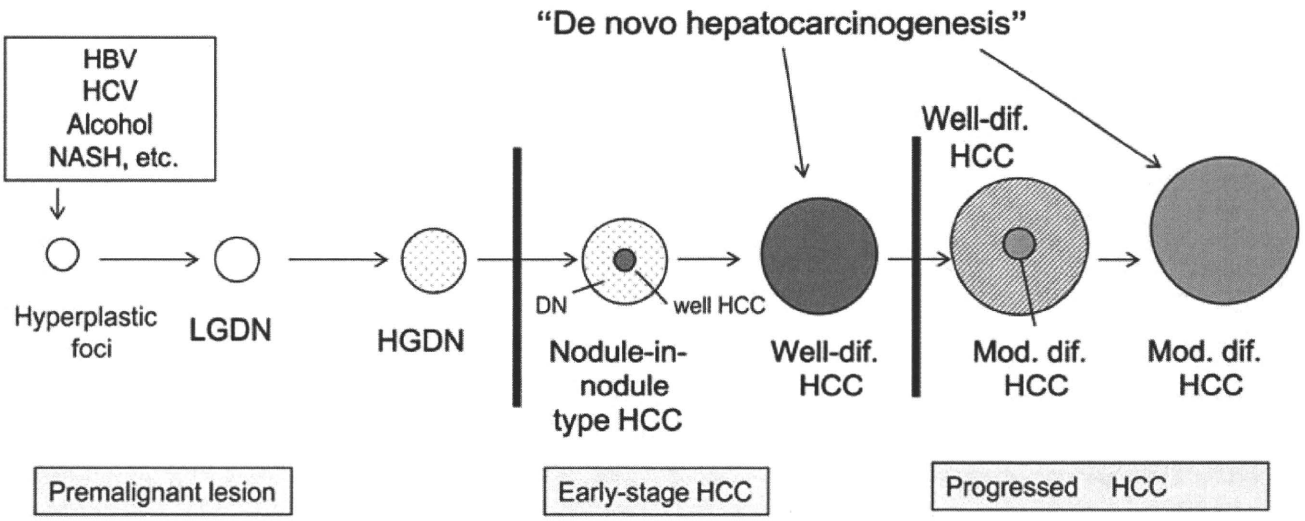

Figure 3 Schematic representation of multistep progression of human hepatocarcinogenesis. Differentiation between early-stage hepatocellular carcinoma (HCC) and premalignant lesion is extremely important. ○, Hyperplastic foci or low grade dysplastic nodule (LGDN); ○, High grade dysplastic nodule (HGDN); ●, Well-differentiated HCC (well HCC); ●, Moderately differentiated HCC (classical overt HCC). HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

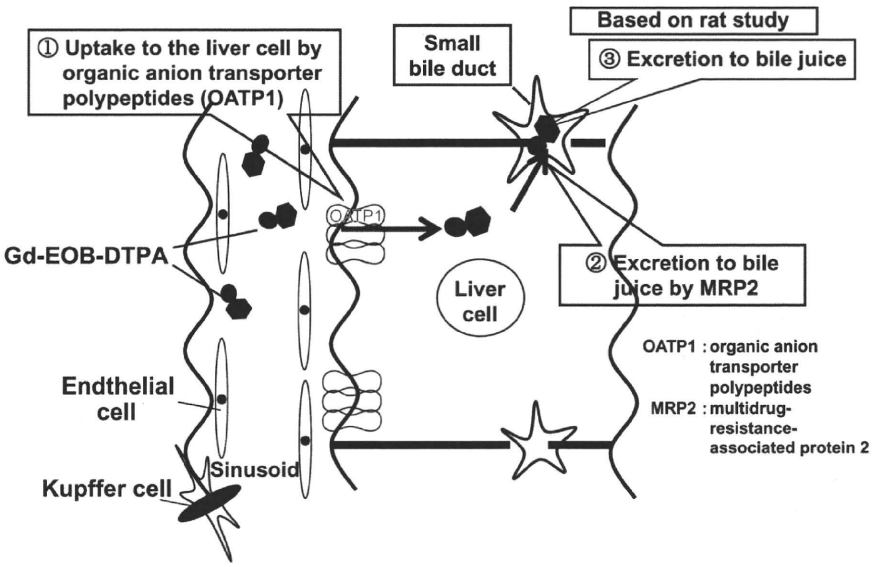

Figure 4 Pharmacokinetics of Gd-EOB-DTPA. Gd-EOB-DTPA is uptaken to the hepatocyte by organic anion transporter peptides (OATP1). Excretion to bile juice is believed to be regulated by multidrug resistance-associated protein (MRP)2.

score;[38,39] and (v) Tokyo Score.[40] In Japan, the JIS score, using both the LCSGJ TNM[41] and Child-Pugh stages, is considered to be the most useful for integrated staging of HCC. The CLIP score has several disadvantages: specification of the tumor-spreading degree is approximate, only AFP is used as a biological malignancy marker, and stratification ability is poor in advanced cases (many cases cluster to a score of 0–2).

The original JIS score used Child-Pugh staging, but the modified JIS score using liver damage instead is frequently used by liver surgeons.[42] The modified JIS score may be useful in planning hepatectomy because LCSGJ liver damage is more strictly classified. Recently, new staging systems for predicting prognosis have been developed; for example, the BALAD score,[43] which consists of the albumin level, bilirubin level, and three tumor markers (AFP, AFP-L3, PIVKA-II). The reported advantages of the BALAD score are that it does not require a tumor-spreading stage. The second method is the biological marker-combined JIS score,[44] which is a combination of the original JIS score and three tumor markers (AFP, PIVKA-II, AFP-L3). This staging system seems to be superior to the original JIS score and BALAD score.[44]

Globally, CLIP scores and BCLC stage are used in Europe and North America as staging systems; however, they have different characteristics: the BCLC stage is basically a treatment-selection system for deciding on a therapeutic strategy, whereas CLIP and JIS scores are prognostic predictors for staging. The CLIP score and BCLC stage tend to predict the prognosis of only large HCCs,

