Hemochromatosis and HCC

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

Surveillance and diagnosis

Surveillance

Recommendations

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

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

Rationale for surveillance

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

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

Who should be screened?

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

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

What modality should be used?

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

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

Optimal interval for screening

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

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

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

Tumor markers

Recommendations

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

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

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

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

α-Fetoprotein

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

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

Des-γ-carboxyprothrombin

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

Lens culinaris agglutinin-reactive fraction of AFP

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

Glypican-3

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

Combination of tumor markers

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

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

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

AFP α-fetoprotein, *AFP-L3* lens culinaris agglutinin-reactive fraction of AFP, *CC* case–control study, *CH* chronic hepatitis, *Co* cohort study, *DCP* des-γ-carboxy prothrombin, *GGTII* hepatoma-specific band of serum γ-glutamyl transferase, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *LC* liver cirrhosis, *NL* normal liver, *NR* not reported

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

Ultrasonography

Recommendations

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

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

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

Efforts have been made to improve both sonography equipment and contrast agents to detect flow in tumors with more sensitivity [184, 185]. Sonography with an intraarterial CO_2 microbubble contrast agent enables the detection of intratumoral hemodynamics. The differential diagnosis of hepatic tumors has become possible with contrast-enhanced, harmonic US based on tumor vascularity [186]. CEUS using Levovist bubbles involves the use of a nonlinear backscatter property of the resonant microbubbles produced by an intravenously administered contrast agent; it allows microflow imaging of nodules and eliminates clutter signals. However, Levovist bubbles easily collapse by ultrasound wave emission because of its fragile property. Therefore, Levovist-enhanced harmonic US images are basically obtained intermittently, and realtime images can be obtained within a short period of time at an early vascular phase and Kupffer imaging in the postvascular phase by a single sweep scan of the liver.

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

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

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

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

CT, MRI, and other imaging modalities

Recommendations

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

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

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

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

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

A study of systematic review on the accuracies of US, spiral CT, and MRI in diagnosing HCC in patients with chronic liver disease revealed that the pooled estimates of the 14 US studies showed a sensitivity of 60% and specificity of 97%; for the ten CT studies, sensitivity was 68% and specificity 93%; and for the nine MRI studies, sensitivity was 81% and specificity 85% [203]. The operative characteristics of CT are comparable, whereas MRI is more sensitive. The performance of CT and MRI is affected by the size of the lesions [204, 205]. Although CT and MRI are reported to have a sensitivity of 60–94.4% and 58.5–93%, respectively, in tumors larger than 1 cm, their sensitivities for detecting tumors smaller than 1 cm are reduced by 33–45 and 33–67%, respectively [204, 206–208]. Furthermore, small, arterially enhancing nodules are common in the cirrhotic liver, and majority of these nodules are benign [209–211]. Therefore, the most important issue remains the identification of small tumors because curative treatments can be optimally applied to improve outcome [212, 213]. If left alone, these tumors can grow aggressively and invasion can occur before tumors reach the 2-cm cutoff size for small HCC [202]. Thus, every attempt, including imaging follow-up or biopsy, should be made to characterize these nodules [205].

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

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

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

Other imaging modalities

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

Diagnostic algorithm

Recommendations

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

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

Diagnostic algorithm of hypervascular HCC

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

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

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

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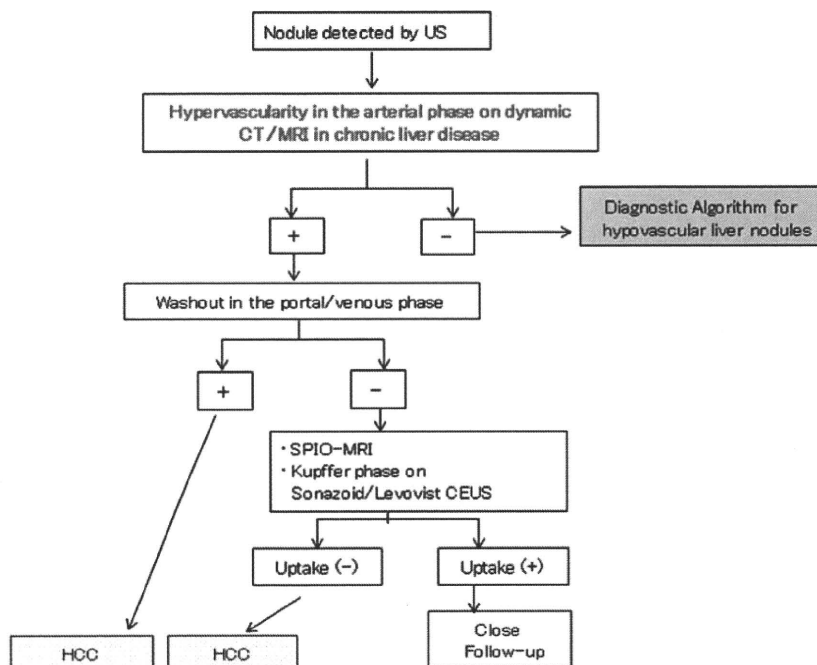
Diagnostic algorithm of hypovascular HCC

