agulated tumor, surrounding liver tissue, and recurrent tumor (residual viable tumor) present complicated echogenicity, and it was not possible even for experienced operators to identify the recurring foci, which are clearly demonstrated as enhanced areas on CT, by B-mode US. Because of the presence of an infinite number of US planes and a different cross-sectional plane from CT [26], it is difficult to identify the viable tumor by referring to CT image. However, defect reperfusion imaging using Sonazoid now makes the detection of locally recurrent foci by CEUS possible, warranting its description as a revolutionary breakthrough.

Depiction of Recurrence after Local Treatment during Periodical Follow-Up

Both local recurrence and intrahepatic distant recurrence during follow-up after local ablation can be detected with 100% accuracy by defect reperfusion imaging, and Sonazoid-CEUS may, therefore, be substituted to some extent for 3-monthly CT examinations, leading to reduced cost and X-ray exposure [23]. On a practical level, it is recommended that CEUS and dynamic CT should be performed one after the other for a 3-month interval according to the Japanese practice guidelines [5]. However, this has to be confirmed by further studies.

Improvements on CT

MDCT has been a major improvement over single helical CT insofar that the collection of volume data for the entire liver within a period of less than 10 s has now become possible. This has been achieved by increasing the number of detector rows and improving the reconstruction algorithm. This technique makes it possible to resolve temporal and spatial data, whereas in the past it has always been necessary to do a traded off in order to render a semblance of clinically useful data in dynamic studies of the liver. Multiple scans have become possible during the arterial-dominant phase, which is time-dependent, and the spatial resolution has improved to allow reconstruction at a millimeter-order voxel level. However, the concern over X-ray exposure remains. CT is considered to have reached the stage of the 'optimal phase' and 'optimal spatial resolution'.

Regarding the diagnosis of hypervascular HCC, a study comparing the results of image reconstruction with collimation at 2.5, 5, and 7.5 mm reported no significant difference in the diagnostic accuracy for lesions of ≤5 mm [31]. From the viewpoint of hemodynamics, few HCCs ≤5 mm in diameter exhibit hypervascularity during the course of their growth, except for intrahepatic metastases, and collimation at 5 mm is therefore considered appropriate for screening [32].

Since the advent of helical CT, two- or three-phase dynamic studies consisting of artery-dominant and portal-dominant phases, with the equilibrium phase, have been essential for the detection and differential diagnosis of nodular lesions of the liver as recommended by the AASLD Guidelines [6] and JSH Guidelines [5]. The artery-dominant phase is extremely important for the diagnosis of hypervascular HCC, but tumor staining is observed for only 7–19 s, and it can be difficult to scan the entire liver in the optimal artery-dominant phase using conventional helical CT. MDCT makes it possible to scan the entire liver multiple times during the artery-dominant phase, and the possibility of detecting tumor staining during the optimal phase has increased. Studies have also reported on the usefulness of double-arterial CT, which scans the early and late arterial phases [33, 34], but subsequent studies by Ichikawa et al. [35], Laghi et al. [36], and Francis et al. [37] failed to show any significant differences compared with the late arterial phase alone.

Indeed, MDCT has clearly improved in the ability to detect the early staining of HCC compared with single-detector CT [38]. This improvement may depend on the properties of the target tumor, the degree of liver cirrhosis affecting the liver hemodynamics, the injection rate and dose of the contrast medium. If the time until the appearance of the contrast medium in the artery was measured using a test dose, imaging at the optimal timing is possible but the routine procedure needs to take into consideration the balance between the simplicity of the procedure, the X-ray exposure dose and diagnostic capacity.

Shortening of the scanning time and improvements in spatial resolution by the introduction of MDCT have markedly improved the quality of three-dimensional CT angiograms to a level nearly comparable to invasive digital subtraction angiography. However, further studies are needed to establish the optimal dose, concentration, and injection rate of the contrast medium, and the timing of scanning [39]. It is desirable to avoid invasive examinations in living liver transplant donors, and three-dimensional CT angiography by MDCT has made conventional angiography almost unnecessary [40].

Low-radiation-dose CT has been attempted as a measure to reduce radiation exposure, but the effectiveness of a noise reduction filter for preventing the deterioration of the image quality is unclear [41]. Further improvements

are needed to make the modality clinically relevant, but it represents a promising direction for the development of CT.

Improvements in MRI

Evaluation of Hemodynamics by Gd-DTPA-MRI

Gd-DTPA (Bayer Schering Pharma, Germany) is a conventional, nonspecific extracellular distribution-type contrast medium with kinetics similar to those of an iodine contrast medium and with a contrast-enhancing effect corresponding to the blood flow distribution. As noted above, dynamic multiphase studies have become possible as a result of the increased numbers of examination by MDCT, and the optimization of its conditions is based on its usefulness and radiation-exposure-free profile. The injection volume of an MRI contrast medium required to obtain a contrast-enhancing effect is much smaller than that of an iodine contrast medium, making it more appropriate for dynamic studies, and its usefulness has been recognized through the spread of high-speed scanning techniques such as gradient echo and fast spin echo. However, many masses $\leq$2 cm in diameter detected by this modality may include false lesions [42]. Ito et al. [43] performed a 6-phase dynamic study and reported the technique's usefulness for differentiating between HCC and false lesions, but the procedure is generally a bit too complicated for routine use.

Diagnosis Using Liver-Specific Contrast Agents

SPIO-MRI (Kupffer Cell Function)

The clinical use of SPIO-MRI with a liver-specific contrast medium has become available, and its usefulness has been reported by a number of authors [44, 45]. SPIO is taken up by the reticuloendothelial system (primarily Kupffer cells), thus producing a contrast-enhancing effect. There are usually no Kupffer cells in metastatic tumors, and SPIO therefore acts as a negative contrast medium for identifying these lesions. Its tumor-detecting ability is high compared to MDCT and has been reported to be comparable to that of CTAP [46–48]. The presence of Kupffer cells in primary tumors of the liver provides an index for discriminating between benign and malignant tumors and for evaluating the degree of differentiation [24, 43, 44]. However, because Kupffer cell function is reduced in patients with advanced liver cirrhosis, its diagnostic capacity for well-differentiated tumors containing residual Kupffer cells is not always satisfactory. Ferumoxide, the first SPIO approved for clinical use, must be intravenously infused over 30 min or longer and is thus inefficient despite its excellent usefulness [47–49]. Ferucarbotran (Resovist, Bayer Schering Pharma), which can be intravenously injected in a bolus, has been widely used until the time of EOB-MRI approval, resulting in marked shortening of the examination time.

There have also been reports of the simultaneous use of a contrast medium with a type of nonspecific extracellular fluid distribution and SPIO, making use of their respective characteristics for the qualitative diagnosis and detection of tumors. Bhartia et al. [50] performed double-contrast imaging in a dynamic study using a gadolinium preparation and SPIO in patients before liver transplantation, and reported satisfactory results in tumors $\geq$10 mm in diameter. Kim et al. [51] administered SPIO and a gadolinium preparation at different times, and evaluated their diagnostic accuracies; the diagnostic accuracy was better with SPIO in hypovascular tumors, but was better with Gd-DTPA in hypervascular tumors. They recommended their combined use to improve the overall detection capacity.

Gd-EOB-DTPA (Hepatocyte Function)

Gd-EOP-DTPA (Bayer Schering Pharma, Germany) has been available for clinical use in Japan since January 2008. It has an excellent ability to detect liver tumors and evaluate hepatocyte function in the hepatobiliary phase, as well as providing information on the nodular hemodynamics by dynamic imaging. It has now become the most frequently used contrast medium in liver MRI. Gd-EOB-DTPA has been used clinically in European countries for several years, and satisfactory results in detecting focal liver lesions have been reported by a multicenter collaborative study [52]. Gd-EOB-DTPA has a high T_1-relaxing effect and is used primarily in T_1-weighted imaging. It serves as an extracellular fluid contrast medium in the early phase after intravenous injection, and the T_1-shortening effect of Gd thus makes evaluation of the hepatic blood flow possible. Although the Gd concentration of Gd-EOB-DTPA is one quarter that of the extracellular fluid MR contrast medium, Gd-DTPA, it has a T_1-shortening effect of about half compared to Gd-DTPA in light of its T_1-relaxing effect. This enables the diagnosis of hypervascular HCC by optimizing dynamic scanning and providing high-quality arterial-phase images [53, 54].

Recent marked improvements in high-speed MRI have also been made regarding the diagnostic accuracy

based on blood flow changes, and its spatial resolution is approaching that of MDCT. High-spatial-resolution three-dimensional Fourier transform-T_1-weighted imaging, such as T_1 high-resolution isotropic volume examination (Philips, Germany) and liver acquisition with volume acceleration (GE Healthcare, Milwaukee, Wisc., USA) used for liver MRI, have become powerful tools to examine the arterial phase on dynamic MRI of the liver. Dynamic MRI of the liver using Gd-EOB-DTPA and three-dimensional Fourier transform-T_1-weighted imaging has a very high diagnostic ability. Dynamic imaging using Gd-EOB-DTPA is therefore useful for the diagnosis of hypervascular HCC [52, 53]. However, as the injection volume per body weight of Gd-EOB-DTPA is about half of Gd-DTPA, the duration of staining of the aorta and hypervascular HCC tends to be short, and optimization of the timing of scanning in the arterial phase during dynamic imaging is thus extremely important. The optimization of imaging in the arterial phase depends largely on the performance of the MRI system. It is necessary to adjust the protocol at each facility to capture the peak tumor staining at the best timing, taking into consideration the scanning time in the scanning sequence used and the design of K-space data collection.

Regarding the portal/venous phase, the washout observed in hypervascular HCC on CT and Gd-DTPA dynamic MRI is an important clue for the diagnosis of HCC, but caution is needed concerning the judgment of washout on Gd-EOB-DTPA. Because the contrast medium during imaging using Gd-EOB-DTPA is present in both the extracellular fluid and the hepatocytes during the equilibrium phase, the tumor-liver contrast during the equilibrium phase is derived from washout of the contrast medium from the tumor, and contrast enhancement of the surrounding liver tissue by the hepatocyte-specific contrast medium, i.e., the mechanism of contrast enhancement during the equilibrium phase differs between dynamic CT/MRI and Gd-EOB-DTPA-MRI. Time-intensity analysis has shown that Gd-EOB-DTPA is already taken up by hepatocytes about 1 min after administration, such that signals from the blood vessels and those from the liver parenchyma are mixed during the portal phase 60–80 s after administration.

Similarly, it must be understood that contrast enhancement observed 2–5 min after the administration of Gd-EOB-DTPA differs from that observed by the use of a conventional extracellular fluid contrast medium. In the late phase, Gd-EOB-DTPA is gradually taken up by hepatocytes via organic anion transporters (OATPAs) such as OATP1B3 [55] or OATP8 [56]. It begins to be taken up by hepatocytes about 1 min after administration, and the T_1-signal intensity of the liver increases serially thereafter. Tumor/liver contrast sufficient for the detection of liver tumors can be achieved in patients with no liver dysfunction about 20 min after the intravenous injection. This mechanism resembles that by which SPIO, another liver-specific MR contrast medium, enhances the contrast depending on the hepatic reticuloendothelial function. Thus, the most important aspect of Gd-EOB-DTPA MRI is that the detection of liver tumors and their differential diagnosis can be achieved via evaluation of both their blood flow characteristics and hepatocyte function.