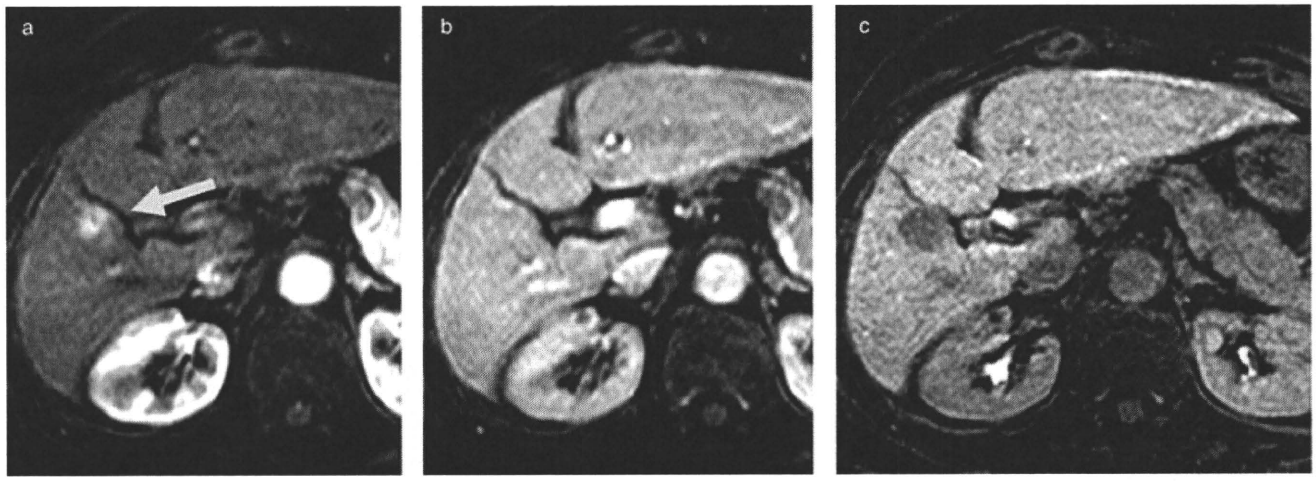

Figure 5 Typical findings of hepatocellular carcinoma (HCC) on Gd-EOB-DTPA magnetic resonance imaging (MRI). (a) Arterial enhancement (arrow) is evident or arterial phase. (b) Slight washout is seen on portal phase. (c) Clean defect is seen on hepatocyte specific phase 20 min later.

Table 1 Relationship between expression of OATP1B3/MRP2 and findings on hepatocyte phase

	Uptake transporter (OATP 1B3)	Excretory transporter (MRP2)	Hepatocyte phase imaging
Dysplastic nodule	+	+	Iso-high intense
Early HCC	(+)	(+)	(Low-intense)
	–	+	Low-intense
Well~Mod.dif.HCC	+ (5%)	+	Iso-high intense
		–	Iso-high intense (green hepatoma)
	– (95%)	–	Low-intense
Poorly dif.HCC	–	–	Low-intense

OATP1, organic anion transporter polypeptides, MRP2, multidrug-resistance-associated protein 2.

Table 2 Accuracy of the differentiation of early hepatocellular carcinoma (HCC) and premalignant lesions by hepatocyte phase Gd-EOB-DTPA magnetic resonance imaging (MRI) for hypovascular hepatocytic nodules

Only resected specimens: 30		Pathological findings	
		e-HCC	DN or RN
Signal intensity in hepato-biliary phase with Primovist	Low—slightly low (24)	23	1
	Iso—high (6)	1	5

AccuracyL 93% (23+5/30). DN, dysplastic nodule; e-HCC, early hepatocellular carcinoma; RN, regenerative nodule.

but the JIS score is most useful to predict the prognosis of many small liver cancers.

Attention needs to be paid to the fact that the BCLC stage corresponds to the Japanese treatment algorithm, but is not a prognostic prediction staging system. For countries incapable of detecting HCC early or in developing countries with insufficient screening systems and diagnostic instruments, the CLIP score may provide good stratification as a prognostic prediction system. In the future, the JIS score may be used worldwide when surveillance systems for early detection of HCC become more common.

For practical purposes, the following conditions are essential for comprehensive analysis or staging of all cases of liver cancer: the system should: (i) be simple; (ii) have no missing data; (iii) be able to be used by anyone anywhere; (iv) be easy to memorize; and (v) be superior for stratifying early, intermediate, advanced, and terminal cases. Considering these conditions, the JIS score or bm-JIS score may be the most appropriate among current systems for the overall stratification of liver cancer cases in Japan.

Hepatic arterial infusion chemotherapy for advanced HCC

Until sorafenib was introduced, there was no effective anticancer drug for advanced liver cancer. 'Far advanced liver cancer represents stage IVa liver cancer accompanied by vascular invasion and stage IVb liver cancer accompanied by distant metastasis, for which low-dose fluorouracil platinum (FP) (5FU and cisplatinum)[45] therapy, and hepatic arterial infusion of 5FU in combination with IFN treatment[46] have been established as an effective treatment option in Japan. In fact, response rate (complete response + partial response [CR+PR]) reaches to 46% according to the Nationwide Survey by LCSGJ[6] (Fig. 10). In addition, it is well established that overall survival of the responder is superior to

