Chapter 2   Diagnosis and Surveillance

Section 1   Surveillance

- **Introduction**

In Japan, approximately 80% patients with hepatocellular carcinoma (HCC) also suffer from chronic hepatitis B or C, and the majority of these patients develop the complication of cirrhosis. Although the number of patients without a background of viral hepatitis has increased in recent years, HCC is an extremely prominent cancer among high-risk group patients.

Ultrasound and tumor marker testing play a major role and are widely used in HCC surveillance of high-risk group patients at present. In order to demonstrate the efficacy of surveillance, it must be shown that early detection increases opportunities for the administration of curative therapy and contributes to an improvement in prognosis. However, currently, there is insufficient evidence to elucidate whether HCC prognosis is improved with surveillance using only ultrasound or ultrasound combined with tumor marker testing. Furthermore, randomized controlled trials (RCTs) are likely to be discontinued in the future, mostly because of ethical concerns. In actual clinical settings, if visualization is poor on ultrasound, the test interval can be shortened, testing can be combined with computed tomography (CT)/magnetic resonance imaging (MRI), or other measures can be adopted to decrease the risk of missing a finding. At present however, there is insufficient evidence to elucidate the recommended test interval for ultrasound and tumor marker testing and whether testing should be combined with CT/MRI.

Considering the fact that HCC surveillance has been widely adopted and that RCTs are currently difficult to implement, there is no choice but to recommend that the status quo be confirmed to a certain extent.

We first established "patients with risk factors for HCC" on the basis of the current state of affairs, following which we suggested appropriate surveillance methods and test intervals for HCC

according to currently available evidence.

CQ4　Who are eligible candidates for surveillance?

Recommendation

The risk factors for HCC include liver cirrhosis, chronic hepatitis C, chronic hepatitis B, male gender, older age, alcohol consumption, smoking, obesity, and diabetes mellitus. Of these risk factors, it is recommended that patients with chronic hepatitis C, chronic hepatitis B, or nonviral cirrhosis be screened at regular intervals for HCC **(Grade B)**.

- **Background**

HCC, a cancer with marked regional clustering, is mostly related to hepatitis B virus (HBV) and hepatitis C virus (HCV) and is largely influenced by environmental factors. Even in Japan, approximately 80% HCC patients suffer from chronic hepatitis B or C (L3H00004[1]). Aside from viral factors, the risk factors for hepatocarcinogenesis are believed to include male gender, older age, excessive alcohol consumption, smoking, aflatoxin exposure, obesity, and diabetes mellitus. Here, we examined these risk factors.

- **Scientific Statement**

On a global scale, persistent HBV infection is the most critical risk factor for hepatocarcinogenesis. HBV carriers have a 223-fold risk of developing cancer compared with noncarriers (LF07209[2] Level 2a). Among HBV carriers, HBe antigen-positive patients are at a higher risk of developing cancer compared with HBe antigen-negative patients (relative risk: 6.3-fold; LF03825[3] Level 2a, LF07199[4] Level 2a). Among type B patients with chronic liver disease, the risk is even higher for patients with cirrhosis.

A large-scale Taiwanese study revealed that the risk of carcinogenesis increases with HBV-DNA levels (L3H00041[5] Level 2a), and similar results have been reported in Japan (L3F06264[6] Level

3). Nevertheless, HBV-DNA levels greatly fluctuate with time; therefore, one must be aware of the fluctuation pattern. The risk of carcinogenesis is highest when HBV-DNA levels continually decrease and yet persist at an elevated level (L3F06572[7] Level 2a). Thus far, three articles on comprehensive risk assessment systems, including the use of HBV-DNA levels, have been published (L3F03428[8] Level 2a, L3F05803[9] Level 2a, L3F05804[10] Level 2a).

In addition to HBV infection, persistent HCV infection is one of the most critical risk factors for carcinogenesis. In particular, it is the leading cause of hepatocarcinogenesis in developed nations, including Japan (LF07202[11] Level 4). Cirrhosis characteristically develops before cancer in nearly all patients with a background of hepatitis C who develop cancer (LF03575[12] Level 2a, LF02404[13] Level 2b). The cancer incidence rate associated with type C cirrhosis differs among countries, but the annual rate is extremely high at 3%–8%. Known viral risk factors are elevated HCV-RNA levels and genotype 1 (L3F05805[14] Level 2a). On the basis of a cohort study on patients with advanced fibrosis who received long-term peginterferon therapy, it has been proposed that risk scores based on factors such as age, race, alkaline phosphatase levels, varices, and platelet counts should be included in a comprehensive risk assessment system (L3F05783[15] Level 2a).

Cirrhosis can be a risk factor for hepatocarcinogenesis, even in patients who are negative for both HBV and HCV. Carcinogenesis is observed in patients with Scheuer stage III or IV primary biliary cirrhosis (PBC), while it is extremely rare in stage I or II patients (LF03633[16] Level 2a, LF07167[17] Level 2a).

Statistical data from various countries clearly show that HCC is more common among men than among women, probably because of differences in hepatitis morbidity rate, differences in alcohol consumption, and the effects of androgens.

Despite the abundance of data suggesting that excessive alcohol consumption and alcoholic liver cirrhosis are risk factors for hepatocarcinogenesis, it remains to be determined whether these factors are dose-dependent or are associated with a threshold level (LF07207[18] Level 3,

LF07204[19] Level 3, LF07203[20] Level 3, LF07193[21] Level 3, LF07194[22] Level 3). In addition, alcohol intake increases the risk of hepatocarcinogenesis in patients with chronic hepatitis B or C accompanied by cirrhosis (L3F05773[23] Level 2a, L3F05761[24] Level 2a).

