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.

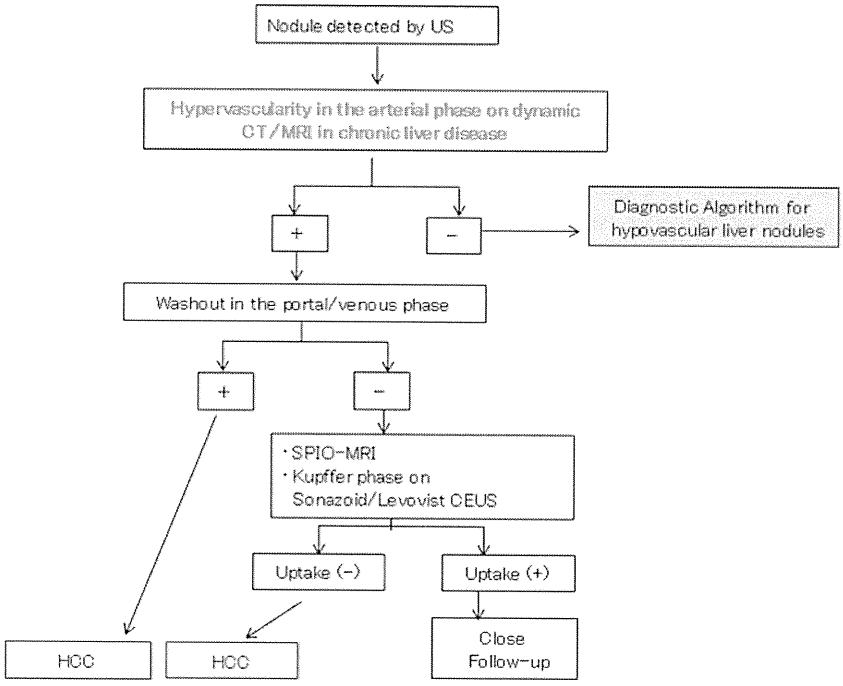

Fig. 1 Diagnostic algorithm of hypervascular HCC

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

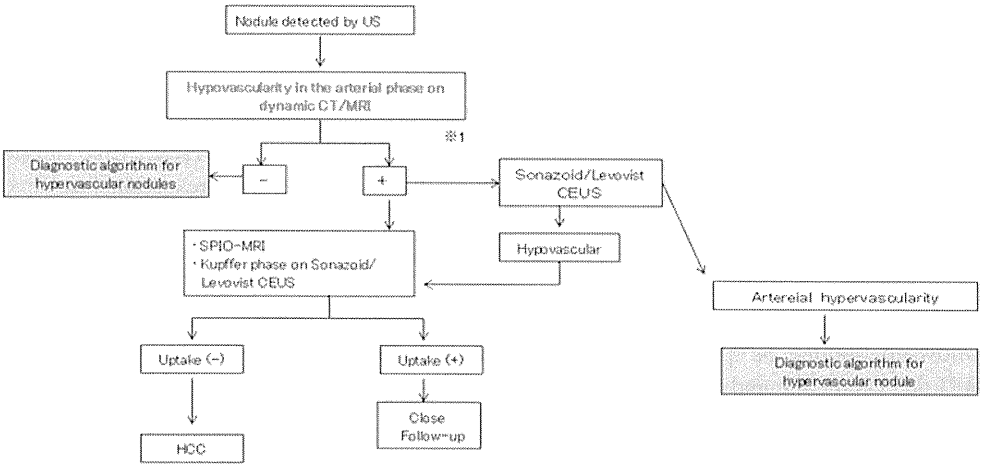

Fig. 2 Diagnostic algorithm of hypovascular HCC

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) SD: 71%	10.7	$P < 0.001$	5.5	$P < 0.001$	1b
	Placebo	303	RR: 0.7% (2 PR) SD: 67%	7.9		2.8		
Cheng et al. [346]	Sorafenib 400 mg bid	150	RR: 2.7% (4 PR) SD: 55%	6.5	$P = 0.014$	2.8	$P < 0.001$	1b
	Placebo	76	RR: 1.32% (1 PR) SD: 29%	4.2		1.4		
Phase II trials								
Siegel et al. [350]	Bevacizumab 5–10 mg/kg every 2 weeks	46	RR: 13% (1 CR and 5 PR) SD: 65% (progression free at 6 months)	12.4		6.9 (PFS)		4
Zhu et al. [352]	Sunitinib 37.5 mg qd for 4 weeks, followed by 2-week rest	34	RR: 2.9% (1 PR) SD: 47%	9.9		4.0		4
Faivre et al. [353]	Sunitinib 50 mg qd for 4 weeks, followed by 2-week rest	37	RR: 2.7% (1 PR) SD: 35.1%	10.3		4.8		4
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) SD: 31%	6.8		NA		4
Philip et al. [368]	Erlotinib 150 mg qd	38	RR: 9% (3 PR in 34 evaluable patients) SD: 50%	13		3.2		4
Thomas et al. [369]	Erlotinib 150 mg qd	40	RR: 0 SD: 42.5%	10.8		6.5		4
O'Dwyer et al. [370]	Gefitinib 250 mg qd	31	RR: 3.2% (1 PR) SD: 22.6%	6.5		2.8 (PFS)		4
Zhu et al. [371]	Cetuximab 400 mg/m^2 loading, then 250 mg/m^2/week	30	RR: 0 SD: 16.7%	9.6		1.4 (PFS)		4

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

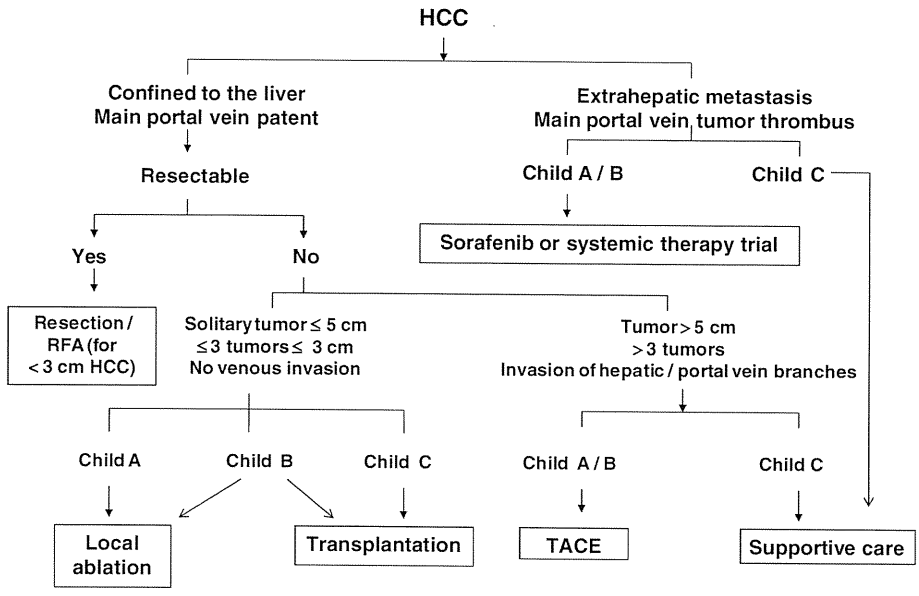

Fig. 3 Treatment algorithm of HCC

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.

