published. In six of these, IFN therapy inhibited the development of HCC in patients with liver cirrhosis C. Two meta-analyses also affirmed the preventive effects of IFN therapy on the development of HCC in patients with liver cirrhosis C. These effects were marked in patients who achieved SVR. Previously, one study examined the inhibitory effects of combination therapy with IFN and ribavirin on HCC in liver cirrhosis C patients, and reported that, in the combination therapy group, the development of HCC was inhibited in comparison with the non-treated group.

Anti-Inflammation Therapy

Glycyrrhizin Preparations

The intravenous administration of glycyrrhizin for chronic hepatitis/liver cirrhosis is commonly performed to improve the transaminase level. No RCT has investigated whether glycyrrhizin preparations inhibit liver carcinogenesis. However, a retrospective cohort study reported that the intravenous administration of glycyrrhizin preparations for chronic hepatitis C decreased the risk of liver carcinogenesis [21]. It is recommended that glycyrrhizin be intravenously administered for prevention of HCC development in patients with chronic hepatitis C when IFN therapy is not effective or indicated.

Ursodeoxycholic Acid

When administering ursodeoxycholic acid (UDCA) to patients with chronic hepatitis C, cytotoxic bile acid may be substituted for UDCA, protecting the hepatocyte membrane. Furthermore, a study suggested that the immunity-regulating and apoptosis-inhibiting actions of UDCA are involved in the protection of the hepatic cell membrane.

To date, no study has reported the preventive effects of long-term UDCA administration on liver carcinogenesis. However, UDCA administration at 600–900 mg/day improved the serum ALT level [22].

Phlebotomy Therapy

Phlebotomy therapy decreases the serum ALT level, suggesting the usefulness of phlebotomy for the treatment of chronic hepatitis C. Kato et al. [23] reported that long-term iron chelation significantly inhibited the development of HCC. In the future, a large-scale comparative study should be conducted.

Consensus Statements

1 Among patients with type B chronic liver disease, the incidence of HCC is high in those with a high HBV DNA level.
2 Nucleoside analogues are useful for preventing HCC in patients with chronic hepatitis B or compensatory liver cirrhosis B.
3 Among patients with chronic hepatitis C, the incidence of HCC is higher in those with marked fibrosis or liver cirrhosis.
4 It is recommended that antiviral therapy with IFN be performed to prevent HCC in patients with chronic hepatitis C. Firstly, virus elimination is important. When it is impossible, the liver function must be normalized.

Surveillance of Hepatocellular Carcinoma

Definition of the Population at High Risk for HCC

Persistent infections with hepatitis B and C viruses (HBV and HCV, respectively) are the highest risk factors for liver carcinogenesis. The carcinogenesis risk for HBV carriers is about 200 times higher than that for non-carriers, and the risk is higher in patients with type C liver cirrhosis than in those with hepatitis B-related cirrhosis. The HCV-associated risk is about 5 times higher than that associated with HBV. The characteristics of HCV-associated carcinogenesis are carcinogenesis in the F4 step in which liver cirrhosis is completed in most cases, and its occurrence in many cases at 60 years of age or older. The yearly carcinogenesis rate of cirrhosis type C is 7–8% in Japan, which is higher than that in Europe or North America; it might be that the mean age of carriers is closely involved. Liver cirrhosis induced by various causes, even though HBV and HCV are negative, is a risk for liver carcinogenesis. Since carcinogenesis occurs in some cases of liver cirrhosis associated with non-alcoholic steatohepatitis (NASH), alcoholic liver disease, primary biliary cirrhosis (PBC), and autoimmune hepatitis (AIH), the course of the disease should be followed paying close attention to carcinogenesis as in cases of viral liver cirrhosis. Alcohol increases the risk of chronic hepatitis B- and C-associated liver carcinogenesis.

Based on the above, patients with chronic hepatitis B and C and non-viral liver cirrhosis are defined as high-risk populations for HCC in both the Consensus-Based Clinical Practice Manual and Evidence-Based Practice Guidelines. Patients with liver cirrhosis types B and C are defined as a super-high-risk population (table 2). Risk factors other than hepatitis virus or liver cirrhosis are also proposed (table 3).

Table 2. Definition of populations at high risk for HCC

A. Super-high-risk population
1. Hepatitis B-related liver cirrhosis
2. Hepatitis C-related liver cirrhosis
B. High-risk population
1. Chronic hepatitis B
2. Chronic hepatitis C
3. Liver cirrhosis (causes other than HBV or HCV)

Table 3. Risk factors other than hepatitis virus infection or liver cirrhosis

Older age
Male gender
Diabetes mellitus
High body mass index (BMI)
High AST
High ALT
Low platelet count (PLT)
Heavy alcohol drinker
High viral load (HBV carrier)

Table 4. Surveillance protocol for early detection of HCC

1. Super-high-risk patients
Every 3–4 months
Ultrasound examination
AFP/PIVKA-II/AFP-L3 measurements
Every 6–12 months
Dynamic CT or dynamic MRI/EOB-MRI
2. High-risk patients
Every 6 months
Ultrasound examination
AFP/PIVKA-II/AFP-L3 measurements

EOB-MRI = Ethoxybenzyl-MRI.

Surveillance Protocol for Early Detection of HCC

For HCC screening, the HCC detection sensitivity of ultrasonography (US) is higher than that of α-fetoprotein (AFP) measurement, but specificities are not markedly different. For liver cirrhosis, a combination of the two methods has been reported to increase detection frequency compared to detection by US or AFP measurements alone.

No clear evidence is available to determine the optimum interval for periodic screening, but HCCs detected in periodic screenings by AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II), and AFP lectin fraction (AFP-L3) measurement, and US are solitary and small in many cases, as compared to those detected in symptomatic patients. Thus, the Evidence-Based Clinical Guidelines [4, 5] proposed performing US and tumor marker measurements 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 appropriate (table 4). At present, 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, but alternate measurements of the AFP and PIVKA-II combination or the AFP and AFP-L3 combination is proposed according to the coverage under the current Japanese health insurance. For cases with a very rough background liver parenchyma because of cirrhosis and obesity with difficulty for US evaluation, periodic imaging screening by dynamic CT (multidetector-row CT (MDCT)) or dynamic MRI/EOB-MRI (ethoxybenzyl-MRI) every 6–12 months is proposed [9] (table 4), which is identical to the protocol in the Evidence-Based Clinical Practice Guidelines.

Consensus Statements

5 Patients at high risk for developing HCC should be entered into surveillance programs. The high-risk population and risk factors are identified in tables 2 and 3.
6 Surveillance for HCC should be performed using both US and tumor markers.
7 In Japan, three tumor markers (AFP, PIVKA-II, AFP-L3) are covered by the national health insurance in clinical settings for HCC surveillance.
8 Patients should be screened at 3- to 6-month intervals based on their risk of developing HCC.
9 The surveillance interval needs to be shortened for patients at higher risk for HCC, as described in table 4.

Pathology of Hepatocellular Carcinoma

For the diagnosis and treatment of HCC, it is important to understand the pathology of HCC growth/progression pattern. Clinicians should know the entity of early HCC and the association between pathological features of liver cancer growth/progression and malignancy.

The liver does not have any epithelial structure, different from the digestive tract; therefore, it is impossible to

evaluate the invasive stage of HCC based on the grade of infiltration. In addition, simultaneous/metachronal multicentric development is relatively frequent, making the definition of early HCC difficult. However, several studies showed that the pathological morphology and biological malignancy grade of HCC changed with an increase in the tumor diameter, suggesting the presence of lesions corresponding to early cancer of other organs [24, 25].

Definition of Early HCC with Respect to Pathological Morphology

According to the 'General Rule of Clinical and Pathological of Primary Liver Cancer', HCC is macroscopically classified into five types: vaguely nodular with indistinct margin-, simple nodular-, simple nodular type with extratumor growth-, and multinodular confluent type [26]. In addition, macroscopic findings of small HCCs are classified into two types: simple nodular and vaguely nodular type with indistinct margin. Histologically, most simple nodular type lesions are composed of moderately differentiated carcinoma, whereas vaguely nodular type with indistinct margin consist of well-differentiated carcinoma without severe atypia. In addition to findings such as small cells with an increase in the N/C ratio, an increase in the cell density, 2- to 3-thin layer arrangement, and a small pseudo-glandular structure, these lesions include the several original portal areas. At the boundary of the tumor, cancer cells proliferate to replace the normal hepatocellular cords in the non-cancerous region; therefore, macroscopically, the tumor border becomes unclear. Nodules with indistinct margin, which reflect the earliest change of hepatocarcinogenesis that can be clinically diagnosed, are defined as 'early HCC'. In patients with early HCC, vascular invasion is very exceptional, and there is no intrahepatic metastasis [24]. It is often difficult to differentiate early HCC from high-grade dysplastic nodules. However, the presence or absence of the infiltration of cancer cells in the portal area involved (stromal invasion) [27, 28] should be evaluated for differentiation.

Vascular Structure of Early HCC

It is well known that advanced HCC is completely supplied by arteries. However, early HCC is supplied by the portal venous flow at various levels, i.e. early HCC is supplied by both portal and arteries. However, the number of portal regions in cancer tissue accounts for approximately 25% of that in the non-cancerous region. In addition, arterial tumor vessels are undeveloped; portal and arterial blood may be decreased. On the other hand, arterial tumor vessels develop with an increase in the tumor diameter. However, tumors measuring approximately 10 mm in diameter show insufficient development, and vascularization of the tumor stroma, that is, the capillarization, is also insufficient. Therefore, early HCC does not show hypervascularity on angiography or contrast-enhanced CT.

Fatty Change of Early HCC

Although early, small liver cancer is often visualized as a hyperechoic nodule on US, most lesions reflect the fatty change of the nodule. The fatty change of HCC was the most frequent (approx. 40%) in lesions measuring 10–15 mm in tumor diameter, and the incidence decreases with an increase in the diameter and a reduction in the grade of differentiation. Based on this, fatty change is regarded as a morphological characteristic of early HCC. As previously described, with respect to the pathogenesis of such fatty change, portal blood flow and arterial blood flow may reduce via a decrease in the portal area in lesions measuring 10–15 mm in tumor diameter, and cancer may transiently show ischemia due to the insufficient development of arterial tumor vessels, causing fatty change [29].