As discussed above, Gd-EOB-DTPA also achieves arterial staining of hypervascular HCC due to its extracellular fluid T_1-shortening effect, but the staining of capsule-like structures is weak in the arterial phase of contrast-enhanced MRI using the usual dose of Gd-EOB-DTPA [53]. In contrast, in the hepatocyte phase, HCC with no normal hepatocytes fails to take up the contrast medium and is imaged as a low-signal area on T_1-weighted imaging [57, 58].

The frequent use of Gd-EOB-DTPA-MRI has drawn attention to the presence of HCCs showing no signal reduction in the hepatocyte phase, despite tumors being hypervascular. If OATP1B3 or OATP8 is preserved, EOB is taken up by cancer cells. However, hepatocytes cannot excrete it; because of possible impairment of excretory transporter polypeptide, they are demonstrated as iso- or high intense in the hepatocyte phase. This phenomenon might be related to retention of bile juice, which appears green by formalin fixation; such resected specimens have long been known as 'green hepatomas', though it is difficult to determine their overall frequency. However, knowledge of the presence of a green hepatoma (or bile-producing/slow-bile-excreting HCC) and its characteristic features on imaging is important. This assumption regarding green hepatomas is just a hypothesis. The true mechanism or relation to transporter expression must be clarified in future studies.

Gd-EOB-DTPA-MRI can clearly discriminate hypovascular HCCs from dysplastic nodules, which were difficult to differentiate by conventional CTHA or CTAP [59, 60] in the resected series only. However, false-positive and false-negative lesions have been reported by other studies using liver biopsy specimens [61]. There have also been sporadic reports demonstrating that tumors showing signal reduction in the hepatocyte phase of EOB-MRI included dysplastic nodules, and that tumors showing no signal reduction in the hepatocyte phase included early

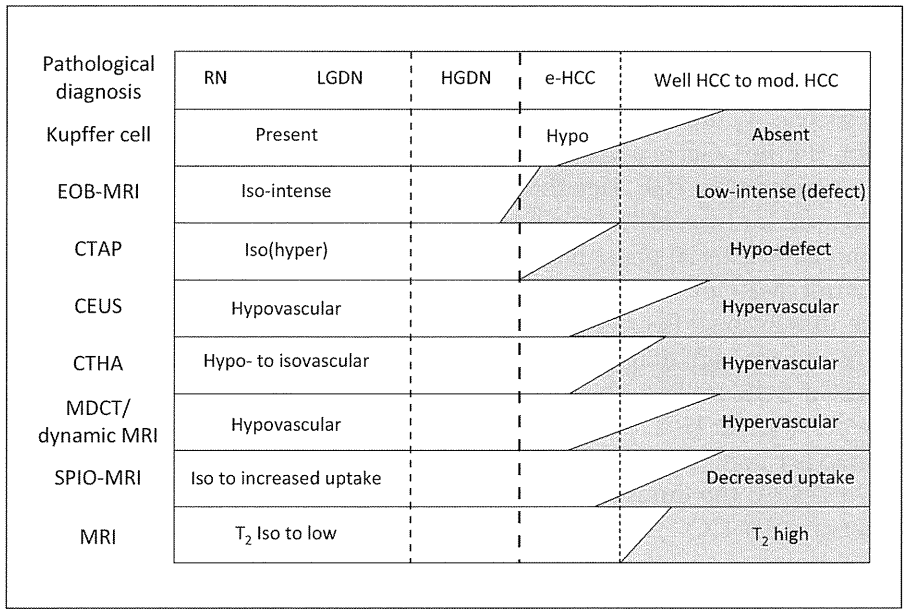

Fig. 5. Imaging findings of hepatocellular nodules in cirrhotic liver [cited from 59, with permission]. Imaging diagnosis of hepatocellular nodule associated with liver cirrrhosis. EOB-MRI is the most sensitive tool in the differentiation between early HCC and dysplastic nodules. Well = Well differentiated; mod. = moderately differentiated; RN = regenerative nodule; LGDN = low-grade dysplastic nodules; HGDN = high-grade dysplastic nodules; e-HCC = early HCC.

HCC (early well-differentiated HCC). In the light of the fact that the diagnosis of early HCC is impossible without the thorough examination of resected specimens, features such as stromal invasion cannot be diagnosed definitively without examination of the entire resected sample, the report by Ichikawa et al. [62] based exclusively on the examination of resected samples is highly reliable. This study involved the diagnosis of all samples by a specialist in liver pathology, that is an author of the liver pathology consensus paper [63], and suggested that Gd-EOB-MRI is the best imaging tool and may have a differential diagnostic ability comparable to that of a pathologist specializing in the liver (table 3; fig. 5).

However, nodules that show no signal reduction in the hepatocyte phase and are diagnosed as clearly well-differentiated HCC on the basis of histological examination of biopsy specimens may include those that have undergone pathological changes of carcinogenesis at a stage before signal reduction. Moreover, the possibility of the presence of exceptional cases of dysplastic nodules among the lesions showing signal reduction in the hepatocyte phase cannot be excluded. Importantly, the diagnosis and natural course of patients with hypovascular lesions that show signal reduction only in the hepatocyte phase should be studied extensively and the findings compared with those in resected specimens. Research on the natural course of hypovascular hepatocellular nodules with decreased intensity on hepatocyte phase of EOB-DTPA is strongly warranted.

Table 3. Accuracy of the differentiation of early HCC and premalignant lesions by hepatocyte phase Gd-EOB-DTPA-MRI for hypovascular hepatocytic nodules

Only resected specimens: n = 30	Pathological findings	
	e-HCC	DN or RN
Signal intensity in hepatobiliary phase with Gd-EOB-DTPA		
Low to slightly low (n = 24)	23	1
Iso to high (n = 6)	1	5

Accuracy: 93% (23 + 5/30). e-HCC = Early HCC; DN = dysplastic nodule; RN = regenerative nodule.

As discussed above, Gd-EOB-MRI is expected to approach a pathological examination in terms of its diagnostic accuracy of early HCC, but the decision of optimal timing of treatment remains an issue. Careful comparison with the natural course is, thus, also needed in this respect, particularly in nodules accompanied by typical hypervascular HCC in the different sites of the liver, rather than treating hypovascular nodules showing signal reduction in the hepatocyte phase without clear evidence of malignancy. Several observation studies suggest that the potential of malignant transformation of such nodules is high, and the doubling time and period of hypervascular change of hypovascular nodules showing low intensity on hepatocyte phase signal

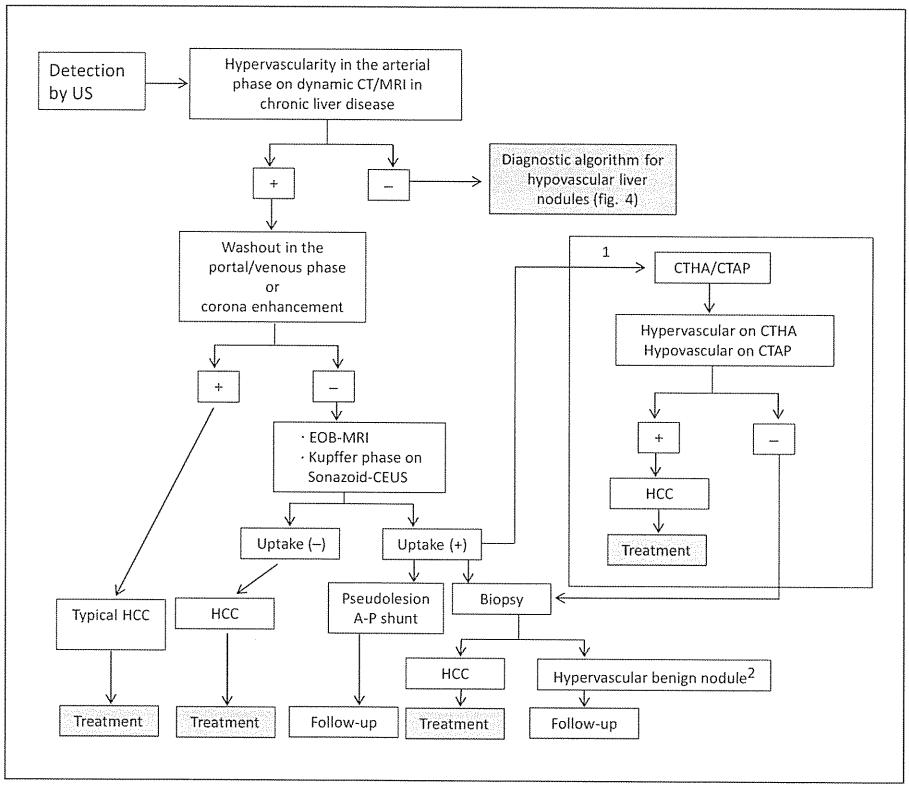

Fig. 6. Diagnostic and treatment algorithms for hypervascular liver nodules according to the consensus-based diagnostic and treatment guidelines established by the JSH 2010. 1 = Recommended only at appropriate institutions; 2 = hypervascular benign nodules of focal nodular hyperplasia, adenoma, etc.

compared with those showing no signal reduction. Further studies concerning the natural history are eagerly awaited.

Angiography

Angiography is no longer performed simply for the diagnosis of HCC, particularly hypovascular HCC, because improvements in CT, MRI, and US mean that clearly hypervascular HCC can be readily diagnosed using noninvasive modalities [5, 6]. Angiography is performed only when transarterial treatment is intended, i.e. interventional angiography with treatments such as hepatic arterial infusion chemotherapy or transarterial chemoembolization.

However, angiography is still performed in combination with CT, i.e. CTHA and CTAP for detailed evaluation of the blood flow of even hypervascular nodules, or to determine whether the blood supply of a hypovascular nodule is arterial- or portal-dominant. CTHA has an excellent diagnostic capacity for hypervascular HCC, but is associated with the problem of a high frequency of detecting pseudolesions caused by the overemphasis of the AP shunt. The detection of pseudolesions is also common with CTAP. However, these remain the ultimate techniques for the staging of patients with HCCs, and the discrimination between dysplastic nodules and early HCC is based on the blood supply pattern, but this is inferior to hepatocyte EOB-MRI.

It has recently been reported that the diagnostic capacity of a combination of noninvasive MDCT and SPIO-MRI was comparable to that of CTHA or CTAP [64], and therefore CTHA and CTAP may thus be gradually eliminated from the daily clinical practice even in Japan, where CTHA and CTAP used to be aggressively performed.

CTAP used to be regarded as the most sensitive modality for detecting the initial changes of malignant transformation in the multistep process of hepatocarcinogenesis from a dysplastic nodule to early HCC [65, 66]. However, changes in malignant transformation can now be more sensitively captured in the hepatocyte phase of Gd-EOB-DTPA-MRI, earlier than a decrease in the portal blood flow detected by CTAP, and the roles of CTHA and CTAP therefore will become limited in the future [5, 67].