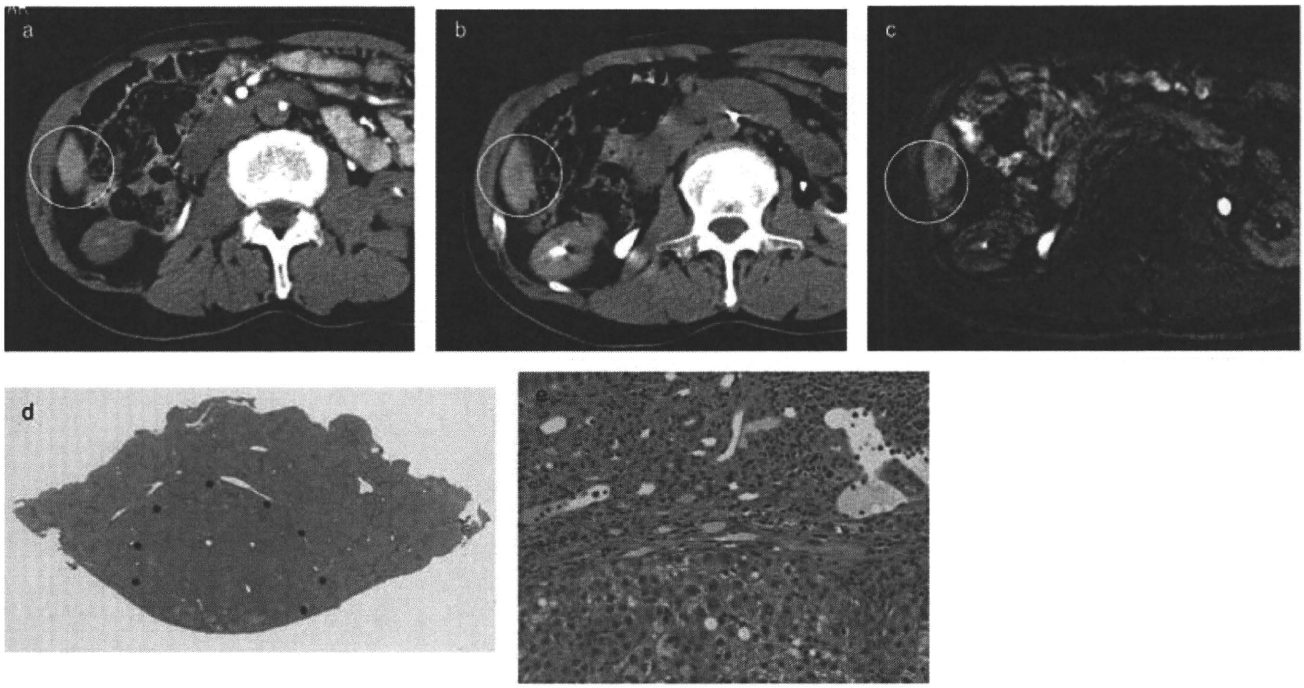

Figure 6 Early hepatocellular carcinoma (HCC), which was confirmed by Gd-EOB-DTPA magnetic resonance imaging (MRI). (a) Computed tomography hepatic arteriography (CTHA) does not show any hypervascularity. (b) CT during arterial portgraphy (CTAP) shows slight low dense mass on Segment 6. (c) Gd-EOB-DTPA magnetic resonance imaging (MRI) shows low intense mass at the hepatocyte phase, strongly suggestive of early HCC. (d) Pathological findings of resected specimen clearly shows vaguely nodular type HCC, suggesting early HCC. (e) Microscopical findings clearly show well-differentiated HCC with stromal invasion, which is a strong diagnostic clue of early HCC.

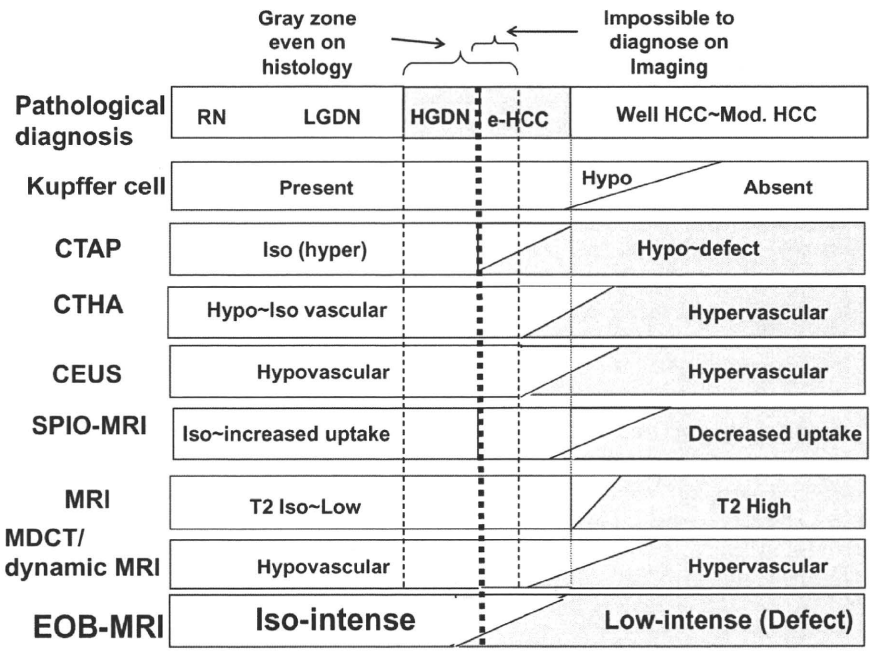

Figure 7 Gd-EOB-DTPA magnetic resonance imaging (MRI) is the most sensitive technique in the detection of initial phenotypic change of human hepatocarcinogenesis among various pre-existing imaging modalities. CEUS, contrast-enhanced ultrasound; CTAP, CT during arterial portgraphy; CTHA, computed tomography hepatic arteriography; EOB, EthOxyBenzl; HGDN, high grade dysplastic nodule; LGDN, low grade dysplastic nodule; MDCT, multidetector row CT; MRI, magnetic resonance imaging; SPIO, super paramagnetic iron oxide.

that of non-responders or best supportive care groups. However, intra-arterial infusion is complex because establishment of a reservoir port for arterial infusion is necessary; therefore, this technique is not performed in Western counties.