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

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

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

Fig. 1 Diagnostic algorithm of hypervascular HCC

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

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

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

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

Treatment

Liver resection and transplantation

Recommendations

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

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

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

Liver resection

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

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

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

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

Liver transplantation

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

Fig. 2 Diagnostic algorithm of hypovascular HCC
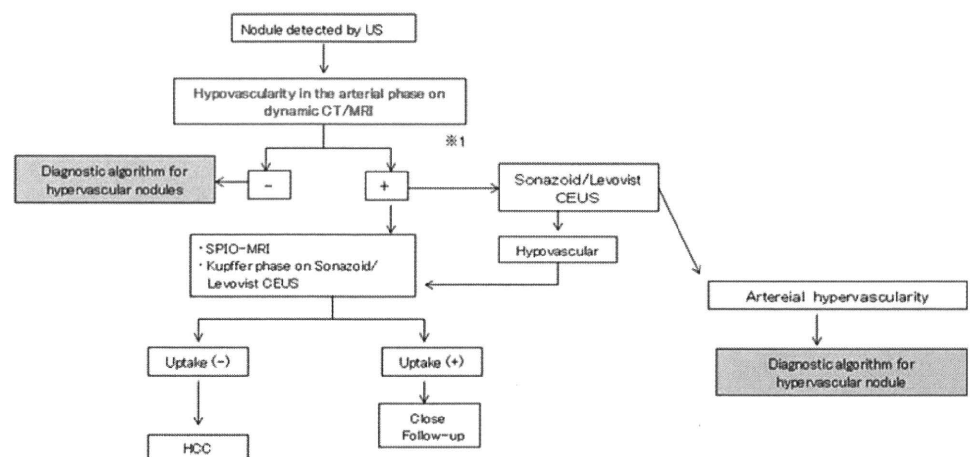
criterion of solitary tumor 6.5 or less cm or three or fewer nodules with the largest lesion of 4.5 or less cm and total tumor diameter of 8 or less cm for liver transplantation. Their study showed that the long-term survival after transplantation for such patients were similar to that of liver transplantation for HCCs within the Milan criteria. Although the expanded criteria have been supported by some other studies [268], there are inadequate data in the literature to validate the long-term survival results using expanded criteria. Furthermore, it has to be noted that Yao's criteria were based on pathologic examination of explants rather than preoperative radiological imaging, which often underestimates the size of the tumor compared with measurement of tumor size in the explants. Currently, most centers worldwide still adopt Milan criteria in selection of patients for liver transplantation.

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

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

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

Ablation

Recommendations

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

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

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

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

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

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

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

Transarterial chemoembolization

Recommendations

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

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

Although the normal liver receives a dual blood supply from the hepatic artery and the portal vein, advanced HCC is supplied almost exclusively by the hepatic artery [313]. Hepatocarcinogenesis is a multistep process involving parenchymal arterialization, sinusoidal capillarization, and development of neoangiogenesis, causing gradual change in portal to arterial blood supply [314]. The blood supply of HCCs varies according to their developmental stage and growth pattern. Although well-differentiated or early HCC is supplied by the portal vein and the hepatic artery, encapsulated nodular HCC is totally supplied by the hepatic artery [315]. This specific arterial vascular profile provides the rationale for therapeutic local chemotherapy and hepatic artery occlusion of HCCs by TACE [316]. TACE exploits the preferential hepatic arterial supply of HCC for targeted delivery of chemotherapeutic agents, usually mixed with lipiodol followed by embolization or reduction in arterial flow using various types of particles, while sparing the surrounding liver parenchyma [317]. This combination of highly concentrated chemotherapy and arterial embolization may induce highly concentrated chemotherapy and ischemic damage on the tumor, which is likely to be synergistic in producing tumor necrosis [318]. This reduction in arterial inflow causes not only ischemic necrosis within the tumors, which may increase tumor kill, but also significantly increases in tumor drug concentrations [319].