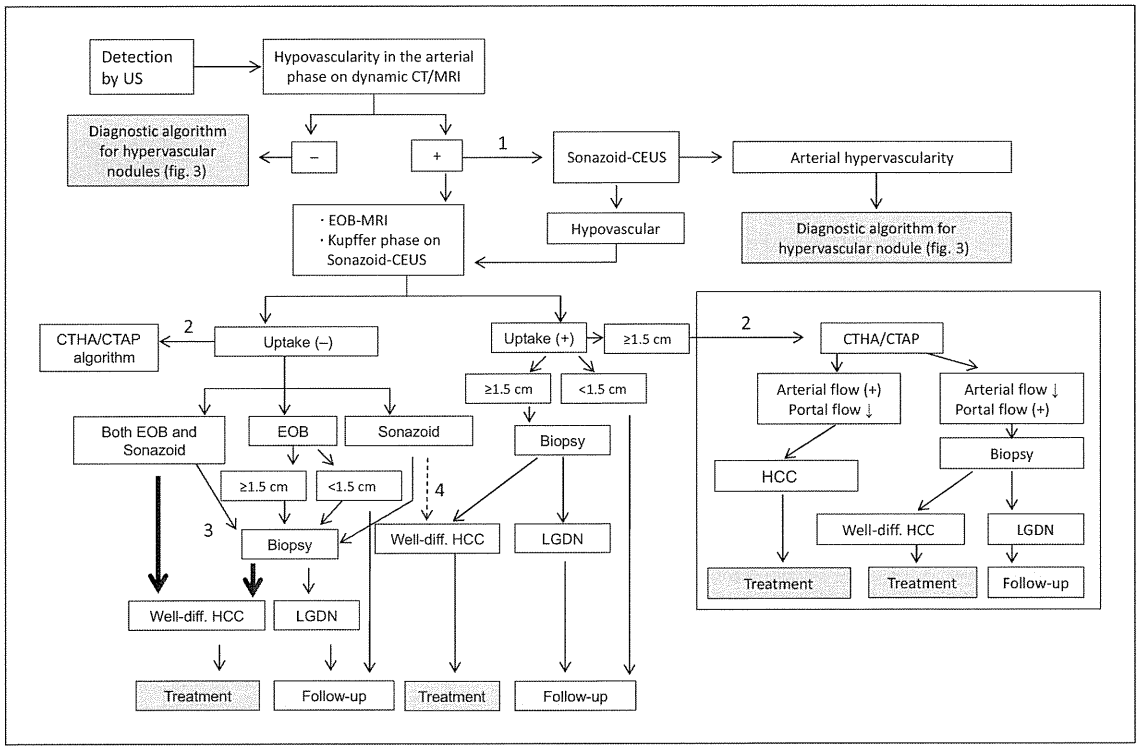

Fig. 7. Diagnostic and treatment algorithms for hypovascular liver nodules according to the consensus-based diagnostic and treatment guidelines established by the JSH 2010. 1 = When the nodule is hypovascular on dynamic CT or dynamic MRI, Sonazoid-CEUS is recommended to confirm whether it is truly a hypovascular nodule; 2 = recommended only at appropriate institutions; 3 = biopsy is not always necessary in this setting; 4 = the cases with decreased uptake of Sonazoid without decreased uptake of EOB are rare. Well-diff. = Well-differentiated; LGDN = low-grade dysplastic nodules.

Positron Emission Tomography

Positron emission tomography (PET) using fluorodeoxyglucose has gradually become commonly used for the staging and diagnosing of the malignant grade of HCC. However, the diagnostic usefulness of fluorodeoxyglucose-PET for HCC is not very high. PET is superior to other modalities regarding its ability to detect poorly differentiated HCC and it is useful to detect extrahepatic metastases. It is also valuable for assessing the treatment response after molecular targeted therapy for far-advanced HCC with extrahepatic spread.

Conclusion

Integrated medicine has already been initiated, advancing the diagnosis of liver tumors by performing all available imaging modalities including CEUS, CT, SPIO-MRI, and EOB-MRI, and comprehensively evaluating the findings. The present era requires modalities to be selected according to diagnostic efficiency. The JSH issued diagnostic algorithms for hypervascular and hypovascular liver cancers in 2007 [67] and revised them in 2010 [5] (fig. 6, 7). In 2007, EOB-MRI and Sonazoid-CEUS had not yet been clinically available. SPIO-MRI has currently been replaced by EOB-MRI, and Levovist-CEUS has been completely replaced by Sonazoid-CEUS in the updated diagnostic algorithms. Similarly, the role of CTHA and CTAP also needs to be reconsidered in the near future, as EOB-MRI now provides more reliable information regarding differentiation between early HCC and dysplastic nodules.

Disclosure Statement

The author declares that he has no financial conflict of interest.

References

1 Kudo M: Contrast Harmonic Imaging in the Diagnosis and Treatment of Hepatic Tumors. Tokyo, Springer, 2003, pp 1–253.
2 Kudo M, Hatanaka K, Maekawa K: Defect reperfusion imaging, a newly developed novel technology using Sonazoid in the treatment of hepatocellular carcinoma. J Med Ultrasound 2008;16:169–175.
3 Kudo M, Hatanaka K, Maekawa K: Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78(suppl 1):40–45.
4 Makuuchi M, Kokudo N, Arii S, Igaki H, Ikai I, Kaneko S, et al: Surveillance algorithm and diagnostic algorithm for hepatocellular carcinoma. Hepatol Res 2010;40(suppl 1):1–144.
5 Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, et al: Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guideline Proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–364.
6 Bruix J, Sherman M: Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.
7 Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al: Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430.
8 Hatanaka K, Chung H, Kudo M, Haji S, Minami Y, Maekawa K, et al: Usefulness of the post-vascular phase of contrast-enhanced ultrasonography with sonazoid in the evaluation of gross types of hepatocellular carcinoma. Oncology 2010;78(suppl 1):53–59.
9 Hatanaka K, Kudo M, Minami Y, Maekawa K: Sonazoid-enhanced ultrasonography for diagnosis of hepatic malignancies: comparison with contrast-enhanced CT. Oncology 2008;75(suppl 1):42–47.
10 Kudo M, Hatanaka K, Kumada T, Toyoda H, Tada T: Double-contrast ultrasound: a novel surveillance tool for hepatocellular carcinoma. Am J Gastroenterol 2011;106:368–370.
11 Hatanaka K, Kudo M, Minami Y, Ueda T, Tatsumi C, Kitai S, et al: Differential diagnosis of hepatic tumors: value of contrast-enhanced harmonic sonography using the newly developed contrast agent, Sonazoid. Intervirology 2008;51:S61–69.
12 Wen YL, Kudo M, Zheng RQ, Ding H, Zhou P, Minami Y, et al: Characterization of hepatic tumors: value of contrast-enhanced coded phase-inversion harmonic angio. AJR Am J Roentgenol 2004;182:1019–1026.
13 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K: Hepatocellular carcinoma: depiction of tumor parenchymal flow with intermittent harmonic power Doppler US during the early arterial phase in dual-display mode. Radiology 2001;220:349–356.
14 Inoue T, Kudo M, Watai R, Pei Z, Kawasaki T, Minami Y, et al: Differential diagnosis of nodular lesions in cirrhotic liver by post-vascular phase contrast-enhanced US with Levovist: comparison with superparamagnetic iron oxide magnetic resonance images. J Gastroenterol 2005;40:1139–1147.
15 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K: Contrast-enhanced subtraction harmonic sonography for evaluating treatment response in patients with hepatocellular carcinoma. AJR Am J Roentgenol 2001;176:661–666.
16 Minami Y, Kudo M, Kawasaki T, Kitano M, Chung H, Maekawa K, et al: Transcatheter arterial chemoembolization of hepatocellular carcinoma: usefulness of coded phase-inversion harmonic sonography. AJR Am J Roentgenol 2003;180:703–708.
17 Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Chung H, et al: Evaluation of post-treatment response of hepatocellular carcinoma with contrast-enhanced coded phase-inversion harmonic US: comparison with dynamic CT. Radiology 2001;221:721–730.
18 Minami Y, Kudo M, Kawasaki T, Chung H, Ogawa C, Shiozaki H: Treatment of hepatocellular carcinoma with percutaneous radiofrequency ablation: usefulness of contrast harmonic sonography for lesions poorly defined with B-mode sonography. AJR Am J Roentgenol 2004;183:153–156.
19 Minami Y, Kudo M, Chung H, Kawasaki T, Yagyu Y, Shimono T, et al: Contrast harmonic sonography-guided radiofrequency ablation therapy versus B-mode sonography in hepatocellular carcinoma: prospective randomized controlled trial. AJR Am J Roentgenol 2007;188:489–494.
20 Wen YL, Kudo M, Zheng RQ, Minami Y, Chung H, Suetomi Y, et al: Radiofrequency ablation of hepatocellular carcinoma: therapeutic response using contrast-enhanced coded phase-inversion harmonic sonography. AJR Am J Roentgenol 2003;181:57–63.
21 Minami Y, Kudo M, Hatanaka K, Kitai S, Inoue T, Hagiwara S, et al: Radiofrequency ablation guided by contrast harmonic sonography using perfluorocarbon microbubbles (Sonazoid) for hepatic malignancies: an initial experience. Liver Int 2010;30:759–764.
22 Minami Y, Kudo M: Hepatic malignancies: correlation between sonographic findings and pathological features. World J Radiol 2010;2:249–256.
23 Kudo M: Radiofrequency ablation for hepatocellular carcinoma: updated review in 2010. Oncology 2010;78(suppl 1):113–124.
24 Inoue T, Minami Y, Chung H, Hayaishi S, Ueda T, Tatsumi C, et al: Radiofrequency ablation for hepatocellular carcinoma: assistant techniques for difficult cases. Oncology 2010;78(suppl 1):94–101.
25 Minami Y, Kudo M: Contrast-enhanced harmonic ultrasound imaging in ablation therapy for primary hepatocelular carcinomaprimary hepatocelular carcinoma. World J Radiol 2009;31:86–91.
26 Kudo M: Local ablation therapy for hepatocellular carcinoma: current status and future perspectives. J Gastroenterol 2004;39:205–214.
27 Zhou P, Kudo M, Minami Y, Chung H, Inoue T, Fukunaga T, et al: What is the best time to evaluate treatment response after radiofrequency ablation of hepatocellular carcinoma using contrast-enhanced sonography? Oncology 2007;72(suppl 1):92–97.
28 Minami Y, Chung H, Kudo M, Kitai S, Takahashi S, Inoue T, et al: Radiofrequency ablation of hepatocellular carcinoma: value of virtual CT sonography with magnetic navigation. AJR Am J Roentgenol 2008;190:W335–341.
29 Minami Y, Kudo M, Chung H, Inoue T, Takahashi S, Hatanaka K, et al: Percutaneous radiofrequency ablation of sonographically unidentifiable liver tumors. Feasibility and usefulness of a novel guiding technique with an integrated system of computed tomography and sonographic images. Oncology 2007;72(suppl 1):111–116.
30 Minami Y, Kudo M: Radiofrequency ablation of hepatocellular carcinoma: current status. World J Radiol 2010;2:417–424.
31 Kawata S, Murakami T, Kim T, Hori M, Federle MP, Kumano S, et al: Multidetector CT: diagnostic impact of slice thickness on detection of hypervascular hepatocellular carcinoma. AJR Am J Roentgenol 2002;179:61–66.
32 Haider MA, Amitai MM, Rappaport DC, O'Malley ME, Hanbidge AE, Redston M, et al: Multi-detector row helical CT in preoperative assessment of small (< or =1.5 cm) liver metastases: is thinner collimation better? Radiology 2002;225:137–142.
33 Kim T, Murakami T, Hori M, Takamura M, Takahashi S, Okada A, et al: Small hypervascular hepatocellular carcinoma revealed by double arterial phase CT performed with single breath-hold scanning and automatic bolus tracking. AJR Am J Roentgenol 2002;178:899–904.
34 Murakami T, Kim T, Takamura M, Hori M, Takahashi S, Federle MP, et al: Hypervascular hepatocellular carcinoma: detection with double arterial phase multi-detector row helical CT. Radiology 2001;218:763–767.
35 Ichikawa T, Kitamura T, Nakajima H, Sou H, Tsukamoto T, Ikenaga S, et al: Hypervascular hepatocellular carcinoma: can double arterial phase imaging with multidetector CT improve tumor depiction in the cirrhotic liver? AJR Am J Roentgenol 2002;179:751–758.