Recently, maintenance of the blood IFN level using pegylated IFN (PEG-IFN), and its efficacy in combination with an oral 5FU prodrug, S-1, (PEG-IFN + S1 combination therapy),[47] have been demonstrated to some extent. Further investigation, including a

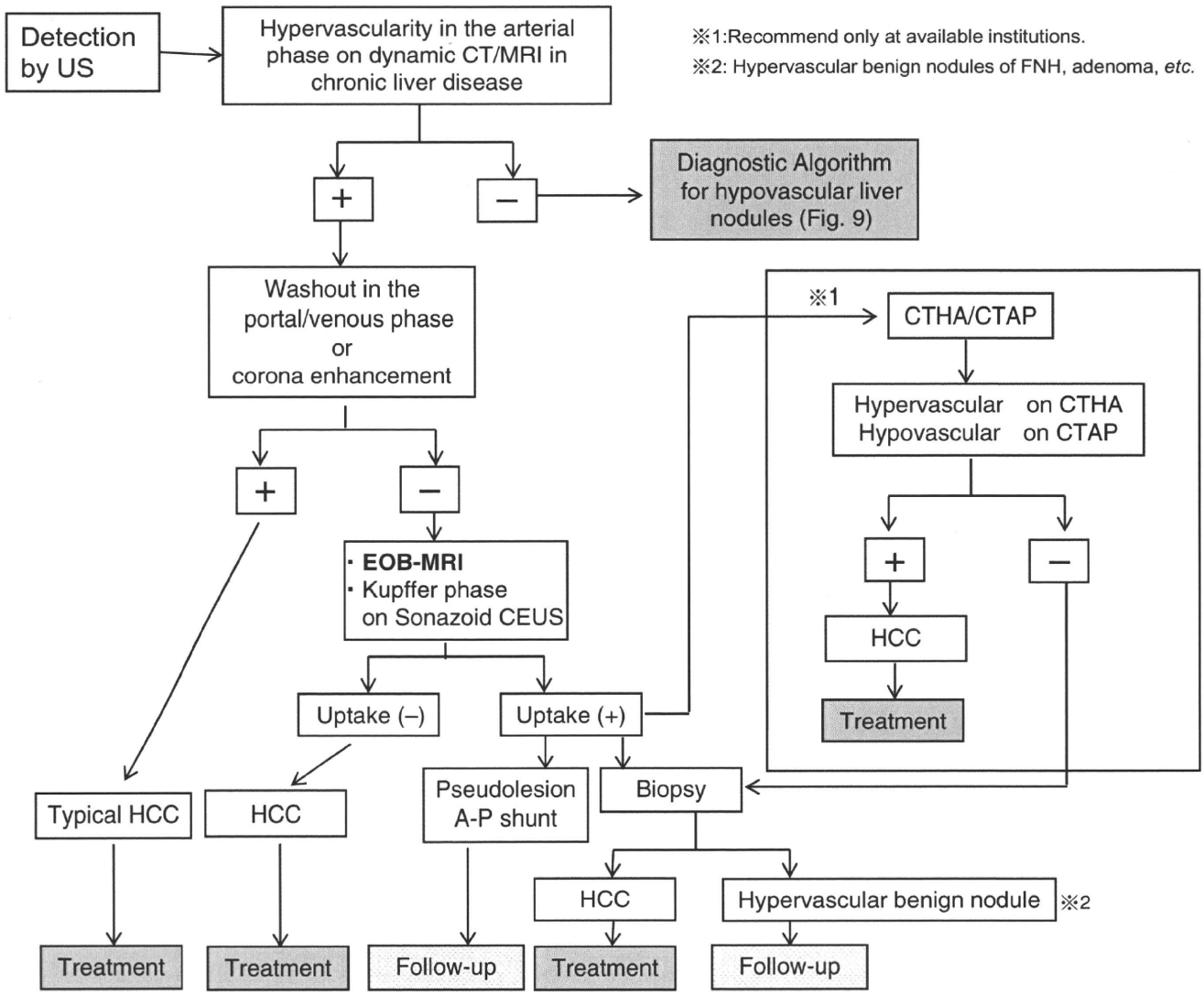

Figure 8 Diagnostic and treatment algorithm for hypervascular liver nodules according to clinical practice manual recommended by Japan Society of Hepatology (partially modified and cited from Narita et al. 2009[30]). CEUS, contrast-enhanced ultrasound; CT, computed tomography; CTAP, CT during arterial portgraphy; CTHA, computed tomography hepatic arteriography; EOB, EthOxyBenzl; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound.

prospective randomized study, is necessary. Moreover, hepatic intra-arterial infusion chemotherapy is not recommended in the AASLD guidelines.[5] Although the response rate is high, efficacy, especially survival benefit of intra-arterial infusion chemotherapy and that using an intractable delivery port system should be confirmed by further randomized studies.

New treatment option: Molecular targeted agent, Sorafenib

Molecular-targeted drugs are agents that exploit genetic differences between cancer and normal cells and specifically inhibit molecules involved in cancer growth and metastasis. The earliest successful agents have been Imatinib, Trastuzumab, and Gefitinib, all breakthrough agents developed from basic studies on tyrosine kinase or serine-threonine-mediated intracellular signal transduction.

Although HCC is the 3rd greatest cause of cancer death worldwide, the molecular mechanism(s) of its growth and progression have not been fully clarified. It is a hypervascular tumor, similar to renal cell carcinoma, but until recently, the efficacy of angiogenesis inhibitors alone has been limited. Sorafenib is a multikinase inhibitor that clearly prolongs the overall survival in patients with advanced HCC by 44%;[48] it has been approved for advanced HCC in Western countries since 2007, and is regarded as standard of care treatment option for advanced HCC with vascular invasion or extrahepatic metastases.