Diagnostic Imaging of Early HCC

As many lesions of early HCC are hypovascular, they are difficult to demonstrate on CT through a hemodynamic basis; the correct diagnosis rate is not high. Recently, diagnostic imaging of intrahepatic nodular lesions by contrast-enhanced MRI with Gd-EOB-DTPA has been introduced. For Gd-EOB-MRI to be used to evaluate the hepatocellular function, lesions with a decreased intense at the hepatocyte phase are regarded as HCC. The CT diagnosis rate (including CTHA and CTAP) when lesions with a decrease in portal blood flow were regarded as HCC was approximately 60–70%, whereas the diagnosis rate of HCC by EOB-MRI is approximately 90% [30]; MRI may improve the diagnostic accuracy of early HCC. However, the presence of HCC with isointense and dysplastic nodule with low intense on hepatocyte phase of Gd-EOB-MRI has been indicated.

Macroscopic Classification of HCC and Malignancy Grade

The association between macroscopic findings and malignancy grade depends on the grade of tissue differentiation. When investigating resected specimens of HCC

Table 5. Pathology of small HCC: relationship between macroscopic classification, histological differentiation and tumor size (all resected cases, nodule diameter ≤3 cm) [cited from 9, with permission]

	n (%)	Well	Well + mod.	Mod.	Mod .+ poor	Tumor size, mm
SNIM	22	19 (86.4)	3 (13.6)	0	0	13.6 ± 5.4
SN	123	6 (4.9)	24 (19.5)	92 (74.8)	1 (0.8)	22.8 ± 5.6
SNEG	45	0	5 (11.1)	40 (88.9)	0	23.1 ± 5.4
CM	19	0	6 (31.6)	11 (57.9)	2 (10.5)	23.9 ± 5.3

SNIM = Small nodule with indistinct margins; SN = simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type. Percent values are shown in parentheses.

Table 6. Pathology of small HCC: macroscopic classification and microscopic findings (all resected cases) [cited from 9, with permission]

	fc	fc-inf	sf	vp	vv	im
SNIM	0	0	2 (9.1)	0	0	0
SN	90 (73.2)	79 (64.2)	65 (52.8)	23 (18.7)	3 (2.4)	5 (4.1)
SNEG	38 (84.4)	35 (77.8)	35 (77.8)	20 (44.4)	2 (4.4)	12 (26.7)
CM	1 (5.3)	1 (5.3)	14 (73.7)	12 (63.2)	3 (15.8)	5 (26.3)

fc = Capsular formation; fc-inf = capsular infiltration; sf = septum formatin; vp = portal vein invasion; vv = hepatic vein invasion; im = intrahepatic metastasis; SNIM = small nodule with indistinct margins; SN = simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type.
Percent values are shown in parentheses.

measuring ≤3 cm, approximately 85% of vaguely nodular type with indistinct margin lesions (early HCC) consisted of uniform, well-differentiated cancer tissue. The remaining 15% contained an area consisting of moderately differentiated HCC tissue, in which dedifferentiation was noted, showing unclear/clear 'nodule-in-nodule lesion' (table 5). In vaguely nodular type lesions, intrahepatic metastasis and portal tumor invasion are extremely rare. The mean tumor diameter is approximately ≤15 mm, and these lesions are significantly smaller than other macroscopic types of nodular lesions. Approximately 75% of simple nodular type lesions are classified as moderately differentiated HCC. Histologically, portal invasion is observed in 20%, and intrahepatic metastasis in 4%, suggesting advanced HCC. Simple nodular type with extratumor growth and multinodular confluent type lesions suggest advanced HCC. Most lesions consist of moderately to poorly differentiated HCC tissues. Portal invasion and intrahepatic metastasis are more frequently seen than in simple nodular type lesions (table 6). The number of intrahepatic metastatic foci and distance from the primary nodular are greater than in simple nodular type lesions [30] (table 7). In other words, lesions with high-level biological malignancy may be macroscopically evaluated as simple nodular type with extratumor growth or multinodular confluent type lesions. Therefore, curative treatment to avoid intrahepatic metastasis and recurrence must be kept in mind in these lesions in comparison with vaguely nodular type and simple nodular type HCCs.

Table 7. Pathology of small HCC: distance between main nodule and intrahepatic metastasis [cited from 9, with permission]

	n (%)	Distance, mm			
		≤2	2.1–5	5.1–10.0	>10.1
SN	9	6 (66.7)	1 (11.1)	0 (0.0)	2 (22.2)
SNEG	75	23 (30.7)	12 (16.0)	17 (22.7)	23 (30.7)
CM	65	27 (41.5)	19 (29.2)	13 (20.2)	6 (9.2)
Total	149	56 (37.6)	32 (21.5)	30 (20.1)	31 (20.8)

SN = Simple nodular type; SNEG = simple nodular type with extranodular growth; CM = confluent multinodular type.
Percent values are shown in parentheses.

Table 8. Pathology of small HCC: rate of portal venous invasion/intrahepatic metastasis and size of nodule (all resected specimens) [cited from 9, with permission]

	Nodule size, cm				
	0–1	1.1–2.0	2.1–3.0	3.1–5.0	5.1–10.0
PVI	0	28.3%	33.3%	49%	58.5%
IM	0	6.7%	17.1%	29.6%	43.9%

PVI = Portal venous invasion; IM = intrahepatic metastasis.

Differentiation and Malignancy Grade of HCC

Most early HCC lesions appear as well-differentiated lesions. Macroscopically, they are detected as nodules with an unclear border. However, the tumor diameter increases with dedifferentiation. Moderately to poorly differentiated HCCs, contained in the well-differentiated cancer tissue after dedifferentiation, are more malignant than the peripheral well-differentiated HCC tissue, showing expansive growth, completely replacing the well-differentiated cancer tissue, and leading to classical HCC with clear margin. When examining small HCC with 'nodule-in-nodule', p53 overexpression is detected in approximately 40% of moderately to poorly differentiated cancer tissues in the internal area. In addition, a Ki-67 labeling index, which reflects the proliferative capacity, indicates that the malignancy is advanced when the peripheral well-differentiated HCC (early HCC) shows 'nodule-in-nodule' pattern. This is consistent with the finding that an increase in the tumor diameter was accelerated with the appearance of 'nodule-in-nodule' during clinical follow-up. 'Nodule-in-nodule' type HCC is recognized as being in the dedifferentiation process from early to advanced HCC; clinical management similar to advanced HCC is necessary.

In 'nodule-in-nodule' type HCC, there is a marked difference in vascularity between the marginal well-differentiated and internal moderately to poorly differentiated HCC tissues. On contrast-enhanced US or CT, the marginal well-differentiated cancer tissue is visualized as a hypovascular area, because the development of arterial tumor vessels and the capillarization is insufficient. However, moderately to poorly differentiated cancer tissues in the internal area are visualized as hypervascular area due to sufficient neovascular development. Briefly, the vascular structure of liver cancer is closely correlated with the grade of differentiation. The malignancy of early liver cancer may be predicted to some degree based on hemodynamic findings.

Nodule Size and Malignancy Grade of HCC

The size of HCC is associated with the macroscopic morphology, grade of histological differentiation, and intrahepatic metastasis/portal invasion rates. Most vaguely nodular type lesions measure ≤2 cm, and lesions measuring ≥3 cm are rare. However, simple nodular type with extratumor growth and multinodular confluent type lesions become more frequent with an increase in the tumor diameter. Concerning the grade of histological differentiation, the proportion of lesions consisting of uniform, well-differentiated cancer tissue markedly decreases when the tumor diameter exceeds 2 cm. Most lesions consist of moderately to poorly differentiated HCC tissues. The portal invasion/intrahepatic metastasis rates also increase in proportion to the tumor diameter (table 8). Usually, there is a correlation between an increase in the tumor diameter and malignancy grade. However, exceptionally, large, well-differentiated, slowly expanding HCC is present [32].

Consensus Statements

10 Vaguely nodular type HCCs, which are composed of very well-differentiated HCC, are defined as 'early hepatocellular carcinoma'.
11 Early HCC does not show hypervascularity on angiography or dynamic CT/MRI.
12 Fatty change and stromal invasion are regarded as the morphological characteristics of early nodular HCC.
13 In simple nodular type with extranodular growth and multinodular confluent type HCCs, intrahepatic metastasis and recurrence are more frequent than in lesions with vaguely nodular type and simple nodular type HCCs. This must be kept in mind on the curative treatment.
14 'Nodule-in-nodule' findings of very well-differentiated carcinoma (early HCC) reflect higher malignancy grade than early HCC.

Diagnosis of Hepatocellular Carcinoma

Diagnostic Criteria

The diagnosis of HCC is determined by three factors: the background chronic liver disorder, tumor markers, and imaging diagnosis. When the liver has hepatitis B- and C-related cirrhosis, tumor marker levels are increased, and typical imaging findings are detected, HCC can be definitely diagnosed. Typical imaging findings are hypervascularity in the arterial phase and washout in the portal equilibrium phase on dynamic CT or dynamic MRI. Hypervascularity on CTHA and a perfusion defect on CTAP also leads to a diagnosis of typical HCC. How-

ever, HCC cannot be definitely diagnosed based on a combination of tumor markers and chronic liver disorder alone, or on the elevation of tumor markers alone. Moreover, hypervascular nodules in the arterial dominant phase without washout in the portal equilibrium phase are not typical and more precise investigations are necessary. Hypovascular nodules in the arterial dominant phase also require further examination. Cases meeting all A, B, and C criteria in table 9 are definitely diagnosable as HCC in Japan. Cases not accompanied by the typical imaging findings are diagnosed and treated by the examinations detailed in figures 1 and 2.