36 Laghi A, Iannaccone R, Rossi P, Carbone I, Ferrari R, Mangiapane F, et al: Hepatocellular carcinoma: detection with triple-phase multi-detector row helical CT in patients with chronic hepatitis. Radiology 2003;226: 543–549.
37 Francis IR, Cohan RH, McNulty NJ, Platt JF, Korobkin M, Gebremariam A, et al: Multidetector CT of the liver and hepatic neoplasms: effect of multiphasic imaging on tumor conspicuity and vascular enhancement. AJR Am J Roentgenol 2003;180:1217–1224.
38 Lee KH, O'Malley ME, Haider MA, Hanbidge A: Triple-phase MDCT of hepatocellular carcinoma. AJR Am J Roentgenol 2004; 182:643–649.
39 Tanikake M, Shimizu T, Narabayashi I, Matsuki M, Masuda K, Yamamoto K, et al: Three-dimensional CT angiography of the hepatic artery: use of multi-detector row helical CT and a contrast agent. Radiology 2003;227:883–889.
40 Lee SS, Kim TK, Byun JH, Ha HK, Kim PN, Kim AY, et al: Hepatic arteries in potential donors for living related liver transplantation: evaluation with multi-detector row CT angiography. Radiology 2003;227:391–399.
41 Kalra MK, Maher MM, Blake MA, Lucey BC, Karau K, Toth TL, et al: Detection and characterization of lesions on low-radiation-dose abdominal CT images postprocessed with noise reduction filters. Radiology 2004;232: 791–797.
42 Shimizu A, Ito K, Koike S, Fujita T, Shimizu K, Matsunaga N: Cirrhosis or chronic hepatitis: evaluation of small (< or =2 cm) early-enhancing hepatic lesions with serial contrast-enhanced dynamic MR imaging. Radiology 2003;226:550–555.
43 Ito K, Fujita T, Shimizu A, Koike S, Sasaki K, Matsunaga N, et al: Multiarterial phase dynamic MRI of small early enhancing hepatic lesions in cirrhosis or chronic hepatitis: differentiating between hypervascular hepatocellular carcinomas and pseudolesions. AJR Am J Roentgenol 2004;183:699–705.
44 Asahina Y, Izumi N, Uchihara M, Noguchi O, Ueda K, Inoue K, et al: Assessment of Kupffer cells by ferumoxides-enhanced MR imaging is beneficial for diagnosis of hepatocellular carcinoma: comparison of pathological diagnosis and perfusion patterns assessed by CT hepatic arteriography and CT arterioportography. Hepatol Res 2003;27: 196–204.
45 Imai Y, Murakami T, Yoshida S, Nishikawa M, Ohsawa M, Tokunaga K, et al: Superparamagnetic iron oxide-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading. Hepatology 2000;32:205–212.
46 Ba-Ssalamah A, Schima W, Schmook MT, Linnau KF, Schibany N, Helbich T, et al: Atypical focal nodular hyperplasia of the liver: imaging features of nonspecific and liver-specific MR contrast agents. AJR Am J Roentgenol 2002;179:1447–1456.
47 Mori K, Scheidler J, Helmberger T, Holzknecht N, Schauer R, Schirren CA, et al: Detection of malignant hepatic lesions before orthotopic liver transplantation: accuracy of ferumoxides-enhanced MR imaging. AJR Am J Roentgenol 2002;179:1045–1051.
48 Arbab AS, Ichikawa T, Sou H, Araki T, Nakajima H, Ishigame K, et al: Ferumoxides-enhanced double-echo T2-weighted MR imaging in differentiating metastases from nonsolid benign lesions of the liver. Radiology 2002;225:151–158.
49 Bluemke DA, Weber TM, Rubin D, de Lange EE, Semelka R, Redvanly RD, et al: Hepatic MR imaging with ferumoxides: multicenter study of safety and effectiveness of direct injection protocol. Radiology 2003;228:457–464.
50 Bhartia B, Ward J, Guthrie JA, Robinson PJ: Hepatocellular carcinoma in cirrhotic livers: double-contrast thin-section MR imaging with pathologic correlation of explanted tissue. AJR Am J Roentgenol 2003;180:577–584.
51 Kim MJ, Kim JH, Chung JJ, Park MS, Lim JS, Oh YT: Focal hepatic lesions: detection and characterization with combination gadolinium- and superparamagnetic iron oxide-enhanced MR imaging. Radiology 2003;228: 719–726.
52 Huppertz A, Balzer T, Blakeborough A, Breuer J, Giovagnoni A, Heinz-Peer G, et al: Improved detection of focal liver lesions at MR imaging: multicenter comparison of gadoxetic acid-enhanced MR images with intraoperative findings. Radiology 2004;230: 266–275.
53 Vogl TJ, Kummel S, Hammerstingl R, Schellenbeck M, Schumacher G, Balzer T, et al: Liver tumors: comparison of MR imaging with Gd-EOB-DTPA and Gd-DTPA. Radiology 1996;200:59–67.
54 Jung G, Breuer J, Poll LW, Koch JA, Balzer T, Chang S, et al: Imaging characteristics of hepatocellular carcinoma using the hepatobiliary contrast agent Gd-EOB-DTPA. Acta Radiol 2006;47:15–23.
55 Narita M, Hatano E, Arizono S, Miyagawa-Hayashino A, Isoda H, Kitamura K, et al: Expression of OATP1B3 determines uptake of Gd-EOB-DTPA in hepatocellular carcinoma. J Gastroenterol 2009;44:793–798.
56 Tsuda N, Matsui O: Cirrhotic rat liver: reference to transporter activity and morphologic changes in bile canaliculi – gadoxetic acid-enhanced MR imaging. Radiology 2010;256: 767–773.
57 Saito K, Kotake F, Ito N, Ozuki T, Mikami R, Abe K, et al: Gd-EOB-DTPA enhanced MRI for hepatocellular carcinoma: quantitative evaluation of tumor enhancement in hepatobiliary phase. Magn Reson Med Sci 2005;4: 1–9.
58 Okada M, Imai Y, Kim T, Kogita S, Takamura M, Kumano S, et al: Comparison of enhancement patterns of histologically confirmed hepatocellular carcinoma between gadoxetate- and ferucarbotran-enhanced magnetic resonance imaging. J Magn Reson Imaging 2010;32:903–913.
59 Kudo M: The 2008 Okuda lecture: management of hepatocellular carcinoma: from surveillance to molecular targeted therapy. J Gastroenterol Hepatol 2010;439–452.
60 Kudo M: Will Gd-EOB MRI change the diagnostic algorithm for hepatocellular carcinoma? Oncology 2010;S87–93.
61 Kogita S, Imai Y, Okada M, Kim T, Onishi H, Takamura M, et al: Gd-EOB-DTPA-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading and portal blood flow. Eur Radiol 2010;20:2405–2413.
62 Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, et al: Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol 2010;45:133–141.
63 Kojiro M, Wanless I, Alves V, et al: Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 2009;49:658–664.
64 Imai Y, Murakami T, Hori M, Fukuda K, Kim T, Marukawa T, et al: Hypervascular hepatocellular carcinoma: combined dynamic MDCT and SPIO-enhanced MRI versus combined CTHA and CTAP. Hepatol Res 2008;38:147–158.
65 Kudo M: Multistep human hepatocarcinogenesis: correlation of imaging with pathology. J Gastroenterol 2009;44(suppl 19):112–118.
66 Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M: Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. Radiology 2002;225: 143–149.
67 Kudo M, Okanoue T, Japan Society of Hepatology: Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. Oncology 2007;72(suppl 1):2–15.

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Complete Response of Advanced Hepatocellular Carcinoma with Multiple Lung Metastases Treated with Sorafenib: A Case Report

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Key Words

Hepatocellular carcinoma · Sorafenib · Hepatic necrosis · Lung metastasis · Complete response

Abstract

Sorafenib, an oral multikinase inhibitor, has demonstrated clinical efficacy in patients with advanced hepatocellular carcinoma (HCC). However, in the SHARP trial (Sorafenib HCC Assessment Randomized Protocol trial) and the Asia-Pacific trial (conducted in the Asia-Pacific region), no cases of complete response (CR) were reported. Thereafter, only a relatively small number of CR cases were reported worldwide for sorafenib therapy. We herein report a case of CR in a patient treated with sorafenib for 4 months. The patient had advanced HCC with multiple lung metastases, and there has been no recurrence after 8 months following cessation of administration. To our knowledge, this is the first time a female treated with sorafenib alone for HCC has had a CR.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer globally, the third most common cause of cancer-related death, and a major health problem [1]. Surgical and locoregional procedures [especially percutaneous radiofrequency ablation (RFA)] can be curative for early stage HCC. However, because no effective therapies for advanced HCC are available, HCC that is diagnosed at an advanced stage or with progression after locoregional procedures has a dismal prognosis [2]. Recently, two large phase III clinical trials, the SHARP trial (Sorafenib HCC Assessment Randomized Protocol trial) and the Asia-Pacific trial (conducted in the Asia-Pacific region), clearly demonstrated that sorafenib (Nexvar; Bayer Healthcare Pharmaceuticals), an oral multikinase inhibitor, is an active and effective therapy leading to a significant improvement in both progression-free survival and overall survival in patients with unresectable advanced HCC. However, there were no cases of complete response (CR) among the 449 patients treated with sorafenib in these trials [3, 4]. As far as we are aware, there have been few reports of patients achieving CR when treated with sorafenib alone [5–12].