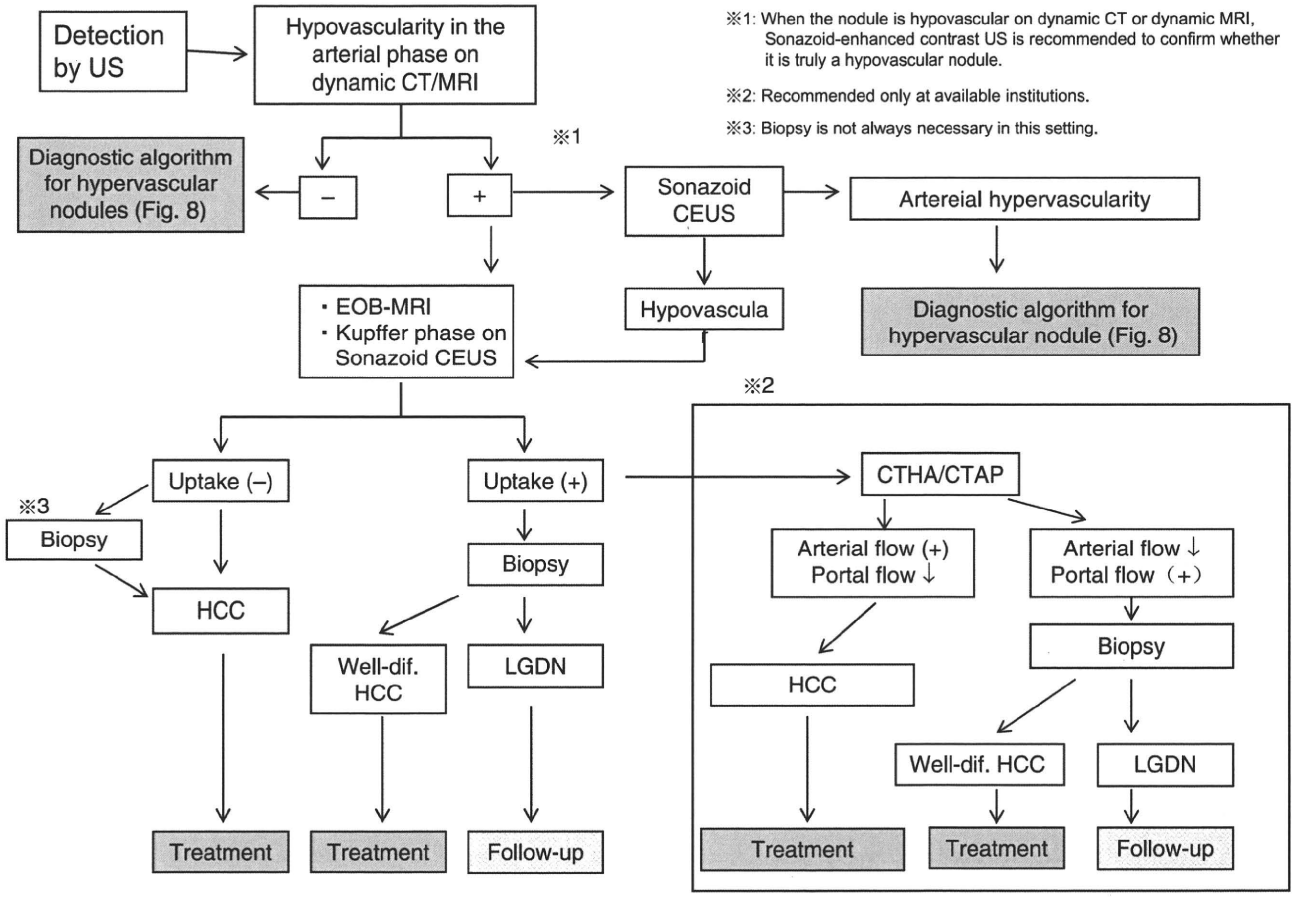

Figure 9 Diagnostic treatment algorithm for hypovascular liver nodules according to Japan Society of Hepatology (cited from Kudo et al. 2007[50]). CEUS, contrast-enhanced ultrasound; CT, computed tomography; CTAP, CT during arterial portgraphy; CTHA, computed tomography hepatic arteriography; EOB, EthOxyBenzl; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; LGDN, low grade dysplastic nodule; MRI, magnetic resonance imaging; US, ultrasound.

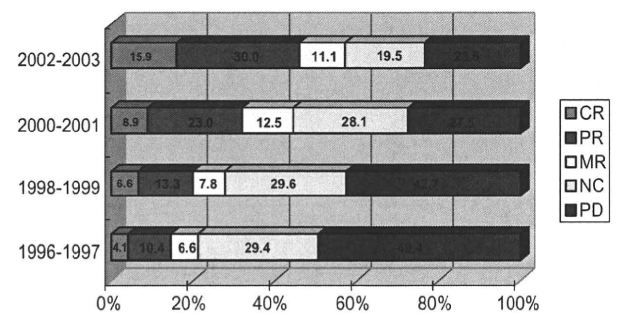

Figure 10 Response rate of hepatic arterial infusion chemotherapy (HAIC) from 1996 to 2003 reported by Nation-wide survey of Liver Cancer Study Group of Japan. Response rate during 2002–2003 reached 45.9%, which is very high. CR, complete response; MR, minor response; NC, no change; PD, progressive disease; PR, partial response. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

Sorafenib, developed by Bayer HealthCare (Germany), is a low-molecular-weight compound discovered by screening inhibitors of Raf kinase, an important molecule in the mitogen activating protein (MAP) kinase cascade located downstream of growth factor receptors. Sorafenib exhibits strong inhibitory activity for not only wild type c-Raf, but also for V600E mutant b-Raf and other receptor tyrosine kinases involved in angiogenesis and cell growth, such as vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor (PDGFR), Fms-related tyrosine kinase-3 (Flt-3), and c-Kit.

The phase III study for HCC (SHARP trial)[48] was performed as a randomized double-blind placebo-controlled multicenter study initiated in March 2005. The subjects had advanced HCC at ECOG PS 0–2 with Child-Pugh A liver function and no previous systemic chemotherapy. There were two study groups, Sorafenib (400 mg b.i.d.) and placebo treatment, and the primary end point was overall survival (OS). Secondary endpoints were time to progression (TTP).