Table 9. Diagnostic criteria of typical HCC[1]

A. Background liver disease (one positive factor)
Hepatitis B-related liver disease
Hepatitis C-related liver disease
Liver cirrhosis
B. Tumor markers (at least one positive study)
AFP ≥200 ng/ml associated with a rising trend over time
PIVKA-II (≥40 mAU/ml) with a rising trend over time
AFP-L3 (>15%)
C. Typical imaging findings (one positive study)[2]
Arterial phase hypervascularity with portal-venous phase washout on dynamic CT, dynamic MRI or CEUS
Hypervascularity on CTHA with perfusion defect on CTAP

[1] A+B+C, A+C, B+C, C: HCC confirmed A+B, B: HCC highly suspicious, thus, dynamic CT/MRI is required.

[2] Nodules with atypical imaging study, namely, hypervascularity without portal/venous washout or hypovascular nodule on arterial phase should undergo further study (as shown in fig. 1 and 2).

Multistep Development of HCCs and Abnormal Blood Flow

Many cases of HCCs originate from HBV and HCV infections via multistep development. Premalignant lesions and early HCCs are mainly fed by a portal venous flow in contrast to overt HCCs, which are supplied by an arterial flow. Thus, there may be no objection to indicating a hypervascular HCC for treatment.

However, how to diagnose a typical HCC is the most problematic issue when the hemodynamic pattern is not typical for a HCC. Although the Guidelines for Evidence-Based Clinical Practice for the Treatment of Liver Cancer [4, 5] do not suggest any detailed imaging diagnostic criteria for atypical nodules, a more detailed algorithm referring to these issues has been proposed in the new practice manual (fig. 1).

Diagnostic Modalities of HCC

Dynamic CT

Dynamic CT using MDCT acquires images within several seconds during a single respiratory pause if the slice thickness is about 5 mm and is superior for detection of hypervascular HCC. On dynamic CT of the liver, 100–120 ml of contrast medium is rapidly infused within 30 s. The arterial dominant phase is generally acquired at around 30–45 s following the initiation of the injection of contrast medium [33]. A characteristic of HCC is a corona-shaped enhancement in the late arterial phase or portal venous dominant phase [34]. The vascular and extracellular contrast medium concentrations reach equilibrium about 200 s after infusion; scanning at this time point is called the equilibrium or parenchymal phase. In a typical HCC, attenuation decreases in the equilibrium phase.

In MDCT, time resolution is high and acquisitions of the arterial, portal, and equilibrium phases have markedly increased the ability to qualitatively diagnose tumorous lesions. The diagnosis of a typical hypervascular HCC is easy because the lesion is detected as a high attenuation area in the arterial phase, corona enhancement is noted in the late arterial or the portal phase, and this becomes a low attenuation area in the equilibrium phase. However, the frequency of obtaining typical findings varies depending on CT equipment and acquisition conditions. Diagnostic accuracy of hypervascular HCCs by CT has been reported to be 68–91% [35–37].

Contrast-Enhanced US

Sonazoid-enhanced US are classified into the two phases: the vascular and Kupffer phases (fig. 3).

Vascular Phase

The sensitivity of contrast-enhanced US with Sonazoid to detect intranodular blood flow in liver tumors is extremely high. The sensitivity of 4-phase imaging (plain, arterial, portal, and equilibrium phases) by MDCT, as a gold standard, for detecting intranodular blood flow is similar to or superior to that of MDCT. In addition, in most patients in whom there is no intranodular blood flow in the arterial phase on contrast-en-

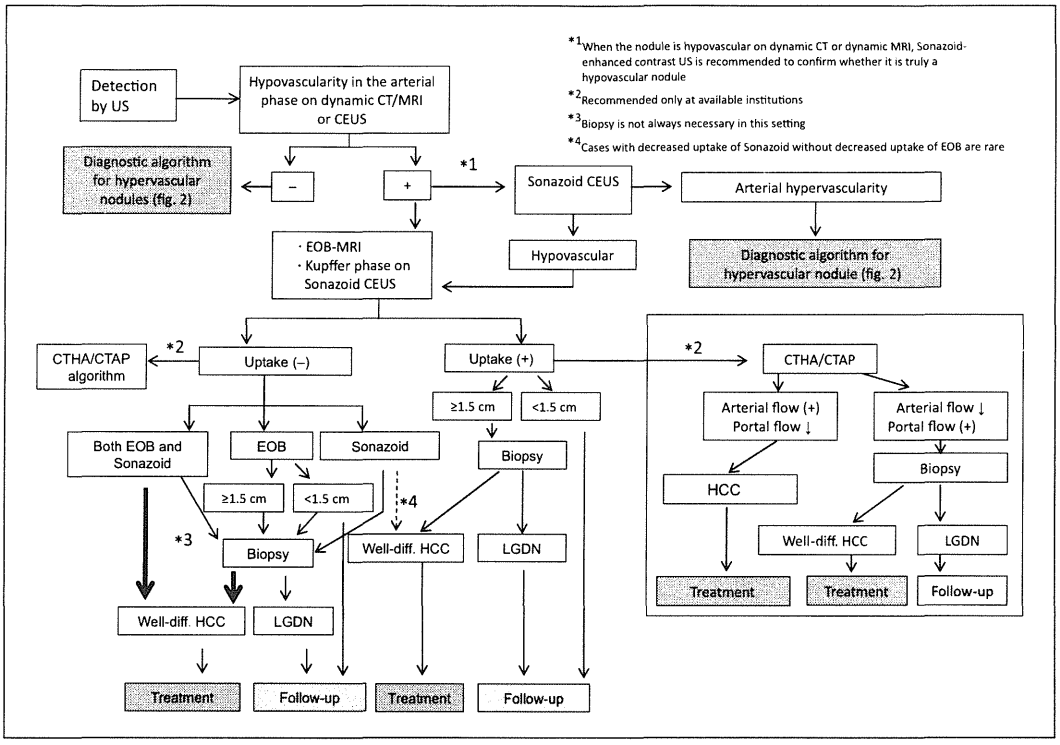


Fig. 1. Diagnostic and treatment algorithms for hypovascular liver nodules (JSH 2010) [cited from 9, with permission].

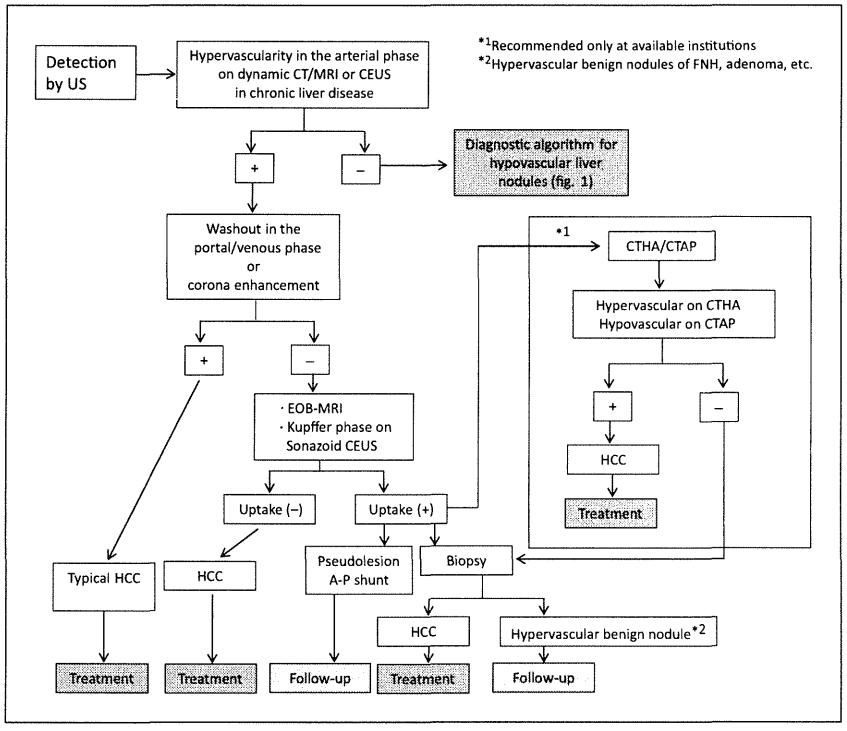


Fig. 2. Diagnostic and treatment algorithms for hypervascular liver nodules (JSH 2010) [cited from 9, with permission].

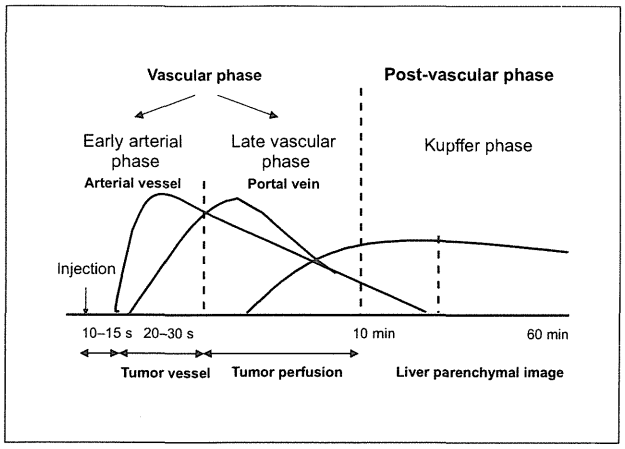


Fig. 3. Phases of contrast-enhanced US with Sonazoid. There are two phases: vascular and post-vascular phase.

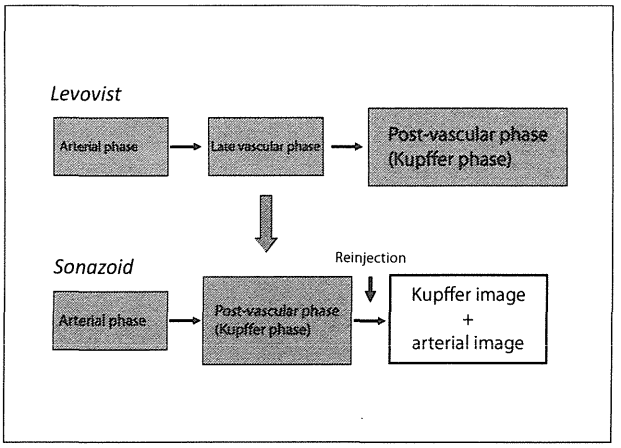


Fig. 4. Basic concept of defect reperfusion imaging: Reinjection at the Kupffer phase plays an important role.

hanced US, contrast-enhanced CT does not show any enhancing area in the arterial phase. However, in some patients without intranodular blood flow on dynamic CT, contrast-enhanced US reveals arterial blood flow. Briefly, contrast-enhanced US may be more sensitive than CT for the detection of intranodular arterial blood flow [38]. Basically, contrast-enhanced US should be performed as a precise examination tool of intranodular blood flow in nodules detected on B-mode US. When using Sonazoid, the Kupffer phase is very stable, differing from that with Levovist, SonoVue or Definity. Therefore, initially, entire liver scanning should be conducted in the Kupffer phase, and, additionally, Sonazoid should be intravenously injected into Kupffer defect sites (defect reperfusion imaging), which facilitates cancer detection to making a definitive diagnosis. In the future, contrast-enhanced US may be applied for screening [39, 40] and staging, which have been considered to be impossible using CEUS with blood pool agents, such as SonoVue or Definity.