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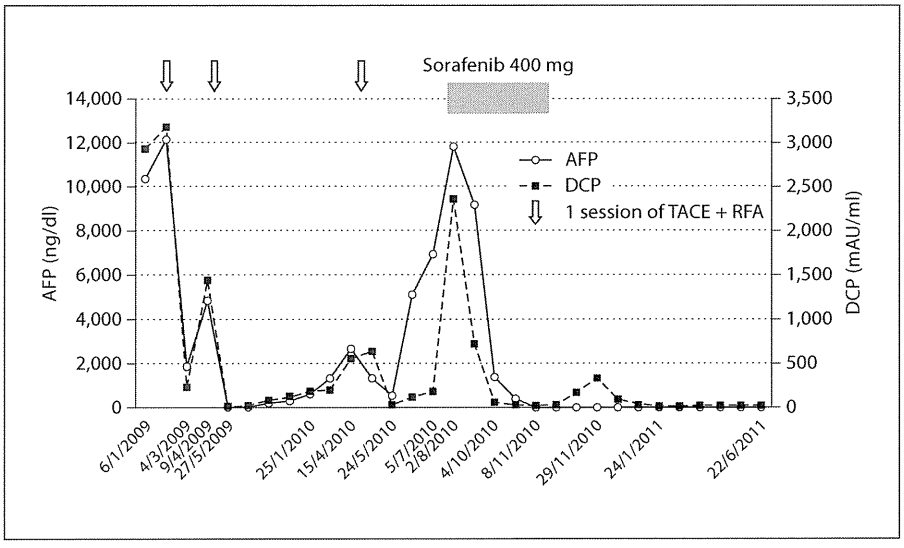

Fig. 1. Changes in AFP and DCP levels. The duration of treatment with sorafenib is indicated by the gray bar. The administration of sorafenib resulted in a dramatic reduction in serum AFP and DCP levels.

We herein report a case of CR in a patient treated with sorafenib for 4 months. The patient had advanced HCC with multiple lung metastases. There was no recurrence for 8 months after the cessation of administration, which was due to the development of hepatic failure as a serious adverse event of sorafenib.

Case Presentation

A 76-year-old Japanese female diagnosed with HCC and hepatitis C virus (HCV)-related liver cirrhosis, and who had previously received percutaneous ethanol injections in 2006, was referred to our department in January 2009 because of elevated α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels. She was 150 cm tall and weighed 53 kg. Based on her history of HCV, elevated tumor markers, and typical radiological findings for classical HCC in the right lobe of the liver on dynamic CT scan, we diagnosed recurrence of HCC without performing a biopsy. The tumor was solitary and 4.5 cm in diameter. The AFP and DCP levels were 10,341 ng/ml and 2,929 mAU/ml, respectively (fig. 1). We performed transcatheter arterial chemoembolization (TACE) for HCC followed by RFA in February 2009 and additional RFA for local tumor progression in April 2009 and April 2010. Subsequently, AFP and DCP levels decreased to 526 ng/ml and 32 mAU/ml, respectively. However, 3 months later, AFP increased to 5,127 ng/ml and DCP to 125 mAU/ml, and CT scan showed the presence of more than 60 HCC-derived lung metastases (fig. 2), even though the intrahepatic tumor was well controlled.

At that time, the significant laboratory test results of the patient were as follows: alanine aminotransferase (ALT) 90 IU/l, aspartate aminotransferase (AST) 131 IU/l, total bilirubin 1.2 mg/dl, albumin 3.0 g/dl, PT INR 1.16, AFP 6,952 ng/ml, and DCP 187 mAU/ml. The patient had no ascites or encephalopathy and had a Child-Pugh score of 6 (Child-Pugh class A) with an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Therefore, oral sorafenib therapy was initiated at 400 mg, once daily (half the standard dosage), for multiple lung metastases of HCC from July 2010.

After 2 weeks, AFP increased to 11,800 ng/ml and DCP to 2,365 mAU/ml. After 3 weeks, the lung metastases were slightly enlarged on chest CT scan. However, after 3 months, both tumor markers markedly decreased (fig. 1) and the lung metastases had almost disappeared on chest CT scan (fig. 2). After 4 months, the lung metastases had completely disappeared and the patient achieved CR (fig. 2).

However, because of hepatic encephalopathy and deterioration of liver function from Child-Pugh class A to C 4 months after starting sorafenib, we were forced to cease sorafenib administration (fig. 3a). Four days following administration cessation, ALT and AST levels suddenly increased dramatically to 1,454 and 1,653 IU/l, respectively. CT scan revealed that multicentric hepatic necroses, not apparent 4 days earlier, had appeared suddenly in the right and left lobes of the liver (fig. 3b). Thereafter, the patient was managed conservatively and after

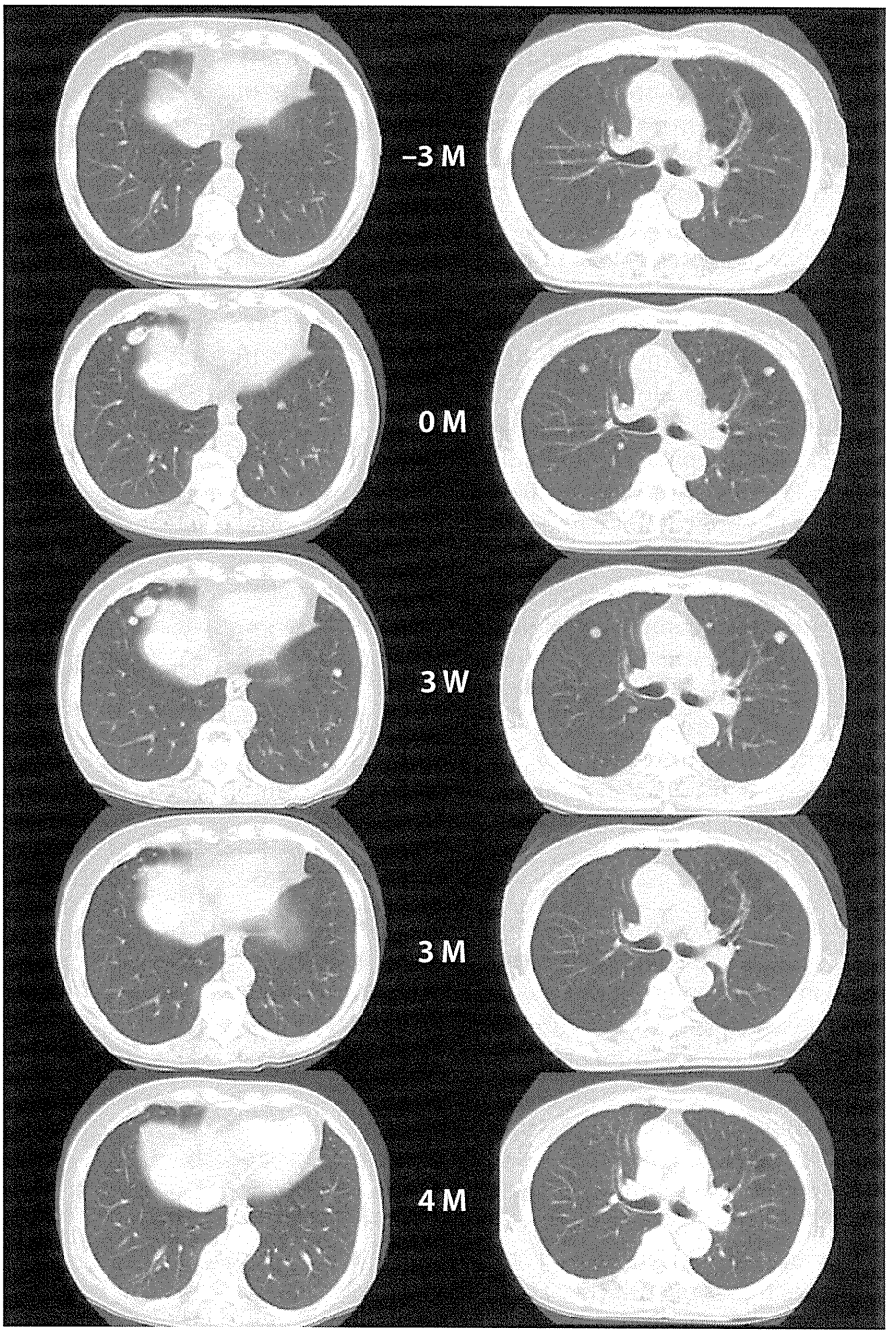

Fig. 2. Changes in chest CT scans. Follow-up CT scans show that multiple lung metastases were slightly enlarged after 3 weeks. After 3 months, they had almost disappeared. After 4 months, they had completely disappeared and the patient achieved radiological CR. The maximum diameter of lung metastases 3 weeks after commencement of therapy was 2 cm.

several weeks her liver function gradually improved. At the most recent follow-up, the patient remained in remission 8 months after the cessation of sorafenib therapy, without clinical or imaging evidence of disease recurrence. Both tumor markers were within the normal range; liver function improved to a Child-Pugh score of 7 (Child-Pugh class B) and her ECOG performance status was 1.

Discussion

Sorafenib is a multikinase inhibitor with reported activity against Raf-1, B-Raf, VEGFR2, PDGFR, and c-Kit receptors, among other receptor tyrosine kinases and serine threonine kinase [13]. It can reduce tumor progression in HCC patients because of its effect on tumor

proliferation and angiogenesis. Two large phase III clinical trials, the SHARP trial and Asia-Pacific trial, clearly demonstrated that sorafenib had efficacy in terms of overall survival in patients with unresectable advanced HCC [3, 4]. According to the SHARP trial, 299 patients had sorafenib therapy; of these, only 2% had a partial response and 71% had stable disease [according to the Response Evaluation Criteria in Solid Tumors (RECIST)]. No patient had a CR [3]. In the Asia-Pacific trial also, among the 150 patients treated with sorafenib, none showed a CR [4]. In a search of the literature, only 10 HCC patients worldwide were found to have achieved a CR with sorafenib (table 1) [5–12]. So et al. [5] first reported a CR in a patient with hemochromatosis and metastatic HCC treated with sorafenib. Wang et al. [7] reported a CR in a patient with HCV and HCC with portal vein tumor thrombosis treated with a reduced dose of sorafenib. Kudo et al. [8], Curtit et al. [11], and Irtan et al. [12] reported a complete histological response in a patient who underwent surgery after sorafenib therapy. All cases were male and most showed an acute decrease in AFP levels before CR was achieved [5–12]. It takes less than 6 months to achieve CR in most cases (table 1). Therefore, it should be possible to determine within 6 months whether sorafenib is effective in most HCC patients when they achieve a dramatic therapeutic response.