References

1. Centre for Evidence-Based Medicine. Levels of evidence 2001 [cited 1 Dec 2008]. http://www.cebm.net/index.aspx?o=1025
2. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in Five Continents, vol. VIII. Lyon: IARC Scientific; 2002. Publication No.: 155
3. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22707 men in Taiwan. Lancet 1981;2:1129–1133
4. Tsukuma H, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med 1993; 328:1797–1801
5. Chen CJ, Liang KY, Chang AS, Chang YC, Lu SN, Liaw YF, et al. Effects of hepatitis B virus, alcohol drinking, cigarette smoking and familial tendency on hepatocellular carcinoma. Hepatology 1991;13:398–406
6. Yang HI, Lu SN, Liaw YF, You SL, Sun CA, Wang LY, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002;347:168–174
7. Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, et al. Additive effect modification of hepatitis B surface antigen and e antigen on the development of hepatocellular carcinoma. Br J Cancer 1996;73:1498–1502
8. Lu SN, Lin TM, Chen CJ, Chen JS, Liaw YF, Chang WY, et al. A case–control study of primary hepatocellular carcinoma in Taiwan. Cancer 1988;62:2051–2055
9. Lin TM, Chen CJ, Lu SN, Chang AS, Chang YC, Hsu ST, et al. Hepatitis B virus e antigen and primary hepatocellular carcinoma. Anticancer Res 1991;11:2063–2065
10. Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005;97:265–272
11. Chan HL, Tse CH, Mo F, Koh J, Wong VW, Wong GL, et al. High viral load and hepatitis B virus subgenotype Ce are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26:177–182
12. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73
13. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. Am J Gastroenterol 2006;101:1797–1803
14. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Chung H, et al. Evaluation of posttreatment response of hepatocellular carcinoma with contrast-enhanced coded phase-inversion harmonic US: comparison with dynamic CT. Radiology 2001; 221:721–730
15. Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, et al. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst 2008;100:1134–1143
16. Yuen MF, Sablon E, Yuan HJ, Wong DK, Hui CK, Wong BC, et al. Significance of hepatitis B genotype in acute exacerbation, HBeAg seroconversion, cirrhosis-related complications, and hepatocellular carcinoma. Hepatology 2003;37:562–567

17. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 2000;118:554–559
18. Sumi H, Yokosuka O, Seki N, Arai M, Imazeki F, Kurihara T, et al. Influence of hepatitis B virus genotypes on the progression of chronic type B liver disease. Hepatology 2003;37:19–26
19. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, et al. A case–control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Japan HBV Genotype Research Group. Hepatology 2001;33:218–223
20. Fang ZL, Yang J, Ge X, Zhuang H, Gong J, Li R, et al. Core promoter mutations (A(1762)T and G(1764)A) and viral genotype in chronic hepatitis B and hepatocellular carcinoma in Guangxi, China. J Med Virol 2002;68:33–40
21. Chiou HE, Wang TE, Wang YY, Liu HW. Efficacy and safety of thalidomide in patients with hepatocellular carcinoma. World J Gastroenterol 2006;12:6955–6960
22. Chen BF, Liu CJ, Jow GM, Chen PJ, Kao JH, Chen DS. High prevalence and mapping of pre-S deletion in hepatitis B virus carriers with progressive liver diseases. Gastroenterology 2006;130:1153–1168
23. Chen CH, Hung CH, Lee CM, Hu TH, Wang JH, Wang JC, et al. Pre-S deletion and complex mutations of hepatitis B virus related to advanced liver disease in HBeAg-negative patients. Gastroenterology 2007;133:1466–1474
24. Chou YC, Yu MW, Wu CF, Yang SY, Lin CL, Liu CJ, et al. Temporal relationship between hepatitis B virus enhancer II/basal core promoter sequence variation and risk of hepatocellular carcinoma. Gut 2008;57:91–97
25. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. Gastroenterology 2003;124:327–334
26. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112:463–472
27. Tradati F, Colombo M, Mannucci PM, Rumi MG, De Fazio C, Gamba G, et al. A prospective multicenter study of hepatocellular carcinoma in Italian hemophiliacs with chronic hepatitis C. The Study Group of the Association of Italian Hemophilia Centers. Blood 1998;91:1173–1177
28. Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. Hepatology 1995;21:650–655
29. Sun CA, Wu DM, Lin CC, Lu SN, You SL, Wang LY, et al. Incidence and cofactors of hepatitis C virus-related hepatocellular carcinoma: a prospective study of 12,008 men in Taiwan. Am J Epidemiol 2003;157:674–682
30. Serfaty L, Aumaitre H, Chazouilleres O, Bonnand AM, Rosmorduc O, Poupon RE, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998;27:1435–1440
31. Niederau C, Lange S, Heintges T, Erhardt A, Buschkamp M, Hurter D, et al. Prognosis of chronic hepatitis C: results of a large, prospective cohort study. Hepatology 1998;28:1687–1695
32. Fattovich G, Ribero ML, Pantalena M, Diodati G, Almasio P, Nevens F, et al. Hepatitis C virus genotypes: distribution and clinical significance in patients with cirrhosis type C seen at tertiary referral centres in Europe. J Viral Hepat 2001;8:206–216
33. Bruno S, Silini E, Crosignani A, Borzio F, Leandro G, Bono F, et al. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. Hepatology 1997;25:754–758
34. Bruno S, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. Hepatology 2007;46:1350–1356
35. Chuang WL, Chang WY, Lu SN, Su WP, Lin ZY, Chen SC, et al. The role of hepatitis B and C viruses in hepatocellular carcinoma in a hepatitis B endemic area. A case–control study. Cancer 1992;69:2052–2054
36. Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer 1999;85:2132–2137
37. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol 1997;12:S294–S308
38. Yu MC, Tong MJ, Coursaget P, Ross RK, Govindarajan S, Henderson BE. Prevalence of hepatitis B and C viral markers in black and white patients with hepatocellular carcinoma in the United States. J Natl Cancer Inst 1990;82:1038–1041
39. Tagger A, Donato F, Ribero ML, Chiesa R, Portera G, Gelatti U, et al. Case–control study on hepatitis C virus (HCV) as a risk factor for hepatocellular carcinoma: the role of HCV genotypes and the synergism with hepatitis B virus and alcohol. Brescia HCC Study. Int J Cancer 1999;81:695–699
40. Kaklamani E, Trichopoulos D, Tzonou A, Zavitsanos X, Koumantaki Y, Hatzakis A, et al. Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. JAMA 1991;265:1974–1976
41. Thio CL, Seaberg EC, Skolasky R Jr, Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002;360:1921–1926
42. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US–Canadian multicenter study. J Hepatol 2007;47:527–537
43. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108
44. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. Hepatology 1995;22:1027–1033
45. Lee CM, Lu SN, Changchien CS, Yeh CT, Hsu TT, Tang JH, et al. Age, gender, and local geographic variations of viral etiology of hepatocellular carcinoma in a hyperendemic area for hepatitis B virus infection. Cancer 1999;86:1143–1150
46. Lu SN, Su WW, Yang SS, Chang TT, Cheng KS, Wu JC, et al. Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan. Int J Cancer 2006;119:1946–1952
47. Yoshida H, Tateishi R, Arakawa Y, Sata M, Fujiyama S, Nishiguchi S, et al. Benefit of interferon therapy in hepatocellular carcinoma prevention for individual patients with chronic hepatitis C. Gut 2004;53:425–430
48. Yu MC, Tong MJ, Govindarajan S, Henderson BE. Nonviral risk factors for hepatocellular carcinoma in a low-risk population, the non-Asians of Los Angeles County, California. J Natl Cancer Inst 1991;83:1820–1826
49. Tanaka K, Hirohata T, Takeshita S, Hirohata I, Koga S, Sugimachi K, et al. Hepatitis B virus, cigarette smoking and alcohol consumption in the development of hepatocellular carcinoma: a case–control study in Fukuoka, Japan. Int J Cancer 1992;51:509–514
50. Mohamed AE, Kew MC, Groeneveld HT. Alcohol consumption as a risk factor for hepatocellular carcinoma in urban southern African blacks. Int J Cancer 1992;51:537–541

51. Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol 2002;155:323–331
52. Chiesa R, Donato F, Tagger A, Favret M, Ribero ML, Nardi G, et al. Etiology of hepatocellular carcinoma in Italian patients with and without cirrhosis. Cancer Epidemiol Biomarkers Prev 2000;9:213–216
53. Wang JS, Huang T, Su J, Liang F, Wei Z, Liang Y, et al. Hepatocellular carcinoma and aflatoxin exposure in Zhuqing Village, Fusui County, People's Republic of China. Cancer Epidemiol Biomarkers Prev 2001;10:143–46
54. Chen CJ, Wang LY, Lu SN, Wu MH, You SL, Zhang YJ, et al. Elevated aflatoxin exposure and increased risk of hepatocellular carcinoma. Hepatology 1996;24:38–42
55. Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. Cancer Epidemiol Biomarkers Prev 1994;3:3–10
56. Ross RK, Yuan JM, Yu MC, Wogan GN, Qian GS, Tu JT, et al. Urinary aflatoxin biomarkers and risk of hepatocellular carcinoma. Lancet 1992;339:943–946
57. Wang LY, Hatch M, Chen CJ, Levin B, You SL, Lu SN, et al. Aflatoxin exposure and risk of hepatocellular carcinoma in Taiwan. Int J Cancer 1996;67:620–625
58. Chen CL, Yang HI, Yang WS, Liu CJ, Chen PJ, You SL, et al. Metabolic factors and risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology 2008;135:111–121
59. London WT, Evans AA, McGlynn K, Buetow K, An P, Gao L, et al. Viral, host and environmental risk factors for hepatocellular carcinoma: a prospective study in Haimen City, China. Intervirology 1995;38:155–161
60. Evans AA, Chen G, Ross EA, Shen FM, Lin WY, London WT. Eight-year follow-up of the 90,000-person Haimen City cohort: I. Hepatocellular carcinoma mortality, risk factors, and gender differences. Cancer Epidemiol Biomarkers Prev 2002;11:369–76
61. Yu MW, Chang HC, Liaw YF, Lin SM, Lee SD, Liu CJ, et al. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000; 92:1159–1164
62. Bradbear RA, Bain C, Siskind V, Schofield FD, Webb S, Axelsen EM, et al. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. J Natl Cancer Inst 1985;75:81–84
63. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985;313:1256–1262
64. Elmberg M, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. Gastroenterology 2003;125: 1733–1741
65. Chen DS, Hsu NH, Sung JL, Hsu TC, Hsu ST, Kuo YT, et al. A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. JAMA 1987;257:2597–2603
66. Hsu HM, Chen DS, Chuang CH, Lu JC, Jwo DM, Lee CC, et al. Efficacy of a mass hepatitis B vaccination program in Taiwan. Studies on 3464 infants of hepatitis B surface antigen-carrier mothers. JAMA 1988;260:2231–2235
67. Chen HL, Chang MH, Ni YH, Hsu HY, Lee PI, Lee CY, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. JAMA 1996;276:906–908
68. Chang MH, Shau WY, Chen CJ, Wu TC, Kong MS, Liang DC, et al. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. JAMA 2000;284:3040–3042
69. Kao JH, Chen DS. Recent updates in hepatitis vaccination and the prevention of hepatocellular carcinoma. Int J Cancer 2002; 97:269–271
70. Niederau C, Heintges T, Lange S, Goldmann G, Niederau CM, Mohr L, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. N Engl J Med 1996;334:1422–1427
71. Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. Hepatology 1999;29:971–975
72. Papatheodoridis GV, Manesis E, Hadziyannis SJ. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg-negative chronic hepatitis B. J Hepatol 2001;34:306–313
73. Lampertico P, Del Ninno E, Vigano M, Romeo R, Donato MF, Sablon E, et al. Long-term suppression of hepatitis B e antigen-negative chronic hepatitis B by 24-month interferon therapy. Hepatology 2003;37:756–763
74. van Zonneveld M, Honkoop P, Hansen BE, Niesters HG, Murad SD, de Man RA, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. Hepatology 2004;39:804–810
75. Lau DT, Everhart J, Kleiner DE, Park Y, Vergalla J, Schmid P, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. Gastroenterology 1997;113:1660–1667
76. Yuen MF, Hui CK, Cheng CC, Wu CH, Lai YP, Lai CL. Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: the effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications. Hepatology 2001;34:139–145
77. Lin SM, Yu ML, Lee CM, Chien RN, Sheen IS, Chu CM, et al. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol 2007;46:45–52
78. Craxi A, Camma C. Prevention of hepatocellular carcinoma. Clin Liver Dis 2005;9:329–346
79. Strickland GT. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. Hepatology 2006;43:915–922
80. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004;127:1372–1380
81. Yoshizawa H. Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 2002;62(Suppl 1):8–17
82. Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. Intervirolog 2006;49:7–17
83. Omata M, Yokosuka O, Takano S, Kato N, Hosoda K, Imazeki F, et al. Resolution of acute hepatitis C after therapy with natural beta interferon. Lancet 1991;338:914–915
84. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med 2001;345:1452–1457
85. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, et al. Randomised trial of effects of interferon-alpha on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051–1055
86. Nishiguchi S, Shiomi S, Nakatani S, Takeda T, Fukuda K, Tamori A, et al. Prevention of hepatocellular carcinoma in patients