Six hundred and two patients met the inclusion criteria, and 299 and 303 were randomly allocated to the Sorafenib and placebo

groups, respectively. On interim analysis, the median OS was 10.7 months in the Sorafenib group and 7.9 months in the placebo group, showing 44% improvement (hazard ratio: 0.69, *P*-value = 0.0006). TTP was 5.5 months in the Sorafenib group and 2.8 months in the placebo group, showing 73% prolongation (hazard ratio: 0.587, *P*-value = 0.000007). Grade 3 and 4 adverse events for which a causal relationship with Sorafenib could not be ruled out were diarrhea and skin reaction.

In August 2007, it was reported that Sorafenib also prolonged overall and progression-free survival in a phase III study for HCC performed in the Asia Pacific region, involving 226 Chinese, Korean, and Taiwanese patients. Data demonstrated similar efficacy and safety of Sorafenib on HCC as in the SHARP study.[49] In Japan, a phase I study has been completed, and a phase III study in HCC patients following TACE is currently underway. In addition, a phase III trial for HCC of acyclic Retionid, a vitamin A analog, after resection or RFA is also underway in Japan.

A global phase III trial of Sorafenib as adjuvant therapy after surgery or ablation is now ongoing (STORM trial) and a global phase II trial of Sorafenib as a maintenance therapy with a combination of TACE is also ongoing (SPACE trial). A phase I/II trial of a combination therapy of Sorafenib with hepatic arterial infusion chemotherapy (HAIC) is also ongoing in Japan (SILIUS trial). These results are awaited to confirm its usefulness in the daily clinical practice.

Treatment algorithm for HCC and impact of molecular targeted agents

Evidence-based treatment algorithm for HCC in Japan

Treatment algorithm in the west

The treatment algorithms in Europe and North America were published as the European Association For the Study of the Liver (EASL) consensus in 2001,[35] and then as the AASLD Clinical Practice Guidelines in Hepatology in 2005.[5] Both were prepared based on BCLC staging. The BCLC staging classification consists of stages 0 to D. Palliative treatment only is specified for stage D, while stage 0 is defined as a very-early stage, specifying 2 cm or smaller solitary liver cancers with carcinoma *in situ*, which corresponds to early HCC in Japan. These are solitary, and resection is desirable when portal pressure and bilirubin levels are normal. When portal hypertension is present, other potentially curative treatments, such as liver transplantation and local treatment, are recommended. For solitary or ≤ 3 HCC, ≤ 3 cm lesions with mild portal hypertension, liver transplantation or local ablation is recommended. These are very strict criteria, and only stages 0 and A are indicated for radical treatments, that is, resection, local ablation, and liver transplantation. The intermediate stage (Stage B) specifies multinodular lesions, and the advanced stage (Stage C) specifies cases with vessel invasion or extrahepatic spread. For Stage B patients, TACE is recommended and for Stage C patients Sorafenib is recommended as a standard of care treatment.

A consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology

A Japanese expert panel established a consensus-based treatment algorithm based on therapeutic policies widely used in Japan.[50] Since Sorafenib is proved as a standard of care treatment for advanced HCC with major vascular invasion or extrahepatic spread,[50] a modified version of this consensus-based algorithm has been proposed.[51]

The original algorithm first divides cases based on the presence or absence of extrahepatic lesions, liver function, vascular invasion, number of tumors, and tumor size. It also divides treatment options into curative treatments (resection or local ablation), TACE, arterial infusion chemotherapy, liver transplantation, and palliative treatment. The algorithm essentially follows the evidence-based treatment algorithm,[3] but treatments widely performed in Japan were included by consensus, even though evidence is not always present.

Resection or local ablation is performed for three or fewer nodules of ≤ 3 cm with no extrahepatic lesion, good liver function, and no vascular invasion. In this group, local ablation or resection is potentially curative and a good prognosis can be expected. Although the number of nodules is three or fewer, when the tumor exceeds 3 cm, resection or TACE is selected. Additional local ablation following transarterial treatment (Lipiodol TACE or HAIC) may increase curability. IFN therapy after curative therapy has proved to be useful for improving patient survival;[52] therefore, it is recommended to treat patients with HCV who can tolerate IFN therapy. In the future, Sorafenib may become a first choice of treatment for adjuvant therapy if positive results are obtained by ongoing global clinical trial (STORM trial) (Fig. 11).

For patients with four or more lesions, TACE or HAIC is recommended. Local ablation in combination with TACE or HAIC may be more beneficial for ≤ 5–6 lesions. Sorafenib may be useful as a maintenance therapy between several procedures of TACE in order to reduce the numbers of TACE, thus avoiding the impaired liver function caused by repeated TACE. As a result, it may be beneficial to improve patient survival, but there is not yet solid evidence to support this concept. The positive results of several clinical trials (SPACE trial, TACTIS trial, Brisk-TA trial) (Fig. 11) in this setting awaited before this strategy is introduced in the clinical settings.

For patients with an extrahepatic lesions and good liver functional reserve, Sorafenib is currently the standard of care.

Establishment of an original Japanese treatment algorithm was necessary because the situation in Japan, including the availability of transplantation, is different from that in Western counties. The algorithm established by the Japan Society of Hepatology is not necessarily based on scientific evidence; indeed, consensus-based algorithm was combined with an evidence-based algorithm and opinions of JSH experts. Since it is also difficult to state whether the European or North American algorithm is strictly based on evidence, the JSH consensus-based treatment algorithm may be valid; thus, a treatment algorithm based on large scale of specialists' consensus and treatment strategy performed in real practice in Japan is important. However, this algorithm should be carefully revised through prospective trials for issues lacking evidence.