Kupffer Phase

The Kupffer phase of Sonazoid is very important.

(1) Most lesions of moderately or well-differentiated hypervascular HCC in which arterial blood flow is abundant show a decrease in Sonazoid uptake or defect in the Kupffer phase.

(2) Among precancerous or early HCC lesions, Sonazoid uptake in the Kupffer phase is similar to that of the surrounding liver parenchyma in which arterial blood flow is reduced, with the influx of portal blood flow is preserved.

(3) For the differential diagnosis between a precancerous lesion, dysplastic nodule (DN), and early well-differentiated HCC (early HCC), the two lesions show iso uptake in the Kupffer phase in many cases; therefore, differentiation is difficult. However, hypovascular nodules in which Kupffer uptake is reduced in the Kupffer phase can be diagnosed as early HCC.

Significance of Defect-Reperfusion Imaging (Double Injection CEUS)

Recently, a new procedure (defect-reperfusion imaging) was developed, in which stable Kupffer images of Sonazoid and real-time blood flow imaging are applied, facilitating the accurate local diagnosis and treatment of typical liver cancer that shows arterial enhancement with venous wash on CT, washout in the late phase, and is not visualized as on B-mode US (fig. 4) [39, 41].

Sonazoid is intravenously injected. Presence or absence of Kupffer defect is evaluated in the Kupffer phase ≥10 min after confirming an arterial enhancement area in the vascular phase. In addition, an entire liver scan is necessary to detect a defect site in the Kupffer phase. If a Kupffer defect is found in the liver, Sonazoid is additionally administered whether or not arterial blood flows in the defect site is assessed (defect reinjection test). Regarding the presence of arterial vascularity in the defect area, typical liver cancer can be diagnosed at a rate of approx-

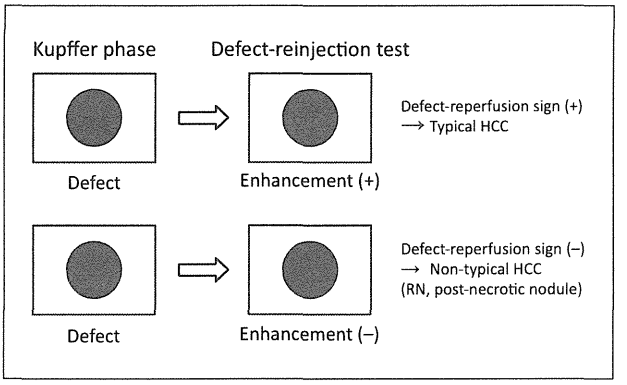


Fig. 5. Value of defect reperfusion imaging in B-mode undetectable nodule. Diagnostic ability of B-mode undetectable HCC by this technique using Sonazoid-enhanced US is 100%.

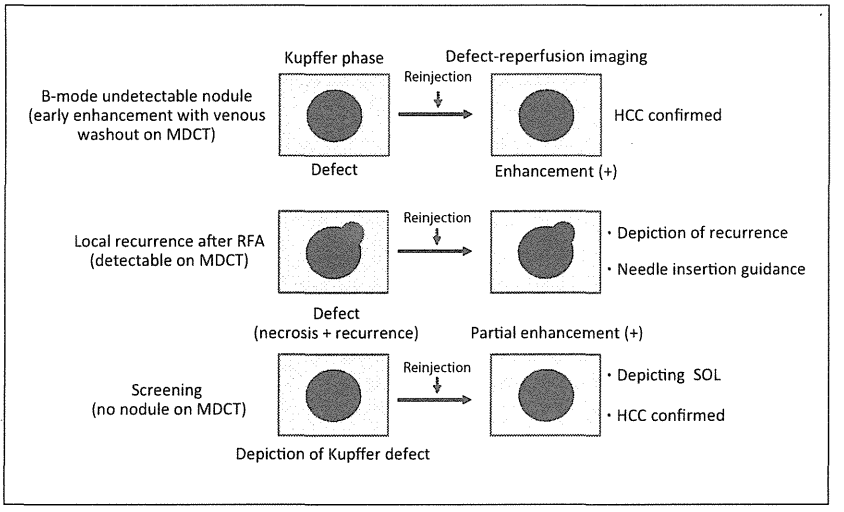


Fig. 6. Defect reperfusion image is useful for confirming B-mode undetectable nodule, local recurrence after RFA and surveillance of HCC in cirrhotic patients.

imately 100% (fig. 5). In addition, concerning nodules that cannot be visualized on B-mode US, it is possible to detect clear defects in the Kupffer phase, although diagnosis is impossible in the vascular phase since the detection of arterial blood flow is impossible to detect. The additional intravenous injection of Sonazoid in this area facilitates the detection of arterial vascularity in the defect site. In this area, Sonazoid contrast-guided radiofrequency thermal ablation (RFA) therapy becomes possible. In this procedure, initially, nodules that cannot be detected on B-mode US are detected as defects in the Kupffer phase. Subsequently, the additional intravenous injection of Sonazoid is performed, and whether or not nodules with defects involve arterial blood flow is evaluated. This procedure may be a breakthrough for diagnostic imaging. This contrast enhancement procedure does not require any specific device or analysis. Concerning typical CT findings, arterial enhancement with venous washout, defects are initially detected in the Kupffer phase, and, subsequently, arterial perfusion in the detect site is confirmed (fig. 5).

The introduction of such an idea facilitates the identification of nodules that show hypervascular typical features on CT, and are unclear on B-mode US, at a probability of approximately 100%. If there are nodules without arterial enhancement by reinjection for defects, they may differ from nodules detected on CT (fig. 6). Therefore, clinically, this procedure is breakthrough as a treatment aid of HCC [42]. In addition, this defect reperfusion imaging method can be applied for various purposes such as HCC screening in liver cirrhosis with rough liver parenchyma, the identification of local tumor progression sites after treatment. In addition, in cases of evaluation of the treatment response after RFA or transcatheter arterial chemoembolization (TACE) and contrast-enhanced guided needle placement it may be also very useful (fig. 6).

Dynamic MRI

The consistency rate of histopathology excised liver after liver transplantation with various imaging findings has been reported, with the sensitivity of dynamic MRI shown to be the highest [43]. In another report, CT, abdominal US, and MRI were compared with regard to evaluations of nodular recurrence after transarterial chemoembolization mixed with lipiodol; again, MRI was the superior modality [44]. However, detectability varies among MRI equipment models, and MRI cannot be readily used in some facilities. Use of MDCT has spread rapidly in Japan, and its usefulness is well established. It may be better to diagnose hypervascular HCC using dynamic MRI or MDCT depending on the conditions found in the institution, but the X-ray exposure problem arising with frequent MDCT images should be kept in mind.

Gd-EOB-MRI

Gd-EOB-MRI Is Superior to SPIO-MRI

A new hepatocyte-specific contrast agent for MRI, Gd-EOB-DTPA (gadoxetate sodium), became commercially available in Japan in January 2008. This contrast agent is taken up by hepatocytes and excreted from the kidney and from the liver through the bile duct. As a result, liver parenchyma is intensely enhanced showing definite hyperintensity in the hepatobiliary phase ≥20 min after intravenous injection based on T_1-weighted images, in addition to the diagnosis based on blood supply. Nodules without liver parenchymal cells, such as liver cancer, are visualized as hypointense. This diagnostic imaging method is simple for hepatologists in addition to radiologists specialized in MRI in comparison with SPIO as a black liver agent (black coloration of the entire liver on T_2-weighted images in which the spatial resolution is poor). Gd-EOB-DTPA-enhanced MRI is a breakthrough for diagnostic imaging of the liver and HCC.

Mechanism of Gd-EOB-DTPA Uptake and Findings with Respect to the Grade of Differentiation of HCC

Approximately 50% of the dose of Gd-EOB-DTPA is taken up by hepatocytes and excreted in bile. The remainder is excreted from the kidney. Hepatocellular uptake may be related to passive diffusion mediated by organic anion transporter 1 (OATP1) in the hepatocellular membrane in rat [45]. Furthermore, ATP-dependent active transport related to multi-drug resistance-associated protein 2 (MRP2) may be involved in excretion from hepatocytes into the capillary bile duct [46].

A recent study reported that Gd-EOB-DTPA uptake in humans depended on OATP1B3 (synonymous with OATP8) [47, 48] among various kinds of human OATP families. Based on these reports, concerning the mechanism via which Gd-EOB-DTPA is taken up in the hepatobiliary phase even when well- or moderately differentiated liver cancer is hypervascular HCC, OATP1B3 expression may be detected in some lesions, and visualized as an iso or high signal intensity in the hepatobiliary phase. According to the study, there was no statistically significant association between OATP1B3 expression and the bile-producing capacity (green hepatoma)/grade of differentiation [47, 48]. It is now considered that the expression of OATP1B3 may be decreased in accordance with the elevation of the grade of malignancy of the hepatocellular nodules. According to the recent immunohistochemical study, low-grade dysplastic nodule showed the same or increased OATP1B3 expression relative to the surrounding liver. On the other hand, around half of high-grade dysplastic nodules, around 80% of early HCCs, around 90% of well- and moderately differentiated HCCs and almost all of poorly differentiated HCCs demonstrated decreased expression [Matsui O., pers. commun., submitted]. Therefore, the majority of HCCs may be detected as hypointense nodule in the hepatobiliary phase when liver function is well preserved. However, in approximately 5–10% of patients with hypervascular, well- or moderately differentiated liver cancer, there was definite expression of OATP1B3 and no reduction in the signal intensity in the hepatobiliary phase, probably due to genetic alteration [47, 48].