with chronic active hepatitis C and cirrhosis. Lancet 2001; 357:196–197
87. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, et al. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 1996; 24:141–147
88. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and non-cirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med 1999;131:174–181
89. Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med 2005;142:105–114
90. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, et al. Effectiveness of interferon alfa on incidence of hepatocellular carcinoma and decompensation in cirrhosis type C. European Concerted Action on Viral Hepatitis (EUROHEP). J Hepatol 1997;27:201–205
91. Papatheodoridis GV, Papadimitropoulos VC, Hadziyannis SJ. Effect of interferon therapy on the development of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a meta-analysis. Aliment Pharmacol Ther 2001; 15:689–698
92. Camma C, Giunta M, Andreone P, Craxi A. Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach. J Hepatol 2001;34:593–602
93. Imai Y, Kawata S, Tamura S, Yabuuchi I, Noda S, Inada M, et al. Relation of interferon therapy and hepatocellular carcinoma in patients with chronic hepatitis C. Osaka Hepatocellular Carcinoma Prevention Study Group. Ann Intern Med 1998; 129:94–99
94. Ikeda K, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, et al. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: a long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. Hepatology 1999; 29:1124–1130
95. Shindo M, Ken A, Okuno T. Varying incidence of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C responding differently to interferon therapy. Cancer 1999; 85:1943–1950
96. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med 2000;132:517–524
97. Yu ML, Lin SM, Chuang WL, Dai CY, Wang JH, Lu SN, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antivir Ther 2006;11:985–994
98. Saito Y, Saito H, Tada S, Nakamoto N, Horikawa H, Kurita S, et al. Effect of long-term interferon therapy for refractory chronic hepatitis c: preventive effect on hepatocarcinogenesis. Hepatogastroenterology 2005;52:1491–1496
99. Arase Y, Ikeda K, Suzuki F, Suzuki Y, Kobayashi M, Akuta N, et al. Prolonged-interferon therapy reduces hepatocarcinogenesis in aged-patients with chronic hepatitis C. J Med Virol 2007; 79:1095–1102
100. Lok AS, Seeff LB, Morgan TR, Di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis c-related advanced liver disease. Gastroenterology [Epub 2008]
101. Wogan GN. Aflatoxins as risk factors for hepatocellular carcinoma in humans. Cancer Res 1992;52:2114s–2118s
102. Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 2004;127:S72–S78
103. Omer RE, Kuijsten A, Kadaru AM, Kok FJ, Idris MO, El Khidir IM, et al. Population-attributable risk of dietary aflatoxins and hepatitis B virus infection with respect to hepatocellular carcinoma. Nutr Cancer 2004;48:15–21
104. La Vecchia C. Coffee, liver enzymes, cirrhosis and liver cancer. J Hepatol 2005;42:444–446
105. Adami HO, Hsing AW, McLaughlin JK, Trichopoulos D, Hacker D, Ekbom A, et al. Alcoholism and liver cirrhosis in the etiology of primary liver cancer. Int J Cancer 1992;51:898–902
106. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498–502
107. La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998;7:315–320
108. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol 2001;54:823–829
109. Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tatara K. Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. Eur J Epidemiol 2000;16:419–423
110. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2005;128:24–32
111. Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997;146:1019–1024
112. Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, et al. Coffee drinking and serum gamma-glutamyltransferase: an extended study of Self-Defense Officials of Japan. Ann Epidemiol 1999;9:325–331
113. Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, et al. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol 1998;27:438–443
114. Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, et al. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. Hepatology 2007;46:430–435
115. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. Gastroenterology 2007;132:1740–1745
116. Tamori A, Habu D, Shiomi S, Kubo S, Nishiguchi S. Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma. Hepatol Res 2007;37(Suppl 2):S303–S307
117. Sakai I, Hashimoto S, Yoda M, Hida T, Ohsawa S, Nakajo S, et al. Novel role of vitamin K2: a potent inducer of differentiation of various human myeloid leukemia cell lines. Biochem Biophys Res Commun 1994;205:1305–1310
118. Miyakawa T, Kajiwara Y, Shirahata A, Okamoto K, Itoh H, Ohsato K. Vitamin K contents in liver tissue of hepatocellular carcinoma patients. Jpn J Cancer Res 2000;91:68–74
119. Carr BI, Wang Z, Kar S, Wang M. Prothrombin inhibits hepatocyte DNA synthesis (DNA-S) and expression of the a5 integrin gene. Proc AACR 1995;36:266
120. Kar S, Carr BI. Growth inhibition and protein tyrosine phosphorylation in MCF 7 breast cancer cells by a novel K vitamin. J Cell Physiol 2000;185:386–393
121. Varnum BC, Young C, Elliott G, Garcia A, Bartley TD, Fridell YW, et al. Axl receptor tyrosine kinase stimulated by the