Our patient, who was treated with sorafenib alone, achieved CR. This case is especially unique and suggestive for five reasons. First, this is the first time a female patient treated with sorafenib alone for HCC has achieved CR. Second, the elevation of both tumor markers and the CT scan showed disease progression after several weeks of starting sorafenib, but subsequently CR was achieved after 4 months. A recent study has suggested that an early AFP response within the first 4 weeks is a surrogate marker predictive of progression-free survival and overall survival in HCC patients treated with antiangiogenic therapies like sorafenib [14]. However, our case suggests that an early decrease in AFP levels is not the only important factor involved in achieving CR. These findings suggest that 1 month may be insufficient to determine whether HCC patients respond to sorafenib. Third, this patient maintained a CR even after the cessation of sorafenib therapy. This indicates that the tumors completely disappeared due to sorafenib therapy alone. Fourth, this is the second case of CR in HCC patients in which the initial sorafenib dose was reduced to half the standard dosage. Our patient received 400 mg once daily due to her petite build. Even though our patient achieved

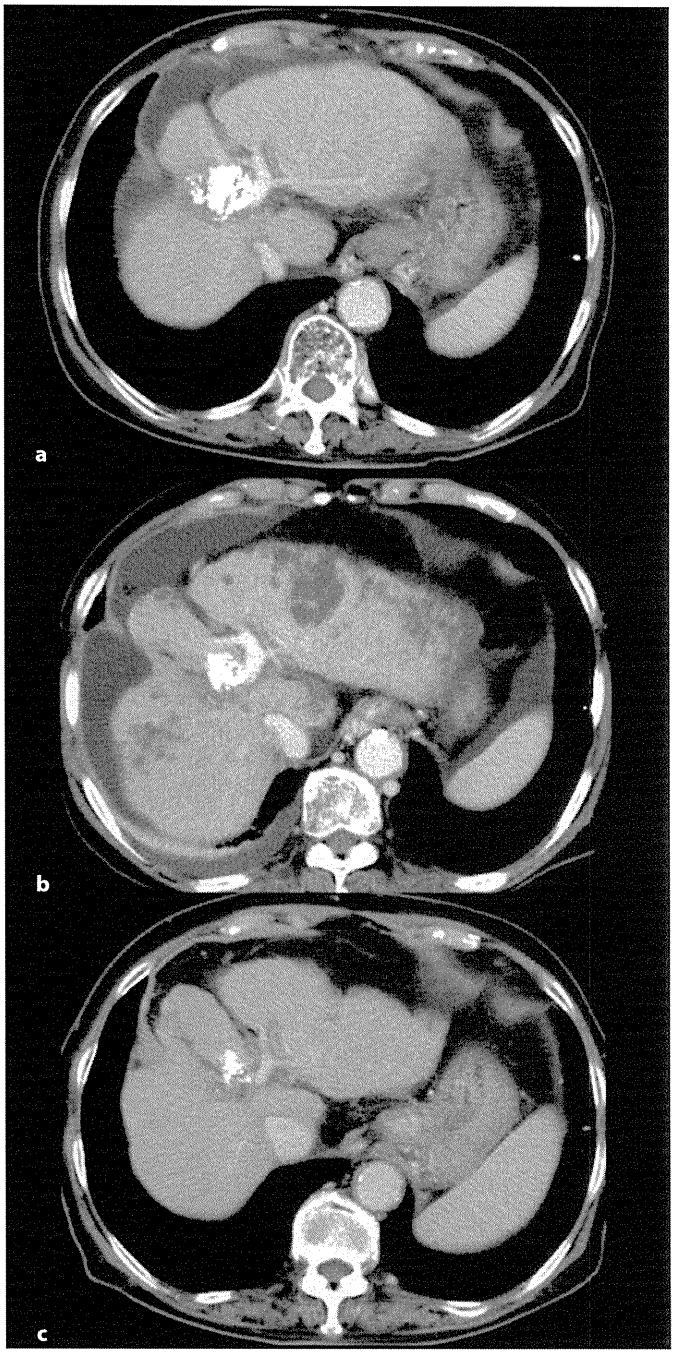

Fig. 3. Changes in abdominal CT scans after cessation of sorafenib therapy. **a** CT taken when sorafenib therapy was suspended because of hepatic encephalopathy and deterioration of liver function. **b** Four days after **a**, ALT and AST levels rose dramatically to 1,454 and 1,653 IU/l, and CT scan revealed the presence of multicentric hepatic necroses in the right and left lobes of the liver. **c** CT at the most recent follow-up revealed slight atrophy of the left lobe of the liver but no recurrence of HCC.

Table 1. CR in patients with HCC treated with sorafenib alone

Case No.	Characteristics[a]	Etiology	Metastasized to	Maximal diameter cm	Initial dose[b] mg	Time to CR months	Time to cessation	Published online	First author	Journal	Comments
1	78, M, USA, unknown	Hemochromatosis	Liver, lung	5.0	400	5	6 months	17/10/08	So [5]	Journal of Hematology & Oncology	First report
2	54, M, USA, Asian	HBV	Lung	4.1	400	18	None	1/9/09	Yeganeh [6]	American Journal of Transplantation	Posttransplant
3	74, M, USA, Caucasian	HCV	Liver (PVTT)	10	200	8	8 months	23/3/10	Wang [7]	Targeted Oncology	Low-dose
4	68, M, Japan, Asian	HBV	Liver, lung	–	400	2	None	8/7/10	Kudo [8]	Oncology	
5	68, M, Japan, Asian	HBV	Liver, lung, lymph node, adrenal gland	5.5	400	1	None				Histological CR
6	69, M, Greece, unknown	HBV + HIV	Liver, lymph node	–	400	6	None	31/8/10	Chelis [9]	Medical Oncology	HIV coinfection
7	84, M, Italy, unknown	HCV	Liver (PVTT)	6.0	400	6	None	17/1/11	Sacco [10]	BMC Gastroenterology	
8	56, M, France, unknown	HCV	Liver	15	400	6	Unknown	24/1/11	Curtit [11]	Journal of Clinical Oncology	Histological CR
9	59, M, France, unknown	Hemochromatosis	Liver (PVTT), lymph node, omentum	10	400	6	Unknown	14/3/11	Irtan [12]	Liver International	Histological CR
10	57, M, France, unknown	HBV	Liver (PVTT)	8	400	12	Unknown				Histological CR

Only 10 HCC patients worldwide have achieved a CR with sorafenib. All cases were male and most showed an acute decrease in terms of AFP levels before CR was achieved. It takes less than 6 months to achieve CR in most cases. PVTT = Portal vein tumor thrombosis.
[a] Presented as age (in years), sex, nationality, race. [b] Dose administered twice daily.

CR on half the usual sorafenib dose, it is unclear whether low-dose sorafenib therapy is as effective as the standard regimen (400 mg twice daily). More studies need to be conducted to clarify the effect of low-dose sorafenib therapy. Fifth, the patient had multicentric hepatic necroses in the right and left lobes of the liver after the cessation of sorafenib. It is assumed that nontumor liver tissues underwent necrosis because there was no evidence of HCC in the liver at that time. To our knowledge, there have been no previous reports of such adverse events in association with sorafenib, while this adverse event could have been caused by antiangiogenic therapies like sorafenib. Further investigation is required to confirm this finding.

In conclusion, we had a rare example of a dramatic therapeutic response in an HCC patient treated with sorafenib. Further studies are needed to elucidate the mechanisms of how CR is achieved at the molecular level and what the molecular biomarkers are in order to identify which patients are most likely to achieve CR. We believe that it is important to make such rare cases known and to search for a breakthrough therapy for advanced HCC.

Disclosure Statement

All authors have no conflict of interest to declare.

References

1 Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.

2 Nowak AK, Chow PK, Findlay M: Systemic therapy for advanced hepatocellular carcinoma: a review. Eur J Cancer 2004;40:1474–1484.

3 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

4 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, et al: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10:25–34.

5 So BJ, Bekaii-Saab T, Bloomston MA, Patel T: Complete clinical response of metastatic hepatocellular carcinoma to sorafenib in a patient with hemochromatosis: a case report. J Hematol Oncol 2008;1:18.

6 Yeganeh M, Finn RS, Saab S: Apparent remission of a solitary metastatic pulmonary lesion in a liver transplant recipient treated with sorafenib. Am J Transplant 2009;9: 2851–2854.

7 Wang SX, Byrnes A, Verma S, Pancoast JR, Rixe O: Complete remission of unresectable hepatocellular carcinoma treated with reduced dose of sorafenib: a case report. Target Oncol 2010;5:59–63.

8 Kudo M, Ueshima K: Positioning of a molecular-targeted agent, sorafenib, in the treatment algorithm for hepatocellular carcinoma and implication of many complete remission cases in Japan. Oncology 2010;78(suppl 1):154–166.

9 Chelis L, Ntinos N, Souftas V, Deftereos S, Xenidis N, Chamalidou E, Maltezos E, et al: Complete response after sorafenib therapy for hepatocellular carcinoma in an HIV-HBV co infected patient: possible synergy with HAART? A case report. Med Oncol 2010, E-pub ahead of print.

10 Sacco R, Bargellini I, Gianluigi G, Bertini M, Bozzi E, Altomare E, Battaglia V, et al: Complete response for advanced liver cancer during sorafenib therapy: case report. BMC Gastroenterol 2011;11:4.

11 Curtit E, Thiery-Vuillemin A, Nguyen T, Heyd B, Pivot X, Di Martino V, Borg C: Complete histologic response induced by sorafenib in advanced hepatocellular carcinoma: a case report. J Clin Oncol 2011;29: 330–332.

12 Irtan S, Chopin-Laly X, Ronot M, Faivre S, Paradis V, Belghiti J: Complete regression induced by sorafenib of locally advanced hepatocellular carcinoma allowing curative resection. Liver Int 2011;31:740–743.

13 Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, et al: Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5:835–844.

14 Shao YY, Lin ZZ, Hsu C, Shen YC, Hsu CH, Cheng AL: Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. Cancer 2010;116: 4590–4596.

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Asian Consensus Workshop Report: Expert Consensus Guideline for the Management of Intermediate and Advanced Hepatocellular Carcinoma in Asia

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Key Words

Hepatocellular carcinoma · Epidemiology · Diagnosis · Treatment · Outcome · Survival · Staging system · Intermediate stage · Advanced stage

Abstract

Hepatocellular carcinoma (HCC) is a highly prevalent disease in many Asian countries, accounting for 80% of victims worldwide. Screening programs improve the detection of early HCC and have a positive impact on survival, but the majority of HCC patients in Asia still present with advanced stage disease. The treatment outcomes of HCC are affected by multiple variables, including liver function, performance status of the patient, and tumor stage. Therefore, it is not easy to apply a multidisciplinary therapeutic approach for optimal management. At present, limited numbers of HCC patients are eligible for curative therapies such as surgery or ablation in Asia. Therefore, most patients are eligible for only palliative treatments. For optimal management, the treatment choice is guided by staging systems and treatment guidelines. Numerous staging systems have been proposed and treatment guidelines vary by region. According to the Barcelona Clinic Liver Cancer (BCLC) guideline based on evidence from randomized clinical trials, only transarterial chemoembolization (TACE) is recommended for intermediate stage HCC and sorafenib for advanced stage HCC. However, treatment guidelines from Asian countries have adopted several other therapeutic modalities such as a surgical approach, hepatic arterial infusion chemotherapy, external radiation, and their combinations based on clinical experiences for intermediate and advanced stage HCC. Although TACE is the main therapeutic modality in the intermediate stage, overall therapeutic outcomes depend on the tumor size. In the advanced stage, the prognosis depends on the tumor status, e.g. major vessel invasion or extrahepatic spread.

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Thus, a new staging system representing prognoses suitable for Asian HCC patients and a corresponding optimal treatment algorithm should be further investigated using evidence-based data, which will finally bring about an Asian consensus for the management of intermediate and advanced stage HCC.