Actually, in clinical practice, in some nodules detected on US, histopathological investigation with biopsy specimens leads to a diagnosis of well-differentiated liver cancer despite the absence of signal-intensity reduction in the hepatobiliary phase; well-differentiated liver cancer in which OATP1B3 expression is maintained may be present.

Another issue is whether signal-intensity reduction is absent in all dysplastic nodules in the hepatobiliary phase. Concerning this issue, biopsy/pathological findings of nodules with signal-intensity reduction in the hepatobiliary phase suggest dysplastic nodules in some cases. However, a study involving resected specimens (not biopsy materials) reported that all dysplastic nodules showed an iso signal intensity in the hepatobiliary phase. Therefore, there may be few dysplastic nodules with such a decrease in OATP1B3 expression according to pathologists specialized in the liver pathology of early HCC (table 10).

In our experience on the study of resected specimens, dysplastic nodules with a low signal intensity are extremely rare [49]. Unless stromal invasion is detected in the sample despite a pitfall of biopsy diagnosis, sam-

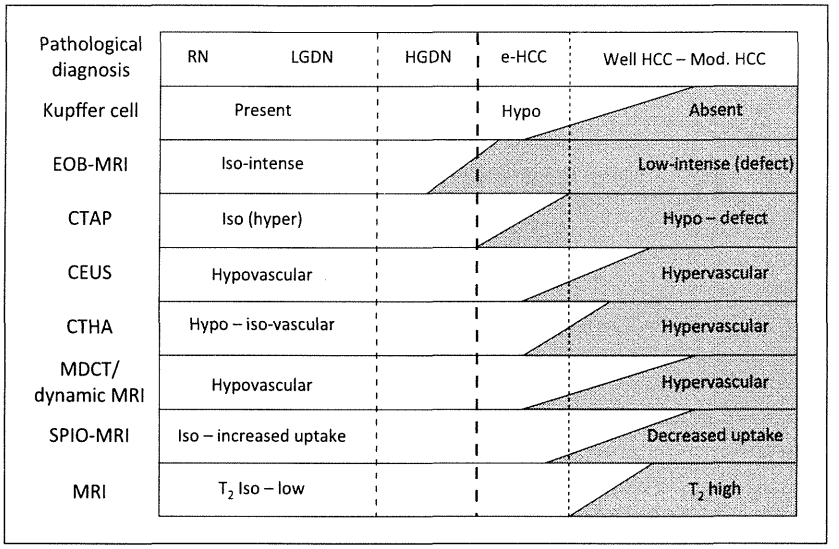


Fig. 7. Imaging findings of hepatocellular nodules in cirrhotic liver [cited from 47, with permission]. Hepatocyte phase of EOB-MRI is the most sensitive technique to detect initial change of multistep hepatocarcinogenesis.

pling errors, or similar cellular/structural atypia, under a biopsy diagnosis of dysplastic nodules, it is sometimes difficult for specialists of liver pathology to make a diagnosis of early HCC. Therefore, biopsy-based pathological diagnosis is limited, and lesions may be underestimated.

Differentiation of Early HCC from Dysplastic Nodules Using Gd-EOB-DTPA-MRI

As described in the above section, blood flow findings are hypovascular in many cases when investigating resected specimens of early HCC. Even when employing CTHA/CTAP, diagnosis of early HCC is difficult. In some patients with early liver cancer, there is a slight decrease in portal blood flow on CTAP. However, CTAP shows iso-perfusion in many patients. Most patients with a reduction in signal intensity in the hepatobiliary phase are diagnosed with early HCC based on resected specimens by specialists of liver pathology [49]. In most patients without a reduction in the signal intensity in the hepatobiliary phase, resected specimens suggest dysplastic nodules. Considering this, functional diagnosis with Gd-EOB-DTPA MRI may facilitate the more sensitive evaluation of initial changes of multistep hepatocarcinogenesis than hemodynamic assessment, SPIO-MRI, Kupffer cell function diagnosis using the Kupffer phase on Sonazoid contrast-enhanced US, or portal blood flow assessment to differentiate early HCC from dysplastic nodules (fig. 7). However the following two issues remain: (1) whether there are dysplastic nodules with a reduction in the signal intensity in the hepatobiliary phase, and (2) whether there are nodules without a reduction in the signal intensity in the hepatobiliary phase in which pathological findings lead to a diagnosis of early HCC. With respect to the two issues, data have now accumulated throughout Japan. However, a consensus has not been reached. To overcome these issues, hypovascular nodules with uptake on SPIO-MRI or in the Kupffer

Table 10. Relationship between the expression of OATP1B3 and findings in the hepatocyte phase

Uptake transporter (OATP1B3 (OATP8))	Hepatocyte phase imaging of EOB-MRI
Dysplastic nodule	
+	Iso-high intensity
– (rare)	Low intensity
Early HCC	
+ (rare)	Iso-intensity
–	Low intensity
Well- to mod. diff. HCC	
+ (5–10%)	Iso-high intensity/iso-high intensity
– (90–95%)	Low intensity
Poorly diff. HCC	
–	Low intensity

OATP = Organic anion transporter polypeptides.

phase of Sonazoid US can be differentiated from hepatocellular nodules. However, in nodules with a reduction in the signal intensity in the hepatobiliary phase of Gd-EOB-DTPA, biopsy findings should be obtained, and the natural course of these nodules must be followed up. It may be important to analyze the grade of malignant potential in a large number of patients.

Angiography

Diagnosis of HCC by angiography including DSA is 69.0%, lower than that (86.9%) of helical CT [50]. Also, detectability more markedly decreases than does CT sensitivity when the tumor size is small. In Japan, very few institutions perform angiography alone for diagnosis, and many facilities routinely perform CT during hepatic arteriography (CTHA) and CT during arterial portography (CTAP) in combination. The rate of detectability of liver cancer by angio-CT is the highest, but specificity is low, and some reports, mainly from Europe and USA, have questioned its diagnostic value. However, observation of corona-like intense staining around liver cancer in the second phase of CTHA (acquisition of images during contrast medium infusion is designated as the first phase, and acquisition after completion of infusion as the second) enables differentiation from pseudo-hypervascular lesions, thus increasing the specificity. The HCC diagnostic ability of arterial injection CT may be highest when second-phase CTHA images are acquired [34]. Sensitivity and specificity of hypervascular HCC diagnoses are highest when both CTHA and CTAP are performed. Since CTHA/CTAP detects nodules <1 cm in diameter, differentiation from pseudo lesions, such as arterial-portal (A-P) shunt or focal nodular hyperplasia (FNH), is necessary.

Diagnostic and Treatment Algorithm of Hypervascular Hepatocellular Carcinoma

For surveillance, abdominal US is a first-line test in many hospitals. As a subsequent examination, MDCT is the most commonly conducted, therefore it was decided as a first-line test in the surveillance algorithm both in the AASLD or JSH guidelines. As dynamic MRI is performed as a first-choice procedure in some hospitals, it should be regarded as similar to MDCT. When the lesion is enhanced in the early arterial phase, a diagnosis of HCC may be made based on washout in the equilibrium phase (table 5). However, FNH and A-P shunt must be ruled out. The number of hepatocytes and Kupffer cells was examined on Gd-EOB-MRI or in the Kupffer phase of Sonazoid contrast-enhanced US. If a defect is confirmed at a low signal intensity in the hepatobiliary phase of Gd-EOB-MRI or in the Kupffer phase of Sonazoid-enhanced US, a diagnosis of HCC can be made (fig. 2).

When low density is noted in the equilibrium phase without an enhancement in the early arterial phase on MDCT, the lesion can be evaluated as hypervascular nodule. CTHA, which is more sensitive, must be performed to examine whether or not it is hypervascular HCC. In institutions where CTHA cannot be conducted, it is necessary to confirm blood flow in the early phase of CO_2 angiography or contrast-enhanced US, or evaluate whether the lesion is hypervascular in the early arterial phase on dynamic MRI.

When abdominal angiography reveals hypovascular tumors, CTHA should be performed if possible, because the sensitivity of the former for the diagnosis of HCC is low. If impossible, CO_2 angiography with high-level spatial resolution should be simultaneously conducted to evaluate the number of hypervascular tumors.

For angiography or CTHA, the possibility of pseudotumors such as A-P shunt must be ruled out. In this case, a diagnosis of hypervascular HCC can be made if there is a decrease in the number of Kupffer cells in the hepatobiliary phase of Gd-EOB-MRI or in the Kupffer phase of Sonazoid-enhanced US. The HCC-diagnosing capacity of Gd-EOB-MRI is similar to that of CTHA/CTAP, therefore these invasive tests may be omitted.

Consensus Statements

15 Typical HCC can be diagnosed by imaging regardless of the size detected if a typical vascular pattern is obtained on dynamic CT, dynamic MRI, CEUS or a combination of CTHA and CTAP. Different from Western guidelines, only one dynamic study showing the typical pattern is sufficient to diagnose HCC even if nodule is <2 cm. The typical imaging pattern includes hypervascularity in the arterial phase and washes out in the portal venous phase.

16 Nodular lesions showing an atypical imaging pattern, such as iso- or hypovascular in the arterial phase or arterial hypervascularity alone without portal venous washout, should undergo the examinations shown in figures 1 and 2. EOB-MRI and Sonazoid-enhanced US play an important role.

17 Elevated AFP (≥20 ng/ml) and PIVKA-II (≥40 mAU/ml) with a rising trend over time and a positive AFP-L3 value (>10%) are highly suggestive of the presence of typical HCC even if US fails to depict an apparent nodule in the liver.

Diagnostic and Treatment Algorithm for Hypovascular Nodules

Among liver cirrhosis-related nodular lesions, hypovascular nodules include low-grade dysplastic nodules (LGDN), high-grade dysplastic nodules (HGDN), which are pathologically regarded as precancerous lesions, early HCC, and nodule-in-nodule type HCC [11, 24, 51, 52]. In this section, the current consensus of diagnosis and treatment algorithms with respect to the treatment of such nodules, especially findings important for the diagnosis and treatment of hypovascular nodules detected on imaging, will be described.