Ongoing clinical trials with molecular targeted agents

In addition to STORM, SPACE trials and TACTICS trials using Sorafenib in combinations with TACE (see earlier), the SILIUS

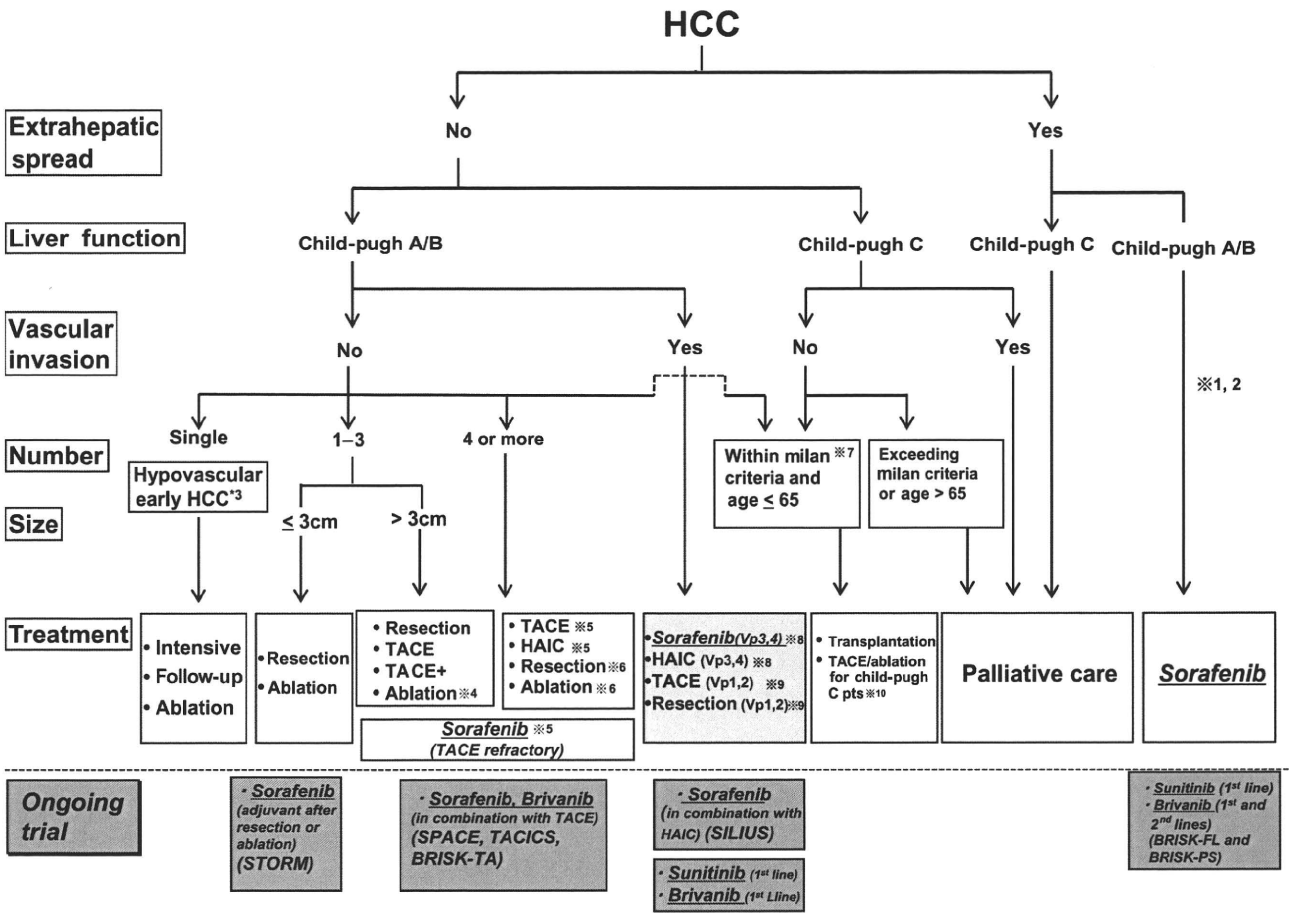

Figure 11 Consensus-based treatment algorithm for hepatocellular carcinoma (HCC) proposed by the Japan Society of Hepatology modified and updated in 2009 from its original version in 2007. Sorafenib is a standard of care for advanced HCC with extrahepatic spread and/or vascular invasion in major branches. Ongoing clinical trials include Sorafenib treatment after resection or ablation (STORM trial), combination therapy of transcatheter arterial chemoembolization (TACE) + Sorafenib (SPACE trial, TACTICS trial) and TACE + Brivanib (BRISK-TA), combination therapy of Sorafenib + Hepatic arterial infusion chemotherapy (HAIC) (SILIUS trial), and finally head-to-head trial between Sorafenib and Sunitinib/Brivanib for advanced HCC. ※1: Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. ※2: Sorafenib is the first choice of treatment in this setting as a standard of care. ※3: Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following cases: (i) when the nodule is diagnosed pathologically as early HCC; (ii) when the nodules show decreased uptake on Gd-EOB-MRI; or (iii) when the nodules show decreased portal flow by computed tomography during arterial portgraphy (CTAP), since these nodules are known to frequently progress to the typical advanced HCC. ※4: Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated. ※5: TACE is the first choice of treatment in this setting. HAIC using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose fluorouracil platinum (FP) (5FU+CDDP) or intra-arterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also a treatment of choice for TACE refractory patients with Child Pugh A liver function. ※6: Resection is sometimes performed even when number of nodules exceeds four. Furthermore, ablation is sometimes performed in combination with TACE. ※7: Milan criteria: Tumor size ≤ 3 cm and tumor numbers ≤ 3; or solitary tumor ≤ 5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for relatively younger patients with frequently or early recurring HCC after curative treatments. ※8: HAIC or Sorafenib is recommended for HCC patients with Vp3 (portal invasion at the 1st portal branch) or Vp4 (portal invasion at the main portal branch). ※9: Resection and TACE is frequently performed when portal invasion is minimal, such as Vp1(portal invasion at the 3rd or more peripheral portal branch) or Vp2 (portal invasion at the 2nd portal branch). ※10: Local ablation therapy or subsegmental TACE is performed even for Child-Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites, and a low bilirubin level (< 3.0 mg/dL). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child-Pugh C patients. A prospective study is necessary to clarify this issue. Even in Child-Pugh A/B patients, transplantation is sometimes performed for relatively younger patients with frequently or early recurring HCC after curative treatments.