vitamin K-dependent protein encoded by growth-arrest-specific gene 6. Nature 1995;373:623–626
122. Habu D, Shiomi S, Tamori A, Takeda T, Tanaka T, Kubo S, et al. Role of vitamin K2 in the development of hepatocellular carcinoma in women with viral cirrhosis of the liver. JAMA 2004;292:358–361
123. Otsuka M, Kato N, Shao RX, Hoshida Y, Ijichi H, Koike Y, et al. Vitamin K2 inhibits the growth and invasiveness of hepatocellular carcinoma cells via protein kinase A activation. Hepatology 2004;40:243–251
124. Mizuta T, Ozaki I, Eguchi Y, Yasutake T, Kawazoe S, Fujimoto K, et al. The effect of menatetrenone, a vitamin K2 analog, on disease recurrence and survival in patients with hepatocellular carcinoma after curative treatment: a pilot study. Cancer 2006; 106:867–872
125. Hotta N, Ayada M, Sato K, Ishikawa T, Okumura A, Matsumoto E, et al. Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma. Hepatogastroenterology 2007;54:2073–2077
126. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994;107:1103–1109
127. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology 1999;116: 1413–1419
128. >Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology 1999; 29:664–669
129. Cuadrado A, Orive A, Garcia-Suarez C, Dominguez A, Fernandez-Escalante JC, Crespo J, et al. Non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma. Obes Surg 2005; 15:442–446
130. Wang RT, Koretz RL, Yee HF Jr. Is weight reduction an effective therapy for nonalcoholic fatty liver? A systematic review. Am J Med 2003;115:554–559
131. Chan HL, de Silva HJ, Leung NW, Lim SG, Farrell GC. How should we manage patients with non-alcoholic fatty liver disease in 2007? J Gastroenterol Hepatol 2007;22:801–808
132. Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Sanchez-Avila F, Montano-Reyes MA, Uribe M. Insulin sensitizers in treatment of nonalcoholic fatty liver disease: systematic review. World J Gastroenterol 2006;12:7826–7831
133. Strohmeyer G, Niederau C, Stremmel W. Survival and causes of death in hemochromatosis. Observations in 163 patients. Ann N Y Acad Sci 1988;526:245–257
134. Hsing AW, McLaughlin JK, Olsen JH, Mellemkjar L, Wacholder S, Fraumeni JF Jr. Cancer risk following primary hemochromatosis: a population-based cohort study in Denmark. Int J Cancer 1995;60:160–162
135. Yang Q, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of multiple-cause mortality data. Ann Intern Med 1998;129:946–953
136. Borgna-Pignatti C, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A, et al. Hepatocellular carcinoma in the thalassaemia syndromes. Br J Haematol 2004;124:114–117
137. Mandishona E, MacPhail AP, Gordeuk VR, Kedda MA, Paterson AC, Rouault TA, et al. Dietary iron overload as a risk factor for hepatocellular carcinoma in black Africans. Hepatology 1998;27:1563–1566
138. Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology 2004;127:S79–S86
139. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417–422
140. Yuen MF, Tanaka Y, Fong DY, Fung J, Wong DK, Yuen JC, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009;50:80–88
141. McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000;32:842–846
142. Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995;22:432–438
143. Lok AS, Lai CL. alpha-Fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection: role in the early detection of hepatocellular carcinoma. Hepatology 1989;9:110–115
144. Bloomer JR, Waldmann TA, McIntire KR, Klatskin G. Alpha-fetoprotein in non-neoplastic hepatic disorders. JAMA 1975; 233:38–41
145. Alpert E, Feller ER. Alpha-fetoprotein (AFP) in benign liver disease. Evidence that normal liver regeneration does not induce AFP synthesis. Gastroenterology 1978;74:856–858
146. Ikoma J, Kaito M, Ishihara T, Nakagawa N, Kamei A, Fujita N, et al. Early diagnosis of hepatocellular carcinoma using a sensitive assay for serum des-gamma-carboxy prothrombin: a prospective study. Hepatogastroenterology 2002;49:235–238
147. Kasahara A, Hayashi N, Fusamoto H, Kawada Y, Imai Y, Yamamoto H, et al. Clinical evaluation of plasma des-gamma-carboxy prothrombin as a marker protein of hepatocellular carcinoma in patients with tumors of various sizes. Dig Dis Sci 1993;38:2170–6
148. Maringhini A, Cottone M, Sciarrino E, Marceno MP, La Seta F, Fusco G, et al. Ultrasonography and alpha-fetoprotein in diagnosis of hepatocellular carcinoma in cirrhosis. Dig Dis Sci 1988; 33:47–51
149. Mita Y, Aoyagi Y, Yanagi M, Suda T, Suzuki Y, Asakura H. The usefulness of determining des-gamma-carboxy prothrombin by sensitive enzyme immunoassay in the early diagnosis of patients with hepatocellular carcinoma. Cancer 1998;82:1643–1648
150. Nomura F, Ishijima M, Horikoshi A, Nakai T, Ohnishi K. Determination of serum des-gamma-carboxy prothrombin levels in patients with small-sized hepatocellular carcinoma: comparison of the conventional enzyme immunoassay and two modified methods. Am J Gastroenterol 1996;91:1380–1383
151. Nomura F, Ishijima M, Kuwa K, Tanaka N, Nakai T, Ohnishi K. Serum des-gamma-carboxy prothrombin levels determined by a new generation of sensitive immunoassays in patients with small-sized hepatocellular carcinoma. Am J Gastroenterol 1999;94:650–654
152. Oka H, Saito A, Ito K, Kumada T, Satomura S, Kasugai H, et al. Multicenter prospective analysis of newly diagnosed hepatocellular carcinoma with respect to the percentage of Lens culinaris agglutinin-reactive alpha-fetoprotein. J Gastroenterol Hepatol 2001;16:1378–1383
153. Suehiro T, Sugimachi K, Matsumata T, Itasaka H, Taketomi A, Maeda T. Protein induced by vitamin K absence or antagonist II as a prognostic marker in hepatocellular carcinoma. Comparison with alpha-fetoprotein. Cancer 1994;73:2464–2471
154. Tanabe Y, Ohnishi K, Nomura F, Iida S. Plasma abnormal prothrombin levels in patients with small hepatocellular carcinoma. Am J Gastroenterol 1988;83:1386–1389