Diagnostic Algorithms for Hypovascular Hepatocellular Nodules (fig. 1)

There has been no diagnostic imaging method to accurately differentiate precancerous lesions such as LGDN and HGDN from early HCC. However, since Gd-EOB-MRI was introduced in 2008, such a situation is rapidly changing.

Among current diagnostic imaging procedures, the following modalities may facilitate the most sensitive tool to detect the initial change of hepatocarcinogenesis: (1) EOB-MRI [49], (2) CTAP [53, 54], (3) contrast-enhanced US [38, 41, 55], (4) CTHA, and (5) MDCT/dynamic MRI, SPIO-MRI (fig. 7). Usually, precancerous lesions show EOB uptake. However, most early liver cancer lesions show a low signal intensity in the hepatobiliary phase of EOB-MRI [49]. Therefore, EOB-MRI may facilitate the earliest, most sensitive assessment of the initial features of early HCC. As the second-most sensitive method, CTAP facilitates the evaluation of initial changes related to hepatocarcinogenesis. However, a partially increased area in intranodular arterial blood flow detected on CTHA or contrast-enhanced US, in which portal blood flow is maintained in the outer area in about two-thirds of early liver cancer nodules, reflects an advanced state of the carcinogenic process. Briefly, hypervascular foci visualized in the nodule (nodule-in-nodule or entirely hypervascular) may biologically reflect small advanced cancer even if histological findings suggest well-differentiated HCC. In some cases, satellite nodules or microvascular invasion is observed at the periphery of the nodule.

According to a study, EOB-MRI shows a decrease in uptake in the hepatobiliary phase in HGDN lesions, therefore a consensus regarding differentiation between benign and malignant tumors has not been reached. Briefly, hypovascular tumors with a decrease in uptake may be basically regarded as early HCC, however DN cannot be ruled out.

Although MDCT and dynamic MRI are relatively sensitive for the detection of arterial blood flow, some hypervascular nodules detected on CTHA or contrast-enhanced US are not visualized as arterial staining, which depends on the timing of imaging, tumor site, and liver function. Hypervascular nodules on MDCT or dynamic MRI may show high intensity on T_2-weighted MRI images.

Based on this, EOB-MRI or Sonazoid contrast-enhanced US should be performed in hypovascular nodules demonstrated on MDCT or dynamic MRI. If there is a decrease in uptake on EOB-MRI or in the Kupffer phase of Sonazoid contrast-enhanced US, malignancy must be initially considered. Furthermore, portal blood flow is reduced on CTAP in some nodules in which EOB-MRI or Kupffer-phase Sonazoid contrast-enhanced US shows uptake, although such cases are rare. When CTHA/CTAP is not conducted, or in institutions in which it is impossible to perform these procedures, biopsy should be conducted in such nodules measuring >1.5 cm, because they may become hypervascular nodules, leading to typical liver cancer. When performing CTHA/CTAP, nodules with increased arterial blood flow or the reduction of portal blood flow are biologically regarded as malignant. In nodules in which arterial blood flow is insufficient in the presence of portal blood flow, biopsy is necessary.

The capability of contrast-enhanced US is dependent on US equipment. However, in institutions in which high-end machines are available, the combination of this procedure and MDCT improves the accuracy of arterial/portal blood flow assessment in comparison with a single method alone. Furthermore, the application of the Kupffer phase and hepatobiliary phase of EOB-MRI makes the prediction of malignancy more accurate.

Concerning nodules that are not visualized as hypervascular nodule on MDCT or dynamic MRI, when both EOB-MRI and Kupffer-phase Sonazoid contrast-enhanced US reveal a reduction in uptake, these nodules should be treated as HCC. In this case, biopsy is not always necessary.

When EOB-MRI shows a reduction in uptake and the nodule size exceeds 1.5 cm, biopsy should be performed if possible. When a diagnosis of typical well-differentiated HCC is made, treatment should be performed. Even when EOB-MRI and Kupffer-phase Sonazoid contrast-enhanced US reveal uptake, CTHA and CTAP may be performed in nodules measuring >1.5 cm. When there is

an increase in arterial blood flow or a decrease in portal blood flow, even though such a case is rare, nodules are regarded as malignant. However, in nodules in which arterial blood flow is low, and portal blood flow is preserved, follow-up may be continued when biopsy suggests benign nodules. However, when biopsy leads to a diagnosis of typical well-differentiated HCC, the treatment of early HCC may be considered.

When EOB-MRI shows uptake, nodules in which biopsy suggests a borderline lesion may be followed up. In conclusion, currently, EOB-MRI is the most useful tool for diagnosing early HCC in hypovascular hepatocellular nodes (fig. 1, 7).

Consensus Statements

18 It is essentially difficult to differentiate a histopathological diagnosis of early HCC from a dysplastic nodule by imaging.
19 Gd-EOB-MRI is the most sensitive tool for detection of any initial change of hepatocarcinogenesis, i.e. low intense mass on hepatocyte image of Gd-EOB-MRI. Therefore, it is recommended that Gd-EOB-MRI be performed as much as is possible.
20 Sonazoid-enhanced contrast US is more sensitive for detection of intranodular hypervascularity than MDCT (dynamic CT) or dynamic MRI. Therefore, to confirm true hypovascularity, Sonazoid-enhanced CEUS is recommended.
21 Decreased intranodular portal flow on CTAP suggests a high malignant potential of a nodule. Therefore, such nodules should be treated as malignant.
22 Nodules with a low uptake of EOB-MRI and a size >1.5 cm should be treated as malignant after confirmation by biopsy.
23 Nodules with hypovascularity and negative findings on EOB-MRI and Kupffer phase imaging of Sonazoid CEUS are likely to be benign. Thus, they can be followed up without treatment when the nodule size is <1.5 cm.
24 Biopsy-proven early HCC should be treated.

Staging for Hepatocellular Carcinoma

Classification of Staging Systems

TNM stages representing the degree of cancer spreading are clinically used for various cancers, not only for HCC. It is well recognized that for HCC stages of not only tumors but also the liver functional reserve are very important for deciding a treatment strategy and prognosis prediction. Thus, HCCs should be treated with an understanding of the importance of the liver cancer staging systems.

Table 11. TNM stage by the Liver Cancer Study Group of Japan [cited from 54, with permission]

Stage	T category	N category	M category
Stage I	T1	N0	M0
Stage II	T1	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	T1, T2, T3, T4	N1	M0
Stage IVB	T1, T2, T3, T4	N0, N1	M1

Currently there are three staging systems for HCC: (1) TNM staging as tumor spreading staging, (2) liver function staging, and (3) systems integrating (1) and (2).

TNM Stage

For TNM staging, UICC or AJCC classification is used internationally, but these are thought inappropriate because the cut-off tumor size is set to 5 cm. Since portal microinvasion and intrahepatic metastasis occurs in 27 and 10% of tumors with a tumor size of ≥2 cm, respectively, a TNM staging classification setting the cut-off size to 2 cm is necessary. TNM stages should be specified by three factors: 2-cm tumor size, solitary or multiple lesions, and the presence or absence of vascular invasion, as used by the Liver Cancer Study Group of Japan (LCSGJ), may be the most appropriate for countries, including Japan, where the early detection of HCC is possible [26] (tables 11, 12).

Liver Damage Stage

There are two liver function staging systems: Child-Pugh staging that is used internationally for a long time, and the liver damage staging established by LCSGJ (table 13). Liver damage staging [26] established by LCSGJ is different from Child-Pugh staging in that the ICG retention rate at 15-min ($ICGR_{15}$) value is incorporated instead of hepatic encephalopathy, and specifications of the prothrombin time and albumin level are more strict. Also, Child-Pugh staging employs scoring in which grades are determined based on the total score, whereas a higher stage with consistency of two items is regarded as

Table 12. T category of TNM stage by the Liver Cancer Study Group of Japan [cited from 26, with permission]

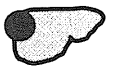
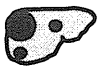
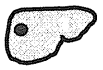
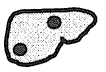
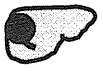
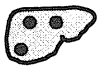
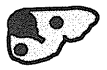
Criteria	T1	T2	T3	T4
(1) Number of tumors: solitary	(2) All three criteria are fulfilled	(3) Two of the three criteria are fulfilled	(4) One of the three criteria is fulfilled	(5) None of the three criteria are fulfilled
(2) Tumor diameter: no more than 2 cm				
(3) No vascular or bile duct invasion: Vp0, Vv0, B0		 	 	

Table 13. Degree of liver damage by the Liver Cancer Study Group of Japan [cited from 26, with permission]

Clinical and laboratory findings	Grade[1]		
	A	B	C
Ascites	none	controllable	uncontrollable
Serum bilirubin, mg/dl	<2.0	2.0–3.0	>3.0
Serum albumin, g/dl	>3.5	3.0–3.5	<3.5
$ICGR_{15}$, %	<15	15–40	>40
Prothrombin activity, %	>80	50–80	<50

[1] Degree of liver damage is designated as class A, B, or C, based on the highest grade containing at least two findings.

Table 14. Definition of the Japan Integrated Staging Score

	Variable			
	0	1	2	3
Child-Pugh stage	A	B	C	
TNM stage[1]	I	II	III	IV

[1] By the Liver Cancer Study Group of Japan.

the grade in LCSGJ liver damage staging. Since LCSGJ liver damage staging was originally designed for cases indicated for hepatectomy, $ICGR_{15}$ is specified as an essential factor. By contrast, Child-Pugh staging was originally widely used for diagnosis of liver functional reserve in cirrhotic patients, including terminal liver cirrhosis cases such as those with hepatic encephalopathy or ascites. However, differential use of the two staging systems is probably what is important. In the surgical field, LCSGJ liver damage staging is used for consideration of hepatectomy, and Child-Pugh staging is widely used for consideration of liver transplantation. The two systems are differentially used corresponding to the clinical objectives.