Introduction

Hepatocellular carcinoma (HCC) is endemic in Asia. It is expected that about 80% of new HCC cases worldwide will develop in Asia [1, 2]. HCC ranks as the first to fifth leading causes of death in many Asian countries. However, there is no consensus guideline to manage HCC in Asia. To build a bridge to a consensus on HCC management in Asia, the first Asia-Pacific Primary Liver Cancer Expert (APPLE 2010) meeting was held in Incheon, Korea, last year. Especially, the first consensus assembly in the APPLE meeting mainly focused on how to manage intermediate and advanced HCC in Asia.

The current standard of care for patients unsuitable for potentially curative therapy is locoregional therapy with transarterial chemoembolization (TACE). For patients with more advanced disease, sorafenib is the standard of care. Sorafenib is a targeted agent with proven survival benefits [3, 4]. Although other novel agents and therapeutic approaches are emerging, such as radioembolization and various targeted agents, further data based on randomized clinical trials (RCT) are needed.

This report is based on experts' reports from three Asian countries (Korea, Japan, and China) and a panel discussion, and it is divided into three topics: (1) definitions of intermediate and advanced HCC in staging systems, (2) treatment strategies for the intermediate stage in Asia, (3) and treatment strategies for advanced HCC in Asia.

Definitions of Intermediate and Advanced HCC in Staging Systems

The terminology of intermediate and advanced HCC comes from the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC staging system is widely recognized and endorsed [5–7]. It includes variables linked to tumor stage and function, physical status, and cancer-related symptoms, and it combines each stage with a treatment algorithm. Patients with intermediate stage HCC are asymptomatic (PS score 0) with multinodular tumors but without vascular invasion or extrahepatic spread and are eligible for locoregional therapy such as TACE. Those with advanced stage HCC are either symptomatic (PS score 1–2) or have evidence of vascular invasion or extrahepatic spread; these patients are eligible for sorafenib. The BCLC system has been externally validated [7, 8] and is endorsed by both the American Association for the Study of Liver Diseases (AASLD) [9] and the European Association for the Study of the Liver (EASL) [10].

Although the BCLC staging classification is an emerging candidate for a standard classification in Western regions, validation across both Eastern and Western regions is required for global application because of the distinct differences between these patient populations and risk factors. Most Asian experts agreed that the BCLC staging system was not perfect to satisfy Asian experts in clinical practice. Early stage means that the disease can be controlled by curative treatment, but the advanced stage is hard to define in this system as advanced stages harbor so many disease categories. Therefore, it should be subcategorized for the application of each unique treatment for the future. Furthermore, the disease is a kind of continuous spectrum. Thus, it may not be easy to separate it into two stages, i.e. intermediate and advanced. The term 'advanced stage' which includes portal vein invasion and distant metastasis seems to harbor a wide spectrum of HCC, which indicates that the advanced HCC stage can be divided into two different groups: locally advanced with portal vein invasion and advanced with extrahepatic metastasis.

At present, most Asian countries have their own HCC staging systems. The Japanese Tumor-Node-Metastasis (TNM) staging system [11] is widely used in Japan and Korea (table 1). This staging system takes into account three criteria for the T stage, i.e. whether the tumor is solitary or multiple, the tumor size (≤2 cm or >2 cm),

Table 1. Japanese TNM staging system

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IVa	T4	N0	M0
	T1–3	N1	M0
IVb	T1–4	N0–1	M1

Table 2. Chinese staging system

Stage	Tumor	Invasion	Lymph node involvement	Distant metastasis	Child-Pugh class
Ia	Solitary ≤3 cm	No	No	No	A
Ib	One or two ≤5 cm, one lobe	No	No	No	A
IIa	One or two ≤10 cm, one lobe or two ≤5 cm, two lobes	No	No	No	A
IIb	One or two >10 cm, one lobe or two >5 cm, two lobes	No	No	No	A
IIIa	Any	PVB/HV/BD	No	No	A
	Any	No	No	No	B
	Any	MPV/IVC	Yes or no	Yes or no	A or B
	Any	Yes or no	Yes	Yes or no	A or B
	Any	Yes or no	Yes or no	Yes	A or B
IIIb	Any	Yes or no	Yes or no	Yes or no	C

PVB = Portal vein branch; HV = hepatic vein; BD = bile duct; MPV = main portal vein; IVC = inferior vena cava.

and the presence of any vascular or bile duct invasion. Patients are thus classified as T1, T2, T3, or T4. For nodes and metastasis, it is similar to other TNM staging systems, based on the presence of lymph node or distant metastasis. Recently, the Japan Integrated Staging (JIS) system was developed by integrating Japanese TNM stages and Child-Pugh grades and was externally validated [12–14]. In contrast, the Chinese staging system considers the Child-Pugh class in addition to tumor factors (number, size, and one or both lobes), vessel invasion, lymph node involvement, and distant metastasis (table 2). As many Asian countries use their own staging systems, it is hard to communicate with reference to staging systems in the Asian-Pacific region. To provide Asian physicians with a common language on which to base treatment decisions and clinical research, it is necessary to have a consensus on the best applicable staging system.

In conclusion, Asian countries have their own staging systems with different constituent variables. Because the real situations vary among Asian countries, it seems not to be easy to reach a consensus on staging systems. The increasing need for a consensus on a new staging system which can upgrade the current staging system was expressed again at the first APPLE meeting. Continued efforts to improve our understanding of this complex disease will enable us to refine staging classifications and guide the optimal therapy according to different stages.

Treatment Strategies for Intermediate HCC

The current distribution of HCC based on the BCLC system spans mostly the intermediate or advanced stage in Asian countries, except Japan [2, 15]. The disease stage obviously affects the treatment modality. TACE is the most widely used locoregional treatment for patients with intermediate stage HCC, and it is considered the standard treatment option for patients with reasonable liver function with large (>5 cm) or multifocal tumors without major vessel invasion or extrahepatic spread. However, TACE cannot induce complete tumor necrosis especially in large tumors [16, 17]. Therefore, overall therapeutic outcomes might depend on the tumor size.

To improve locoregional therapies for patients with unresectable HCC, new liver-directed therapies have emerged. Preliminary results of the use of drug-eluting beads (DEBs) suggest that this approach is associated with a favorable toxicity profile and encouraging antitumor activity [18–20]. In a recent study comparing conventional TACE with DEB-TACE, the DEB-TACE group resulted in a better local response, fewer recurrences, and a longer time to progression compared to the conventional TACE group [21]. Radioembolization with yttrium-90 (^{90}Y)-embedded microspheres is a new method suggesting an effective treatment approach for patients with unresectable HCC [22].

The Japanese treatment guidelines, which covered a majority of early and intermediate stage HCC patients, were revised in 2009 (fig. 1) [23]. In addition, a consensus-

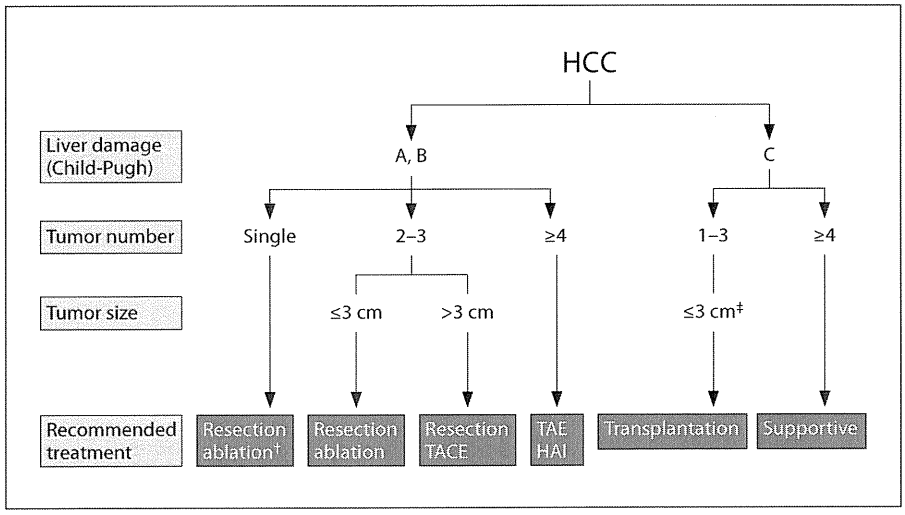

Fig. 1. EBM-based algorithm for HCC management (J-HCC guidelines 2009). Resection or transarterial chemoembolization may be selected for Child-Pugh A class patients with vascular invasion. Chemotherapy may be selected for extrahepatic HCC. Liver transplantation is only for patients ≤65 years of age. † Recommended for Child-Pugh B; ‡ <2 cm for solitary lesions. HAI = Hepatic arterial infusion.

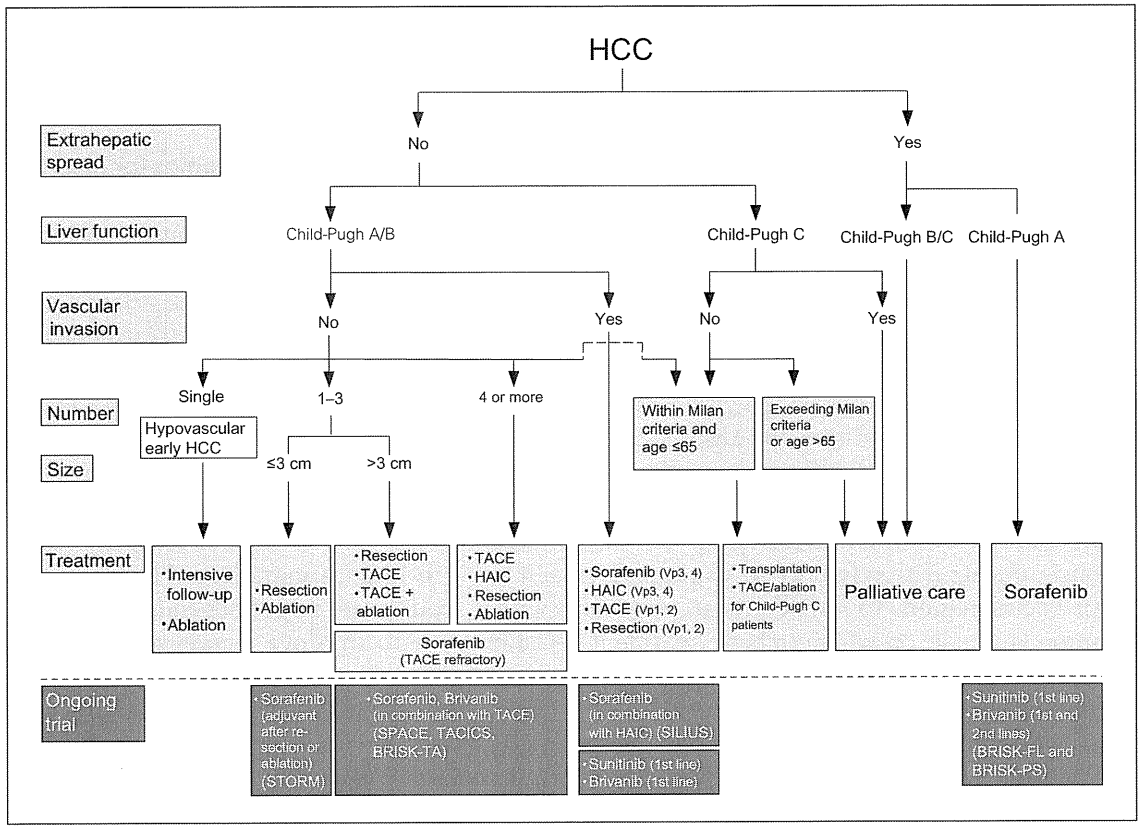

Fig. 2. Consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology (JSH) in 2009 and revised in 2010.