155. Gebo KA, Chander G, Jenckes MW, Ghanem KG, Herlong HF, Torbenson MS, et al. Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. Hepatology 2002;36:S84–S92
156. Cottone M, Turri M, Caltagirone M, Parisi P, Orlando A, Fiorentino G, et al. Screening for hepatocellular carcinoma in patients with Child's A cirrhosis: an 8-year prospective study by ultrasound and alpha-fetoprotein. J Hepatol 1994;21:1029–1034
157. Pateron D, Ganne N, Trinchet JC, Aurousseau MH, Mal F, Meicler C, et al. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. J Hepatol 1994;20:65–71
158. Irwig L, Tosteson AN, Gatsonis C, Lau J, Colditz G, Chalmers TC, et al. Guidelines for meta-analyses evaluating diagnostic tests. Ann Intern Med 1994;120:667–676
159. Tateishi R, Yoshida H, Matsuyama Y, Mine N, Kondo Y, Omata M. Diagnostic accuracy of tumor markers for hepatocellular carcinoma: a systematic review. Hepatol Int 2008;2:17–30
160. Marrero JA, Su GL, Wei W, Emick D, Conjeevaram HS, Fontana RJ, et al. Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in American patients. Hepatology 2003;37:1114–1121
161. Cui R, He J, Zhang F, Wang B, Ding H, Shen H, et al. Diagnostic value of protein induced by vitamin K absence (PIVKAII) and hepatoma-specific band of serum gamma-glutamyl transferase (GGTII) as hepatocellular carcinoma markers complementary to alpha-fetoprotein. Br J Cancer 2003;88:1878–1882
162. Wang CS, Lin CL, Lee HC, Chen KY, Chiang MF, Chen HS, et al. Usefulness of serum des-gamma-carboxy prothrombin in detection of hepatocellular carcinoma. World J Gastroenterol 2005;11:6115–6119
163. Sterling RK, Jeffers L, Gordon F, Sherman M, Venook AP, Reddy KR, et al. Clinical utility of AFP-L 3% measurement in North American patients with HCV-related cirrhosis. Am J Gastroenterol 2007;102:2196–2205
164. Capurro M, Wanless IR, Sherman M, Deboer G, Shi W, Miyoshi E, et al. Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. Gastroenterology 2003;125:89–97
165. Hippo Y, Watanabe K, Watanabe A, Midorikawa Y, Yamamoto S, Ihara S, et al. Identification of soluble NH_2-terminal fragment of glypican-3 as a serological marker for early-stage hepatocellular carcinoma. Cancer Res 2004;64:2418–2423
166. Nguyen MH, Garcia RT, Simpson PW, Wright TL, Keeffe EB. Racial differences in effectiveness of alpha-fetoprotein for diagnosis of hepatocellular carcinoma in hepatitis C virus cirrhosis. Hepatology 2002;36:410–417
167. Soresi M, Magliarisi C, Campagna P, Leto G, Bonfissuto G, Riili A, et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. Anticancer Res 2003;23:1747–1753
168. Arrieta O, Cacho B, Morales-Espinosa D, Ruelas-Villavicencio A, Flores-Estrada D, Hernandez-Pedro N. The progressive elevation of alpha fetoprotein for the diagnosis of hepatocellular carcinoma in patients with liver cirrhosis. BMC Cancer 2007; 7:28
169. Paul SB, Gulati MS, Sreenivas V, Madan K, Gupta AK, Mukhopadhyay S. Evaluating patients with cirrhosis for hepatocellular carcinoma: value of clinical symptomatology, imaging and alpha-fetoprotein. Oncology 2007;72(Suppl 1):117–123
170. Kew MC. Alpha-fetoprotein. In Read AE, editor. Modern Trends in Gastroenterology, vol. 5. London: Butterworths; 1975. p 91
171. Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, et al. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med 1984;310:1427–1431
172. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M. Yet al. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. Cancer 2001;91:561–569
173. Imamura H, Matsuyama Y, Miyagawa Y, Ishida K, Shimada R, Miyagawa S, et al. Prognostic significance of anatomical resection and des-gamma-carboxy prothrombin in patients with hepatocellular carcinoma. Br J Surg 1999;86:1032–1038
174. Sato Y, Nakata K, Kato Y, Shima M, Ishii N, Koji T, et al. Early recognition of hepatocellular carcinoma based on altered profiles of alpha-fetoprotein. N Engl J Med 1993;328:1802–1806
175. Taketa K, Endo Y, Sekiya C, Tanikawa K, Koji T, Taga H, et al. A collaborative study for the evaluation of lectin-reactive alpha-fetoproteins in early detection of hepatocellular carcinoma. Cancer Res 1993;53:5419–5423
176. Aoyagi Y, Isemura M, Yosizawa Z, Suzuki Y, Sekine C, Ono T, et al. Fucosylation of serum alpha-fetoprotein in patients with primary hepatocellular carcinoma. Biochim Biophys Acta 1985;830:217–223
177. Hsu HC, Cheng W, Lai PL. Cloning and expression of a developmentally regulated transcript MXR7 in hepatocellular carcinoma: biological significance and temporospatial distribution. Cancer Res 1997;57:5179–5184
178. Zhu ZW, Friess H, Wang L, Abou-Shady M, Zimmermann A, Lander AD, et al. Enhanced glypican-3 expression differentiates the majority of hepatocellular carcinomas from benign hepatic disorders. Gut 2001;48:558–564
179. Sassa T, Kumada T, Nakano S, Uematsu T. Clinical utility of simultaneous measurement of serum high-sensitivity des-gamma-carboxy prothrombin and Lens culinaris agglutinin A-reactive alpha-fetoprotein in patients with small hepatocellular carcinoma. Eur J Gastroenterol Hepatol 1999;11:1387–1392
180. Tanaka S, Kitamura T, Fujita M, Nakanishi K, Okuda S. Color Doppler flow imaging of liver tumors. AJR Am J Roentgenol 1990;154:509–514
181. Tanaka S, Kitamra T, Fujita M, Kasugai H, Inoue A, Ishiguro S. Small hepatocellular carcinoma: differentiation from adenomatous hyperplastic nodule with color Doppler flow imaging. Radiology 1992;182:161–165
182. Rubin JM, Bude RO, Carson PL, Bree RL, Adler RS. Power Doppler US: a potentially useful alternative to mean frequency-based color Doppler US. Radiology 1994;190:853–856
183. Koito K, Namieno T, Morita K. Differential diagnosis of small hepatocellular carcinoma and adenomatous hyperplasia with power Doppler sonography. AJR Am J Roentgenol 1998;170:157–161
184. Fujimoto M, Moriyasu F, Nishikawa K, Nada T, Okuma M. Color Doppler sonography of hepatic tumors with a galactose-based contrast agent: correlation with angiographic findings. AJR Am J Roentgenol 1994;163:1099–1104
185. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K. Hepatocellular carcinoma: depiction of tumor parenchymal flow with intermittent harmonic power Doppler US during the early arterial phase in dual-display mode. Radiology 2001;220:349–356
186. Kudo M, Tomita S, Tochio H, Mimura J, Okabe Y, Kashida H, et al. Sonography with intraarterial infusion of carbon dioxide microbubbles (sonographic angiography): value in differential diagnosis of hepatic tumors. AJR Am J Roentgenol 1992; 158:65–74
187. Yanagisawa K, Moriyasu F, Miyahara T, Yuki M, Iijima H. Phagocytosis of ultrasound contrast agent microbubbles by Kupffer cells. Ultrasound Med Biol 2007;33:318–325
188. D'Onofrio M, Martone E, Faccioli N, Zamboni G, Malago R, Mucelli RP. Focal liver lesions: sinusoidal phase of CEUS. Abdom Imaging 2006;31:529–536