Integrated Staging System

The third type of staging system actually sees several systems integrating the TNM and liver damage stages. Various staging systems such as: (1) Okuda stage [56], (2) BCLC stage [1], (3) CLIP score, (4) JIS score [58, 59] (table 14), and (5) Tokyo Score [61], have all seen long-time use. The JIS score utilizing both the LCSGJ TNM and Child-Pugh stages is considered the most useful for overall staging of HCC in Japan [59, 60]. The CLIP score has disadvantages: specification of the tumor spreading degree is rough, only AFP is used as a biological malignancy marker, and stratification ability is also poor in advanced cases (many cases cluster to a score of 0–2). By contrast, the JIS score is superior for stratification of scores. The original JIS score employs Child-Pugh staging, but the modified JIS score employing liver damage staging in-

stead of Child-Pugh staging is frequently used in the surgical field [62]. The modified JIS score may be useful for hepatectomy cases because LCSGJ liver damage is more strictly classified. The original and modified JIS scores may be differentially used in accord with the clinical objectives, as with Child-Pugh and liver damage staging. Recently, biomarker combined JIS scores, which better stratify HCC patients than conventional JIS scores [63].

Importance of Integrated Staging Systems

There are several reasons why integrated staging systems are clinically important:

(1) For HCC, TNM staging is insufficient for predicting the prognosis, and a staging system integrating TNM and liver function stages is necessary to accurately predict the prognosis.

(2) Prediction of an accurate prognosis for individual patients.

(3) Establishment of a common scale for selection of the optimum treatment for individual patients.

(4) Identification of the patient population to be treated with the most curative therapy.

(5) Identification of the patient population in which the prognosis is worsened by overtreatment.

(6) Establishment of a fairly common scale for the comparison of outcomes among treatment methods and institutions. Although simple comparisons among treatment methods are difficult, it is useful for comparisons of a modality (resection, local treatment, or TACE) with identical scores among institutions.

(7) Evaluation of therapeutic effects of new treatment methods, for example comparison of therapeutic effects of liver transplantation and a new drug in homogenous populations, i.e. comparison of therapeutic effects between current and novel treatment methods.

(8) A graph contrasting outcomes of transplantation of individual JIS scores to long-term outcomes of preexisting treatment methods of individual JIS scores is useful for deciding indication of liver transplantation and for obtaining informed consent from patients indicated for this treatment.

Current State and Future Perspectives

Globally, CLIP scores or BCLC stage are used in Europe and North America as staging systems. However, these have different bases: the BCLC stage is basically a treatment selection system for deciding on a therapeutic strategy, whereas the CLIP and JIS scores are prognostic prediction stagings. The CLIP score and BCLC stage are useful for use in European and North American systems that tend to detect only large HCCs, but the JIS score is most useful for countries, such as Japan, where many small liver cancers are detected. At present, the JIS score is appropriate for Japan, while CLIP or BCLC score suits Europe and North America.

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 the early detection of HCC or developing countries with insufficient screening systems and diagnostic instruments, the CLIP score may provide good stratification as a prognostic prediction system. The JIS score may be used worldwide when surveillance systems for early detection of HCC become more common and early detection of HCC reaches the same level as found in Japan.

Summary

Various liver cancer staging systems have been proposed. However, for practical purposes the following conditions are essential for comprehensive discussions of all liver cancer cases: (1) the system should be simple, (2) no data lacking, (3) can be applied by anyone anywhere, (4) the system is easy to memorize, and (5) the system is superior for stratifying early, advanced, and terminal groups. Considering these conditions, the JIS score may be the most appropriate staging system for the overall distribution of liver cancer cases in Japan.

Consensus Statements

25 The TNM stage proposed by the Liver Cancer Study Group of Japan is ideal for use in countries like Japan, where many small HCCs <2 cm in diameter are found based on an established nationwide surveillance system. Similarly, the JIS score, biomarker combined JIS score or a modified JIS score appears the best prognostic staging system for use in countries where small HCCs can be detected.

26 BCLC staging proposed by AASLD is a treatment selection staging not a prognostic predictive staging. Therefore, comparisons between treatment selection staging (BCLC) and prognostic predictive staging (CLIP or JIS score) are inappropriate. This issue is really important and should be kept in mind.

Treatment Algorithm of Hepatocellular Carcinoma

Evidence-Based Guidelines in Japan

In a 2005 version of the guidelines, a treatment algorithm was prepared by the Makuuchi Group, Ministry of Health, Labour and Welfare. In 2009, a revision was published [5, 64]. Concretely, treatment is recommended in accordance with the severity of liver disease, number of tumors, and tumor diameter. Initially, it is described that resection or local ablation be performed in solitary tumor patients with liver damage grade A/B. However, local ablation should be selected only in liver damage grade B patients with tumors measuring ≤2 cm in tumor diameter. In liver damage grade A/B patients with 2 or 3 tumors measuring ≤3 cm in tumor diameter, resection or ablation should be conducted. Resection or TACE is selected in those with 2–3 tumors measuring >3 cm. TACE or arterial infusion chemotherapy is recommended in those with multiple (four or more) tumors. In liver damage grade C patients with three or less tumors measuring ≤3 cm, or a solitary tumor measuring ≤5 cm, liver transplantation is recommended if a donor is available. In those with four or more tumors, best supportive care should be performed (fig. 8).

When establishing the 2009 revision, only articles based on high-level evidence were selected from the literature published between 2002 and June 2007. Therefore, a high-level evidence-based molecule-targeting agent reported in 2008 [65] and 2009 [66], sorafenib, was not included. This is somewhat controversial. However, in the footnotes, it was stated that 'chemotherapy is selected in some patients with extrahepatic metastasis'. This was noted considering sorafenib. The other revision point is 'liver transplantation should be performed in patients aged 65 years or younger', which is described in the footnotes. This algorithm consists of evidence described in high-level quality articles. Low-level evidence-based articles are omitted; therefore, this algorithm can be objectively understood, but seems to be a bit conservative. In the future, a practical algorithm involving the new evidence created worldwide should be included in this algorithm.

Treatment Algorithm in the West

The treatment algorithms in Europe and North America were published in the *Journal of Hepatology* as the EASL consensus in 2001, and then as the AASLD Clinical

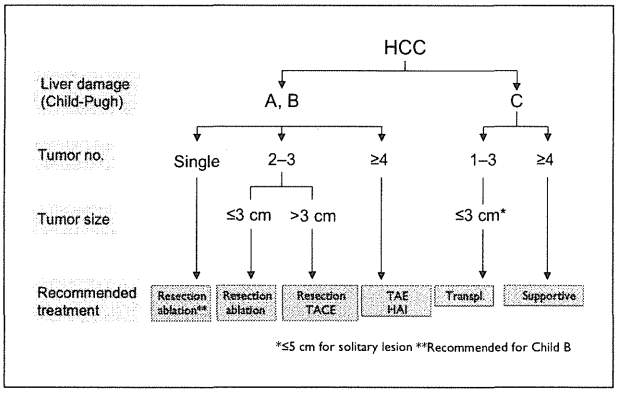


Fig. 8. Evidenced-based algorithm for HCC. Resection or TACE may be selected for liver damage A patients with vascular invasion. Chemotherapy may be selected for extrahepatic HCC. Liver transplantation is only for ≤65-year-olds [cited from 5, with permission].

Practice Guidelines in Hepatology in 2005 [2] followed by an updated version in 2010 [3]. Both these were prepared based on BCLC staging [1, 57]. The BCLC staging classification consists of stages 0 to D. Only palliative treatment 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 and corresponds to early HCC in Japan. These are solitary, and resection is desirable when portal pressure and the bilirubin levels are normal. When portal hypertension is present, other potentially curative treatments, such as liver transplantation and local treatment, are selected. For solitary HCC for three or fewer 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 curative treatments, i.e. resection, local ablation, and liver transplantation. The moderate stage B specifies multinodular lesions, and the advanced stage C specifies cases with portal invasion or extrahepatic spread. For stage B, TACE is selected. For stage C HCCs with vascular invasion and/or extrahepatic spread, sorafenib is a choice of treatment.

These selection criteria do not meet the current conditions performed in Japan. Application of these staging methods is difficult because many parameters and stage classifications (performance status, Child-Pugh, and portal hypertension) are used, and their application in Japan is inappropriate and so unlikely. However, BCLC is basically identical to the simplified evidence-based treatment algorithm established by Makuuchi's group, except for the application of liver transplantation.