based treatment algorithm for HCC was proposed (fig. 2) [24]. In this guideline, hepatic arterial infusion chemotherapy (HAIC) as well as TACE is recommended for the intermediate stage. Furthermore, Japanese treatment guidelines propose that liver transplantation can be performed for some patients with Child-Pugh C liver function. The Korean guidelines for the management of HCC were updated in 2009 (fig. 3) [25]. They regard tumor stage, Child-Pugh class, and performance status as the first aspects to consider when starting treatment. HCC

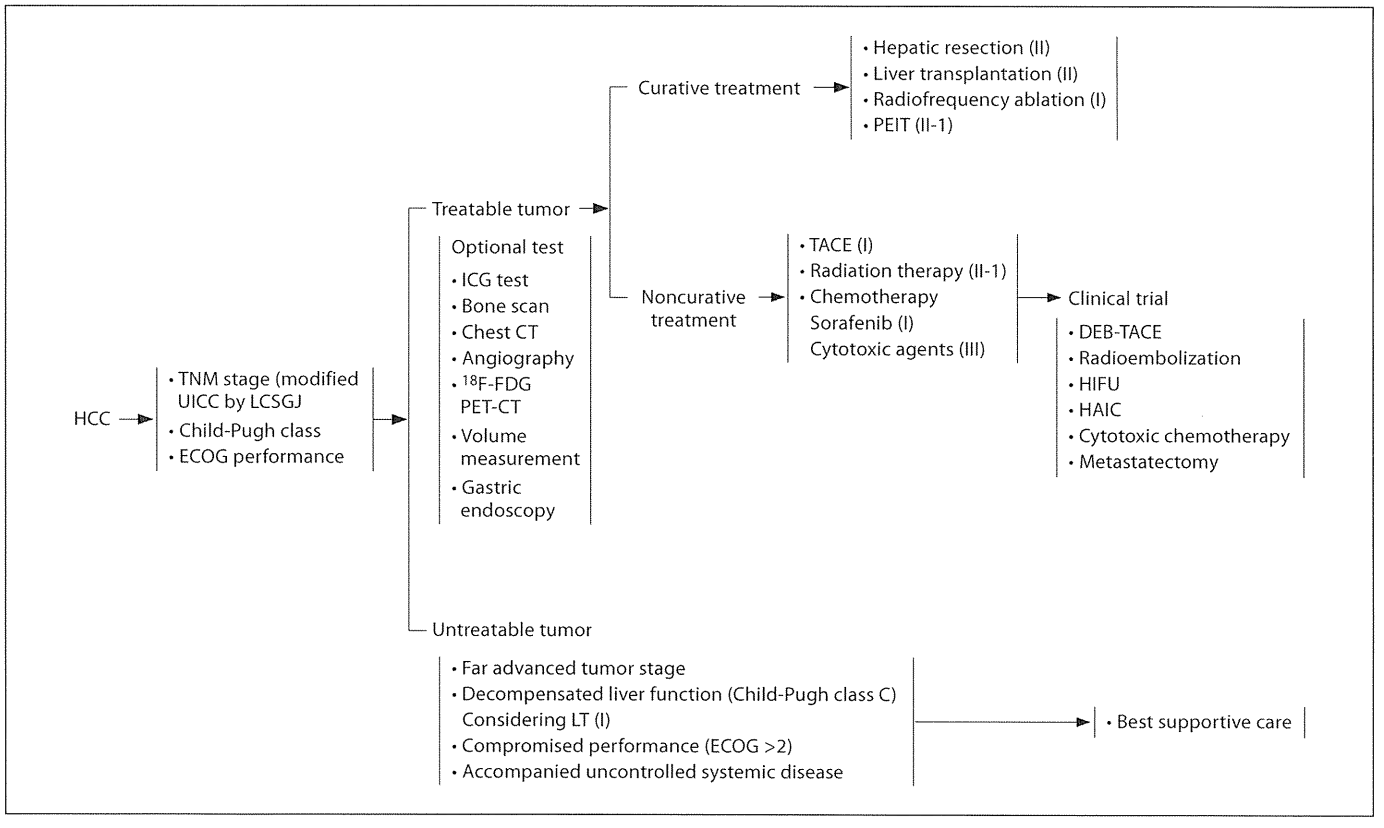

Fig. 3. Therapeutic algorithm for HCC in Korea.

was divided into treatable and nontreatable disease. For treatable HCC, curative or noncurative treatment can be performed. The algorithm of the Korean HCC treatment plan lists hepatic resection, liver transplantation, radiofrequency ablation, and ethanol injection as curative treatments. As the overall surgical mortality is very low, resection can be considered as an option even in intermediate stage HCC based on Asian experts' opinions. According to the treatment algorithm of China proposed by the Shanghai Fudan University Hospital (fig. 4), intermediate stage HCC can be treated with surgical resection, liver transplantation, and sorafenib as well as TACE.

Treatment Strategies for Advanced HCC

As sorafenib is the first targeted agent with survival benefits proven by two large-scale RCT, it is the standard of care for patients with advanced stage disease [3, 4]. However, sorafenib for advanced HCC is still not easy for Asian physicians to prescribe due to high costs [25–27]. For the management of advanced HCC, sorafenib has not yet been approved for reimbursement in most Asian countries due to a big burden on the national insurance budget. Therefore, most Asian experts on this panel agreed that the practical situation in Asian countries should be considered for the creation of practical guidelines. In addition, treatment for locoregional disease is quite different from treatment for systemic disease. Therefore, the advanced stage of HCC should be subdivided into a locally advanced stage and an extrahepatic advanced stage.

There are still many options aside from sorafenib for the locally advanced stage based on experts' opinions [23–30]. According to the treatment algorithm of Asia (Japan, Korea, and China), not only sorafenib but also many therapeutic options such as surgical resection, TACE, HAIC, and external radiation can be tried for the advanced stage. As extrahepatic disease is a systemic disease, sorafenib is the standard systemic therapy. However, in APASL guidelines, systemic chemotherapy can be an option in the practical setting [28].

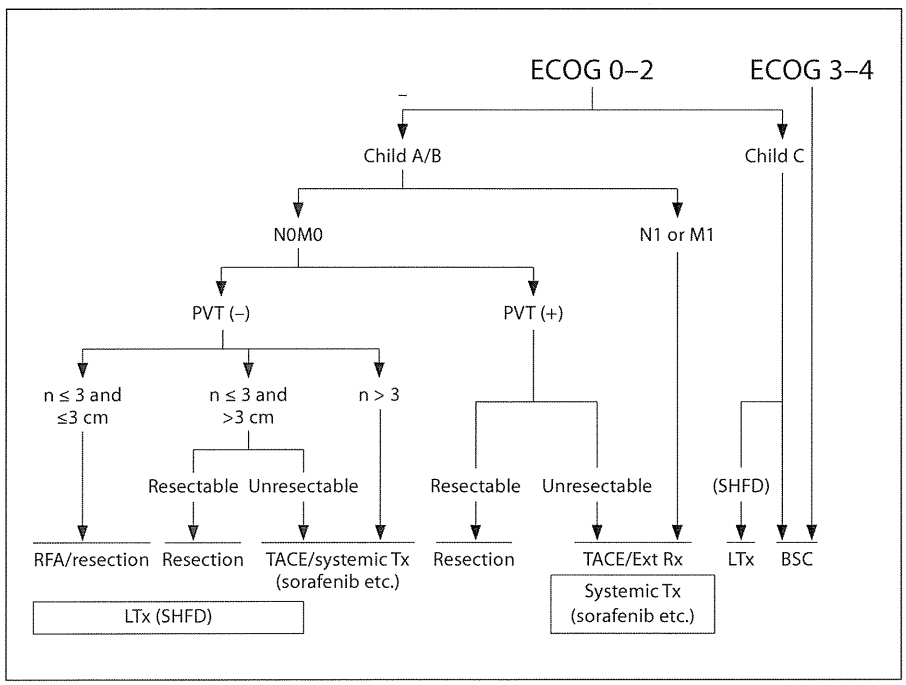

Fig. 4. Treatment algorithm for HCC at the Liver Cancer Institute of Fudan University. RFA = Radiofrequency ablation; Tx = therapy; Ext Rx = external radiation; LTx = liver transplantation.

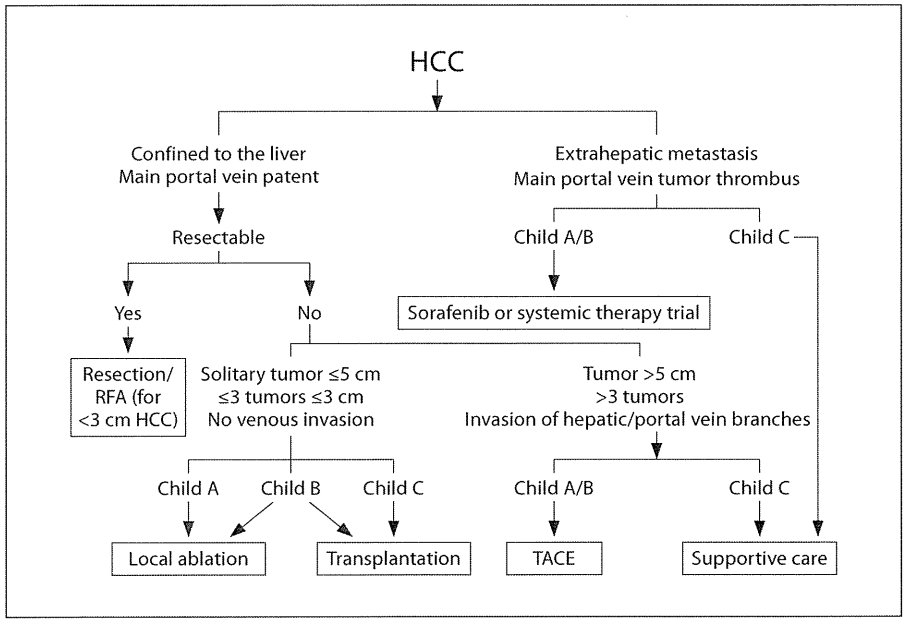

Fig. 5. APASL guideline on the treatment algorithm for HCC. RFA = Radiofrequency ablation.

In order to have a consensus guideline in the Asia-Pacific region, we need enough evidence-based data. Although, the guideline at present is not complete and does not cover various practical situations in Asia, we should try to enhance our practical guidelines in the near future by collecting more evidence based on RCT.

Conclusion

The majority of HCC patients in Asia still presents with intermediate and advanced stage HCC at diagnosis. In the first APPLE meeting, the significant different distribution of intermediate and advanced stage HCC was recognized among Asian countries. Furthermore, the significant differences in the treatment approach according to HCC stages were also identified. A consensus for