189. Hatanaka K, Kudo M, Minami Y, Ueda T, Tatsumi C, Kitai S, et al. Differential diagnosis of hepatic tumors: value of contrast-enhanced harmonic sonography using the newly developed contrast agent, Sonazoid. Intervirology 2008;51(Suppl 1):61–9
190. Chalasani N, Said A, Ness R, Hoen H, Lumeng L. Screening for hepatocellular carcinoma in patients with cirrhosis in the United States: results of a national survey. Am J Gastroenterol 1999;94:2224–2229
191. Collier J, Sherman M. Screening for hepatocellular carcinoma. Hepatology 1998;27:273–278
192. Kobayashi K, Sugimoto T, Makino H, Kumagai M, Unoura M, Tanaka N, et al. Screening methods for early detection of hepatocellular carcinoma. Hepatology 1985;5:1100–1105
193. Federle MP. Use of radiologic techniques to screen for hepatocellular carcinoma. J Clin Gastroenterol 2002;35:S92–S100
194. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236
195. Saab S, Ly D, Nieto J, Kanwal F, Lu D, Raman S, et al. Hepatocellular carcinoma screening in patients waiting for liver transplantation: a decision analytic model. Liver Transpl 2003; 9:672–681
196. Burrel M, Llovet JM, Ayuso C, Iglesias C, Sala M, Miquel R, et al. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. Hepatology 2003;38:1034–1042
197. Van Thiel DH, Yong S, Li SD, Kennedy M, Brems J. The development of de novo hepatocellular carcinoma in patients on a liver transplant list: frequency, size, and assessment of current screening methods. Liver Transpl 2004;10:631–637
198. El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 2008;134:1752–1763
199. Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. Am J Gastroenterol 2003;98: 679–690
200. Kim TK, Jang HJ, Wilson SR. Imaging diagnosis of hepatocellular carcinoma with differentiation from other pathology. Clin Liver Dis 2005;9:253–279
201. Matsui O. Imaging of multistep human hepatocarcinogenesis by CT during intra-arterial contrast injection. Intervirology 2004;47:271–276
202. Marrero JA, Hussain HK, Nghiem HV, Umar R, Fontana RJ, Lok AS. Improving the prediction of hepatocellular carcinoma in cirrhotic patients with an arterially-enhancing liver mass. Liver Transpl 2005;11:281–289
203. Colli A, Fraquelli M, Casazza G, Massironi S, Colucci A, Conte D, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol 2006; 101:513–523
204. Kim SH, Choi BI, Lee JY, Kim SJ, So YH, Eun HW. Diagnostic accuracy of multi-/single-detector row CT and contrast-enhanced MRI in the detection of hepatocellular carcinomas meeting the Milan criteria before liver transplantation. Intervirology 2008;51(Suppl 1):52–60
205. Willatt JM, Hussain HK, Adusumilli S, Marrero JA. MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies. Radiology 2008;247:311–330
206. Ebara M, Ohto M, Watanabe Y, Kimura K, Saisho H, Tsuchiya Y, et al. Diagnosis of small hepatocellular carcinoma: correlation of MR imaging and tumor histologic studies. Radiology 1986;159:371–377
207. Rode A, Bancel B, Douek P, Chevallier M, Vilgrain V, Picaud G, et al. Small nodule detection in cirrhotic livers: evaluation with US, spiral CT, and MRI and correlation with pathologic examination of explanted liver. J Comput Assist Tomogr 2001;25:327–336
208. Krinsky GA, Lee VS, Theise ND, Weinreb JC, Rofsky NM, Diflo T, et al. Hepatocellular carcinoma and dysplastic nodules in patients with cirrhosis: prospective diagnosis with MR imaging and explantation correlation. Radiology 2001;219:445–454
209. Baron RL, Peterson MS. From the RSNA refresher courses: screening the cirrhotic liver for hepatocellular carcinoma with CT and MR imaging: opportunities and pitfalls. Radiographics 2001;21:S117–S132
210. Holland AE, Hecht EM, Hahn WY, Kim DC, Babb JS, Lee VS, et al. Importance of small (≤20-mm) enhancing lesions seen only during the hepatic arterial phase at MR imaging of the cirrhotic liver: evaluation and comparison with whole explanted liver. Radiology 2005;237:938–944
211. Brancatelli G, Baron RL, Peterson MS, Marsh W. Helical CT screening for hepatocellular carcinoma in patients with cirrhosis: frequency and causes of false-positive interpretation. AJR Am J Roentgenol 2003;180:1007–1014
212. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917
213. Arii S, Yamaoka Y, Futagawa S, Inoue K, Kobayashi K, Kojiro M, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology 2000;32:1224–1229
214. Kim YK, Kwak HS, Kim CS, Chung GH, Han YM, Lee JM. Hepatocellular carcinoma in patients with chronic liver disease: comparison of SPIO-enhanced MR imaging and 16-detector row CT. Radiology 2006;238:531–541
215. Bhartia B, Ward J, Guthrie JA, Robinson PJ. Hepatocellular carcinoma in cirrhotic livers: double-contrast thin-section MR imaging with pathologic correlation of explanted tissue. AJR Am J Roentgenol 2003;180:577–584
216. Ward J, Guthrie JA, Scott DJ, Atchley J, Wilson D, Davies MH, et al. Hepatocellular carcinoma in the cirrhotic liver: double-contrast MR imaging for diagnosis. Radiology 2000;216:154–162
217. Yoo HJ, Lee JM, Lee MW, Kim SJ, Lee JY, Han JK. et al. Hepatocellular carcinoma in cirrhotic liver: double-contrast-enhanced, high-resolution 3.0T-MR imaging with pathologic correlation. Invest Radiol 2008;43:538–546
218. Mori K, Yoshioka H, Itai Y, Okamoto Y, Mori H, Takahashi N, et al. Arterioportal shunts in cirrhotic patients: evaluation of the difference between tumorous and nontumorous arterioportal shunts on MR imaging with superparamagnetic iron oxide. AJR Am J Roentgenol 2000;175:1659–1664
219. Choi SH, Lee JM, Yu NC, Suh KS, Jang JJ, Kim SH, et al. Hepatocellular carcinoma in liver transplantation candidates: detection with gadobenate dimeglumine-enhanced MRI. AJR Am J Roentgenol 2008;191:529–536
220. Sakamoto M, Hirohashi S, Shimosato Y. Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol 1991;22:172–178
221. Sakamoto M, Hirohashi S. Natural history and prognosis of adenomatous hyperplasia and early hepatocellular carcinoma: multi-institutional analysis of 53 nodules followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or percutaneous ethanol injection. Jpn J Clin Oncol 1998;28:604–608
222. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. Liver Transpl 2004; 10:S3–S8
223. Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, et al. Characterization of small nodules in cirrhosis by

assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 2005;42:27–34
224. Kudo M, Okanoue T. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. Oncology 2007;72(Suppl 1):2–15
225. Imai Y, Murakami T, Yoshida S, Nishikawa M, Ohsawa M, Tokunaga K, et al. Superparamagnetic iron oxide-enhanced magnetic resonance images of hepatocellular carcinoma: correlation with histological grading. Hepatology 2000;32:205–212
226. Lim JH, Choi D, Cho SK, Kim SH, Lee WJ, Lim HK, et al. Conspicuity of hepatocellular nodular lesions in cirrhotic livers at ferumoxides-enhanced MR imaging: importance of Kupffer cell number. Radiology 2001;220:669–676
227. Heiken JP, Weyman PJ, Lee JK, Balfe DM, Picus D, Brunt EM, et al. Detection of focal hepatic masses: prospective evaluation with CT, delayed CT, CT during arterial portography, and MR imaging. Radiology 1989;171:47–51
228. Kanematsu M, Hoshi H, Imaeda T, Murakami T, Inaba Y, Yokoyama R, et al. Detection and characterization of hepatic tumors: value of combined helical CT hepatic arteriography and CT during arterial portography. AJR Am J Roentgenol 1997; 168:1193–1198
229. Kanematsu M, Hoshi H, Murakami T, Inaba Y, Kim T, Yamada T, et al. Detection of hepatocellular carcinoma in patients with cirrhosis: MR imaging versus angiographically assisted helical CT. AJR Am J Roentgenol 1997;169:1507–1515
230. Choi D, Kim S, Lim J, Lee W, Jang H, Lee S, et al. Preoperative detection of hepatocellular carcinoma: ferumoxides-enhanced MR imaging versus combined helical CT during arterial portography and CT hepatic arteriography. AJR Am J Roentgenol 2001;176:475–482
231. Yoon KT, Kim JK, Kim do Y, Ahn SH, Lee JD, Yun M, et al. Role of ^{18}F-fluorodeoxyglucose positron emission tomography in detecting extrahepatic metastasis in pretreatment staging of hepatocellular carcinoma. Oncology 2007;72(Suppl 1):104–110
232. Yang SH, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, et al. The role of (18)F-FDG-PET imaging for the selection of liver transplantation candidates among hepatocellular carcinoma patients. Liver Transpl 2006;12:1655–1660
233. Shiomi S, Nishiguchi S, Ishizu H, Iwata Y, Sasaki N, Tamori A, et al. Usefulness of positron emission tomography with fluorine-18-fluorodeoxyglucose for predicting outcome in patients with hepatocellular carcinoma. Am J Gastroenterol 2001;96:1877–1880
234. Khan MA, Combs CS, Brunt EM, Lowe VJ, Wolverson MK, Solomon H, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. J Hepatol 2000; 32:792–797
235. Trojan J, Schroeder O, Raedle J, Baum RP, Herrmann G, Jacobi V, et al. Fluorine-18 FDG positron emission tomography for imaging of hepatocellular carcinoma. Am J Gastroenterol 1999;94:3314–3319
236. Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, et al. ^{18}F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. J Gastroenterol 2004;39:961–968
237. Tanimoto A, Wakabayashi G, Shinmoto H, Nakatsuka S, Okuda S, Kuribayashi S. Superparamagnetic iron oxide-enhanced MR imaging for focal hepatic lesions: a comparison with CT during arterioportography plus CT during hepatic arteriography. J Gastroenterol 2005;40:371–380
238. Kojiro M. Pathology of hepatocellular carcinoma. In Okuda K, Tabor E, editors. Liver Cancer. New York: Churchill Livingstone; 1997. p. 165–187
239. Tajima T, Honda H, Taguchi K, Asayama Y, Kuroiwa T, Yoshimitsu K, et al. Sequential hemodynamic change in hepatocellular carcinoma and dysplastic nodules: CT angiography and pathologic correlation. AJR Am J Roentgenol 2002; 178:885–897
240. Hayashi M, Matsui O, Ueda K, Kawamori Y, Gabata T, Kadoya M. Progression to hypervascular hepatocellular carcinoma: correlation with intranodular blood supply evaluated with CT during intraarterial injection of contrast material. Radiology 2002;225:143–149
241. Kudo M. Imaging diagnosis of hepatocellular carcinoma and premalignant/borderline lesions. Semin Liver Dis 1999; 19:297–309
242. Ding H, Kudo M, Onda H, Suetomi Y, Minami Y, Maekawa K. Contrast-enhanced subtraction harmonic sonography for evaluating treatment response in patients with hepatocellular carcinoma. AJR Am J Roentgenol 2001;176:661–666
243. Wen YL, Kudo M, Zheng RQ, Ding H, Zhou P, Minami Y, et al. Characterization of hepatic tumors: value of contrast-enhanced coded phase-inversion harmonic angio. AJR Am J Roentgenol 2004;182:1019–1026
244. Asahina Y, Izumi N, Uchihara M, Noguchi O, Ueda K, Inoue K, et al. Assessment of Kupffer cells by ferumoxides-enhanced MR imaging is beneficial for diagnosis of hepatocellular carcinoma: comparison of pathological diagnosis and perfusion patterns assessed by CT hepatic arteriography and CT arterioportography. Hepatol Res 2003;27:196–204
245. Akriviadis EA, Llovet JM, Efremidis SC, Shouval D, Canelo R, Ringe B, et al. Hepatocellular carcinoma. Br J Surg 1998;85: 1319–1331
246. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519–524
247. Regimbeau JM, Farges O, Shen BY, Sauvanet A, Belghiti J. Is surgery for large hepatocellular carcinoma justified? J Hepatol 1999;31:1062–1068
248. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J Am Coll Surg 2002;194:592–602
249. Ng KK, Vauthey JN, Pawlik TM, Lauwers GY, Regimbeau JM, Belghiti J, et al. Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. Ann Surg Oncol 2005;12:364–373
250. Pawlik TM, Poon RT, Abdalla EK, Ikai I, Nagorney DM, Belghiti J, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005;137:403–410
251. Liu CL, Fan ST, Lo CM, Ng IO, Poon RT, Wong J. Hepatic resection for bilobar hepatocellular carcinoma: is it justified? Arch Surg 2003;138:100–104
252. Choi D, Lim HK, Joh JW, Kim SJ, Kim MJ, Rhim H, et al. Combined hepatectomy and radiofrequency ablation for multifocal hepatocellular carcinomas: long-term follow-up results and prognostic factors. Ann Surg Oncol 2007;14:3510–3518
253. Torzilli G, Makuuchi M, Inoue K, Takayama T, Sakamoto Y, Sugawara Y, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. Arch Surg 1999; 134:984–992
254. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240:698–708 (discussion 708–710)
255. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008;12:842–851