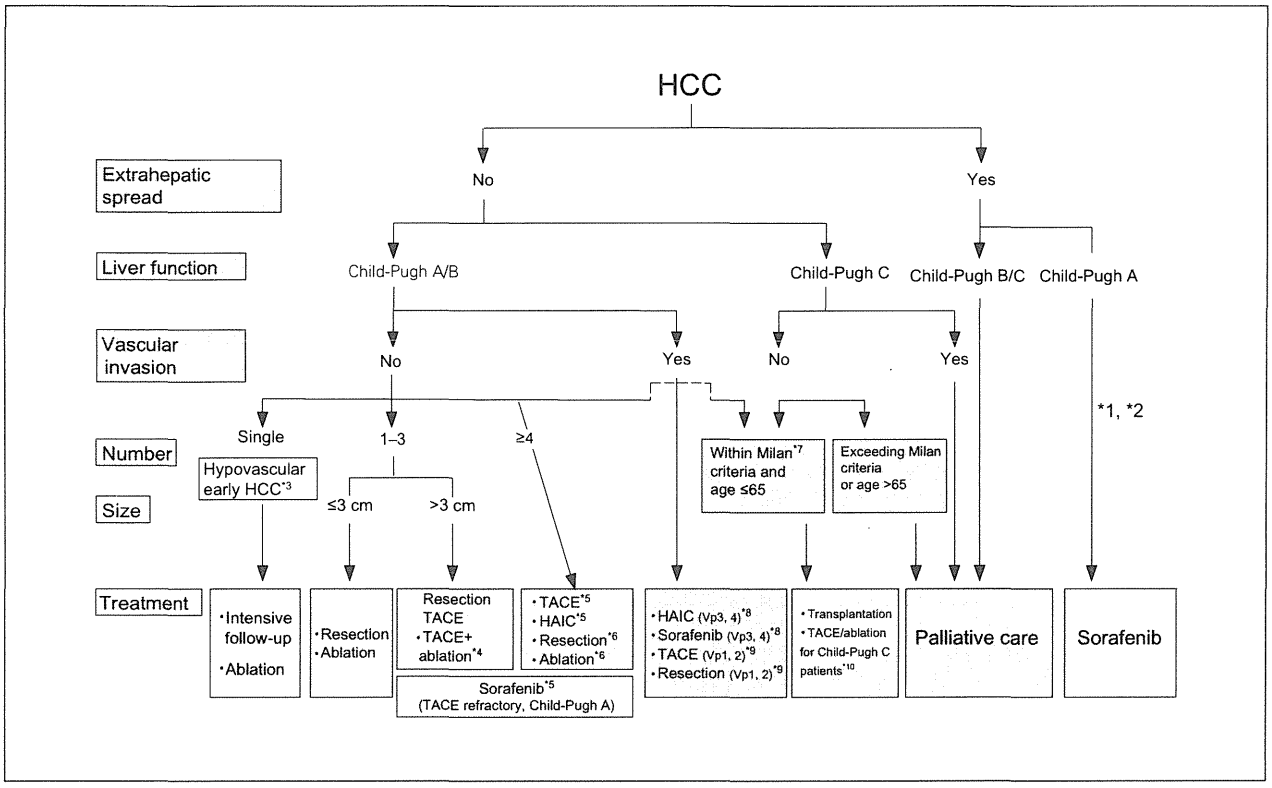


Fig. 9. Consensus-based treatment algorithm for HCC proposed by JSH revised in 2010. Footnotes: *1 = Treatment should be performed as if extrahepatic speed is negative, when extrahepatic spread is not regarded as a prognostic factor. *2 = Sorafenib is the first choice of treatment in this setting as 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: (1) when the nodule is diagnosed pathologically as early HCC, (2) when the nodules show decreased uptake on Gd-EOB-MRI, or (3) when the nodules show decreased portal flow by 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 (hepatic arterial infusion chemotherapy) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5-FU + CDDP) or intra-arterial 5-FU infusion combined with systemic IFN 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 numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. *7 = Milan criteria: tumor size ≤3 cm and tumor number ≤3; or solitary tumor ≤5 cm. Even when liver function is good (Child-Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. *8 = Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal venous invasion at the first portal branch) or Vp4 (portal invasion at the main portal trunk). *9 = Resection and TACE is frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second 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 [cited from 10, 49, with permission].

A Consensus-Based Treatment Algorithm for HCC Proposed by the JSH

For HCC treatment, practice patterns markedly differ between Europe/USA and Japan. For this reason, a unique Japanese algorithm (JSH Consensus 2007) was proposed in 2007 [67]. Consequently, a revised draft was presented at the 45th Meeting of the Japanese Liver Society in 2009 (Congress Chair: Masatoshi Kudo), and an article was published in 2010 [10] (fig. 9). The consensus-based treatment algorithm recommended by this society consists of extrahepatic lesions, hepatic functional reserve, vascular invasion, number of tumors, and tumor diameter. Treatment is classified into curative treatment (resection, local ablation), TACE, arterial infusion chemotherapy, liver transplantation, and best supportive care. Basically, the contents are consistent with the evidence-based treatment algorithm established by the Makuuchi group. However, a consensus-based algorithm is not always based on evidence, but involves routinely employed treatment for which a consensus has been reached in Japan. For example, concerning the item of early HCC, local ablation is performed for the lesions in which biopsy diagnosis, CTHA/CTAP, or gadolinium-DTPA ethoxybenzyl (EOB)-MRI suggests malignancy. In evidence-based guidelines, hypovascular tumors are categorized as 'non-typical for HCC', reflecting lesions without an arterial enhancement. Evidence-based guidelines recommend that these lesions should be followed up. However, among hypovascular tumors, 'early liver cancer' definitively diagnosed based on CTAP, EOB-MRI, or biopsy findings, is known to frequently progress to typical HCC. Based on this fact, treatment is performed in many cases in a routine clinical setting; less invasive ablation therapy is performed rather than resection, which is more invasive. With respect to hypovascular lesions without malignant findings, intensive follow-up is recommended. For management, early hypovascular HCC should be separated from other types of hypervascular liver cancer.

Initially, resection or local ablation therapy should be performed to treat three or less tumors measuring $\leq$3 cm in diameter without extrahepatic lesions/vascular invasion in which the liver function is good. In this group, the prognosis of curative treatment may be favorable. In three or less lesions measuring >3 cm in diameter, resection or TACE is recommended. Curability may be improved by adding ablation therapy to previous transarterial treatment (TACE or lipiodol TACE). Secondly, TACE and arterial infusion chemotherapy are recommended to treat four or more lesions. However, arterial infusion chemotherapy is performed based on expert experience, but there is no solid evidence because there is no randomized controlled trial (RCT). The combination of local ablation therapy and TACE/arterial infusion chemotherapy for five to six or less lesions is beneficial in some cases. Furthermore, resection may be considered for such lesions if possible. In young Child-Pugh A/B hepatic functional reserve patients with early recurrence, liver transplantation is sometimes the choice of treatment when they meet the Milan criteria. In the presence of vascular invasion, resection is performed for patients with third or fourth branch of portal venous invasion if possible. In such patients, TACE can be a choice of treatment. In patients with main trunk or first branch of portal vein, arterial infusion chemotherapy, in addition to hepatic arterial infusion chemotherapy with implanted port, is a choice of treatment.

In Child-Pugh C hepatic functional reserve patients aged 65 years or younger, with an unfavorable liver function in the absence of vascular invasion, meeting the Milan criteria, liver transplantation is recommended. Furthermore, as test therapy, local ablation or subsegmental TACE is conducted in Child-Pugh C hepatic functional reserve patients without hepatic encephalopathy or refractory ascites, showing a bilirubin level of $\leq$3 mg.

However, there is no evidence regarding the survival benefits. In the future, a prospective clinical trial should be conducted. In Child-Pugh C hepatic functional reserve patients with vascular invasion or extrahepatic lesions, the best supportive care is basically selected. In this case, palliative radiotherapy to resolve pain is included. However, when extrahepatic lesions are not a prognostic factor, treatment in accordance with the standard treatment algorithm may improve the prognosis.

In Child-Pugh A hepatic functional reserve patients with extrahepatic lesions, sorafenib should be recommended as a first choice of treatment. This agent is recommended for patients with vascular invasion, especially patients with macrovascular invasion, in addition to arterial injection chemotherapy. In non-responders to TACE/arterial injection chemotherapy, sorafenib may become a treatment option when the hepatic functional reserve is preserved as Child-Pugh A.

The consensus-based treatment algorithm is not always based on scientific evidence. However, it is significant because a consensus has been reached among specialists belonging to the JSH, as demonstrated in BCLC, and therefore their own treatment algorithm is introduced. In the future, evidence-lacking parts must be re-

vised through a prospective study. The treatment algorithm for liver cancer reflects a primary concept for treatment strategies. Basically, it is important to perform individualized treatment in individual patients, considering various conditions.

Definition of TACE Failure

In Japan, repeated TACE is commonly performed for multiple nodules without major vascular invasion or extrahepatic spread in Child-Pugh A or B patients. Even though recurrence becomes very rapid, TACE has been repeatedly performed (sometimes over 10 times). The reason why this is that there was no further treatment option after TACE failure/refractory patients before sorafenib was introduced. Since hepatic arterial infusion chemotherapy is not effective for TACE failure patients, sorafenib is regarded as a first choice of treatment for TACE failure patients. Since up to now there was no clear definition of TACE failure JSH expert panel all agrees that the definition of TACE is mandatory to change the treatment strategy to sorafenib if TACE failure is confirmed.

In this regard, the definition of TACE failure has been proposed for the first time in the world as shown in table 15.

Consensus Statements

27 The following situation should be regarded as TACE failure or refractory:
(a) Intrahepatic lesion.
(i) More than two consecutive incomplete necrosis (depositions (<50%) of lipiodol) are seen by response evaluation CT within the treated tumors at the 4 weeks after adequately performed TACE.
(ii) More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT at the 4 weeks after adequately performed TACE.
(b) Appearance of vascular invasion.
(c) Appearance of extrahepatic spread – continuous elevation of tumor markers even though right after TACE.
(d) Tumor marker – continuous elevation of tumor markers even though right after TACE.
28 Since hepatic arterial infusion chemotherapy (HAIC) is not effective for TACE failure patients, molecular-targeted therapy is the first choice of treatment.

Table 15. Definition of TACE failure [cited and modified from 9, with permission]

Intrahepatic lesion
– More than two consecutive incomplete necrosis (depositions (<50%) of lipiodol) are seen by response evaluation CT within the treated tumors 4 weeks after adequately performed TACE
– More than two consecutive appearances of a new lesion (recurrence) are seen in the liver by response evaluation CT 4 weeks after adequately performed TACE
Appearance of vascular invasion
Appearance of extrahepatic spread
Tumor marker
– Continuous elevation of tumor markers even though right after TACE

Summary

Establishment of an original consensus-based Japanese treatment algorithm was necessary because the situation in Japan, including the availability of transplantation, is different from that found in Western countries. The algorithm established by the JSH is not necessarily based on scientific evidence; indeed consensus-based practices were combined with an evidence-based algorithm. Since it is equally hard to determine if the European or North American algorithm is always based on evidence, the newly established consensus-based treatment algorithm may be a valid guideline. Thus, a treatment algorithm widely agreed on and performed in Japan was presented. However, this algorithm should be revised step by step through prospective investigations of low-evidenced issues. The treatment algorithm for HCC presents the general concept for a therapeutic strategy. It is important to undertake accurate treatments after considering the various conditions found in individual cases.

Consensus Statements

29 The treatment algorithm proposed by the Consensus-Based Clinical Practice Guideline was established based on an evidence-based treatment algorithm and consensus among an expert panel of the JSH. More details are described in the treatment algorithm proposed by the Consensus-Based Clinical Practice Manual.
30 The treatment algorithm proposed by the AASLD is not suitable for application in Japan.
31 Definition of TACE failure is important as described earlier.