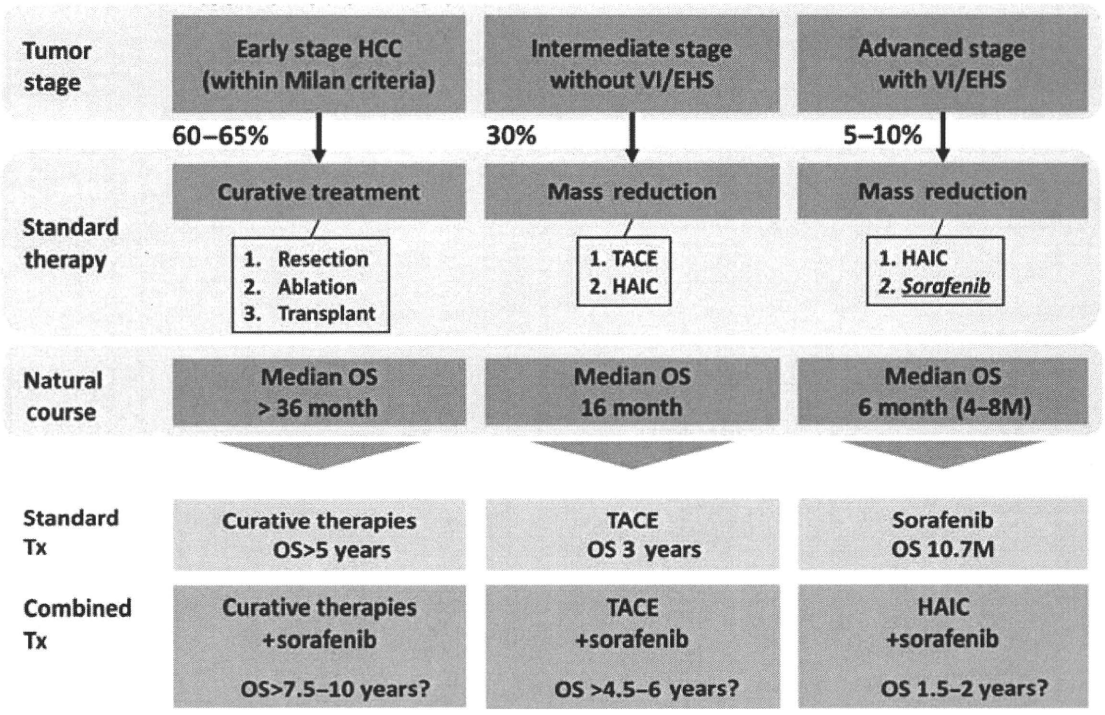

Figure 12 Outcome of standard treatment modality and expected future outcome by combination therapy with Sorafenib or other molecular targeted agents (MTAs). Prolonged life expectancy was calculated as 1.5 to 2.0 times better than the placebo arm by calculating hazard ratio (0.52) and mean survival time (MST) (14.5 *vs.* 10.2 months) by SHARP Subanalysis study, presented at the American Society of Clinical Oncology Meeting in 2008. For early stage hepatocellular carcinoma (HCC) without vascular invasion (VI) and/or extrahepatic spread (EHS), outcome is expected to be prolonged from MST of 5.0 years to 7.5 to 10.0 years by adjuvant use of Sorafenib after resection or ablation. For intermediate stage HCC without VI or EHS, outcome is expected to be prolonged from 3.0 years to 4.5–6.0 years when combination therapy with transcatheter arterial chemoembolization (TACE) is performed. Similarly, for advanced stage HCC with VI and/or EHS, outcome is expected to be prolonged from 10 months to 1.5–2.0 years when hepatic arterial infusion chemotherapy is combined with Sorafenib. HAIC, hepatic arterial infusion chemotherapy.

trial to compare Sorafenib in combination with HAIC is under investigation in Japan. Furthermore, head-to-head trials of Sunitinib versus Sorafenib and Brivanib versus Sorafenib (BRISK-FL trial) for advanced HCC are ongoing globally. Finally, second line trials of Brivanib for Sorafenib failure have been initiated as a global clinical trial (BRISK-PS trial). In addition, Brivanib in combination with TACE (BRISK-TA trial) is also ongoing. The results of all of these trials are eagerly awaited for their hope to provide better outcomes at different stages of HCC (Fig. 11). If positive results are obtained in these trails, the life expectancy at each stage could be much prolonged, at least as calculated theoretically by using hazard ratios incorporated from the SHARP trial. Subanalysis data presented at the ASCO 2008 clearly showed that in HCC patients without vascular invasion or extrahepatic spread hazard ratio of the prolongation of life expectancy is 0.52 and median survival time (MST) is 1.5 times better than placebo arms. If it can be incorporated in earlier stage HCC patients, Sorafenib will prolong the life expectancy approximately 1.5–2.0 times compared with the standard of care group in early and intermediate stage patients (Fig. 12). This could be translated that Sorafenib use in earlier stage in combination with standard of care treatment (resection, ablation, or TACE) will prolong HCC patients' life expectancy (1.5–5.0 years) (Fig. 12).

Conclusion

In this review, recent progress of the management of HCC, including issues from surveillance to molecular-targeted therapy for HCC, has been reviewed. It is strongly expected that this article will enhance the most up-to-date knowledge on HCC for the readers of the *Journal of Gastroenterology and Hepatology*.

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GUIDELINES

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	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.