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

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

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

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

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

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

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

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

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

Systemic therapy

Recommendations

Sorafenib is recommended for the treatment of advanced stage patients (portal vein invasion or extrahepatic spread) who are not suitable for locoregional therapy and who have C-P class A liver function (1b, A).

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

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

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

Sorafenib

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

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

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

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

Antiangiogenic MTT

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

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

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

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

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

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

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

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

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

Anti-EGFR MTT

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

Cytotoxic therapy: single agent and combination

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

Future directions

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

Treatment algorithm

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

Tertiary prevention

Recommendations

Interferon may be effective in reducing the recurrent HBV-related HCC after curative ablation of HCC (1b, B).

Lamivudine may be effective in reducing the recurrent HBV-related HCC after curative ablation of HCC (2c, C).

Interferon-based antiviral treatments after complete removal or ablation of HCV-related HCC may reduce HCC recurrence and improve survival (1b, B).

Tertiary prevention for HBV-related HCC

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

Table 3 Selected clinical trials of cytotoxic therapy for advanced HCC

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

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

Fig. 3 Treatment algorithm of HCC
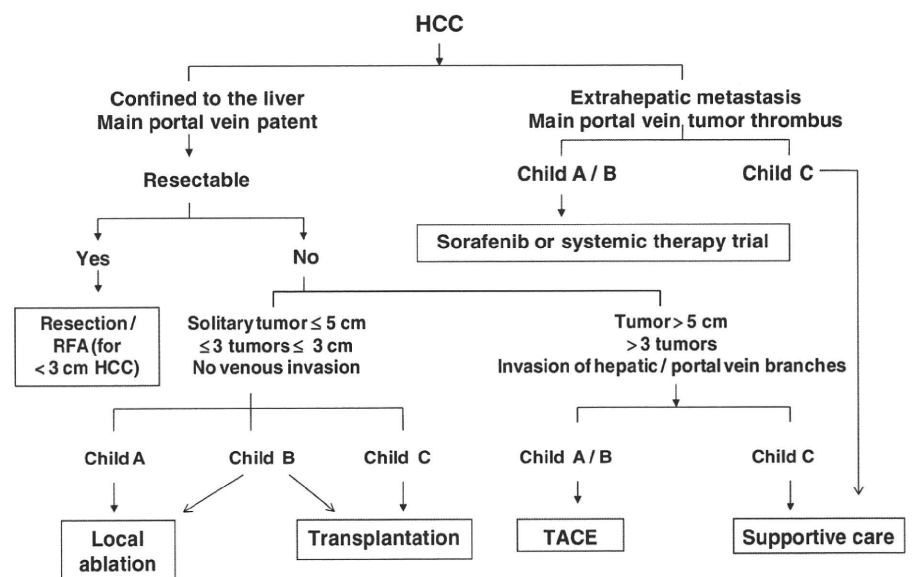
prognosis of HCC treated by hepatectomy remains a concern because of frequent development of tumor recurrence, which is the main cause of death in addition to concomitant hepatic decompensation. IFN has tumoricidal effect against a number of tumors including HCC. An RCT was performed to evaluate the safety and efficacy of adjuvant IFN

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

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

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

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

Tertiary prevention of HCV-related HCC

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

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

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

data were subsequently published [408], postulating that the eradication of premalignant or latent malignant clones is the mechanism of action. The effect is, however, yet to be confirmed in a large-scale RCT. Vitamin K_2 was reported to inhibit HCC development among female patients with cirrhosis, who had received the vitamin for the prevention of osteoporosis [122]. A small RCT suggested that vitamin K_2 was effective in suppressing HCC recurrence and may improve survival [124]. However, subsequent, large-scale RCT met with an early termination because of lacking evidence of effects.

Viral-unrelated tertiary prevention of HCC

Vitamin K_2   Apart from its use as a primary preventive agent for HCC, the use of vitamin K_2 as secondary preventive agent has also been investigated. Otsuka et al. [123] examined the biological effects of extrinsic supplementation of vitamin K_2 in HCC cells in vitro and in vivo. Administration of vitamin K_2 to nude mice inoculated with liver tumor cells reduced both tumor growth and weight loss. It was concluded that, similar to an acyclic retinoid, vitamin K_2 may be a promising therapeutic means for the management of HCC.

A pilot study by Mizuta et al. [124] on HCC patients who had undergone either percutaneous local ablation or surgery suggested that menatetrenone, a vitamin K_2 analogue, may have a suppressive effect on the recurrence of HCC and a beneficial effect on survival.

However, a later study (albeit smaller) by Hotta et al. [125] demonstrated that vitamin K_2 may not be as useful for the prevention of HCC recurrence as for primary prevention.

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

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

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

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