There are studies reporting both positive and negative findings on smoking as a risk factor for hepatocarcinogenesis. However, the results of meta-analysis have shown that smoking increases the risk of hepatocarcinogenesis (relative risk is 1.51-fold higher in smokers than in nonsmokers, L3H00042[25] Level 3).

Two large-scale studies were conducted to examine the relationship between obesity and HCC. The study conducted in Denmark reported that the risk for hepatocarcinogenesis was 1.9-fold higher in obese patients than in nonobese patients (LF12093[26] Level 3), and a prospective study conducted in the United States found that the risk of death from HCC among obese patients (BMI > 35 kg/m^2) was 4.52-fold higher in men and 1.68-fold higher in women (LF12094[27] Level 2a).

In Japan, a study treating decompensated cirrhosis patients with branched-chain amino acid (BCAA) agents was conducted to aim at an endpoint of improved prognosis, and subgroup analysis demonstrated that hepatocarcinogenesis was often observed in patients with a BMI of ≥25 kg/m^2 (LF12096[28] Level 2a).

The relationship between type 2 diabetes mellitus and HCC was examined in a large-scale cohort study conducted in Sweden, Denmark, and North America, and the results showed that the risk of developing liver cancer was 2–4-fold higher among patients with diabetes than among those without (LF12097[29] Level 2b, LF12098[30] Level 2b, LF12099[31] Level 2b). In Japan, Matsuo et al. conducted a case–control study in the Kyushu region with 225 patients, and diabetes was found to be independent of other risk factors such as age and gender (2.5-fold odds ratio; LF12100[32] Level 3).

Marrero et al. investigated the background factors of 105 patients with HCC in order to determine the relationship between nonalcoholic steatohepatitis (NASH) and HCC. The study revealed that HCV was the most common factor with an incidence of 51%, followed by cryptogenic cirrhosis at 29%; furthermore, NASH was present in 50% of these patients (LF12101[33] Level 2b). In Japan,

Hashimoto et al. followed 247 patients with nonalcoholic fatty liver disease (NAFLD) and demonstrated that HCC was present in 10 patients with cirrhosis. The 5-year cumulative cancer incidence among F3–F4 patients with advanced liver fibrosis was reported to be 20% (LF12102[34] Level 2b).

- **Explanation**

The risk factors for hepatocarcinogenesis are independent variables, and the incidence rate of HCC is believed to increase continuously with the number of risk factors. Although several models that comprehensively evaluate multiple risk factors for type B and C hepatitis patients have been proposed, none of these models has been thoroughly verified. A threshold annual rate of cancer incidence should also be set to determine the time of screening initiation. However, this is also a difficult task. Therefore, it was decided that HCC screening be conducted for patients with conventional type B and C chronic liver disease and various types of liver cirrhosis.

- **References**

1) L3H00004 Kudo M, Arii S, Ikai I, Omata M, Kojiro M, Sakamoto M, et al. Report of the 18th Follow-Up Survey of Primary Liver Cancer in Japan (2004–2005) (The Liver Cancer Center Study Group of Japan, follow-up investigation committee). Hepatology Research 2010;51(8):460-84.

2) LF07209 Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. Lancet 1981;2(8256):1129-33.

3) LF03825 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(25):1797-801.

4) LF07199 Fattovich G, Giustina G, Schalm SW, Hadziyannis S, Sanchez-Tapias J, Almasio P, et al. Occurrence of hepatocellular carcinoma and decompensation in western European patients with cirrhosis type B. The EUROHEP Study Group on Hepatitis B Virus and

Cirrhosis. Hepatology 1995;21(1):77-82.

5) L3H00041 Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al;REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295(1):65-73.

6) L3F06264 Ikeda K, Arase Y, Kobayashi M, Someya T, Saitoh S, Suzuki Y, et al. Consistently low hepatitis B virus DNA saves patients from hepatocellular carcinogenesis in HBV-related cirrhosis. A nested case-control study using 96 untreated patients. Intervirology 2003;46(2):96-104.

7) L3F06572 Chen CF, Lee WC, Yang HI, Chang HC, Jen CL, Iloeje UH, et al. Changes in serum levels of HBV DNA and alanine aminotransferase determine risk for hepatocellular carcinoma. Gastroenterology 2011;141(4):1240-8, 1248. e1-2.

8) L3F03428 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(1):80-8.

9) L3F05803 Wong VW, Chan SL, Mo F, Chan TC, Loong HH, Wong GL, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010;28(10):1660-5.

10) L3F05804 Yang HI, Sherman M, Su J, Chen PJ, Liaw YF, Iloeje UH, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010;28(14):2437-44.

11) LF07202 Liang TJ, Jeffers LJ, Reddy KR, De Medina M, Parker IT, Cheinquer H, et al. Viral pathogenesis of hepatocellular carcinoma in the United States. Hepatology 1993;18(6):1326-33.

12) LF03575 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(4):1173-7.

13) LF02404　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(2):463-72.

14) L3F05805　Lee MH, Yang HI, Lu SN, Jen CL, Yeh SH, Liu CJ, et al. Hepatitis C virus seromarkers and subsequent risk of hepatocellular carcinoma:long-term predictors from a community-based cohort study. J Clin Oncol 2010;28(30):4587-93.

15) L3F05783　Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, et al;HALT-C Trial Group. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009;136(1):138-48.

16) LF03633　Jones DE, Metcalf JV, Collier JD, Bassendine MF, James OF. Hepatocellular carcinoma in primary biliary cirrhosis and its impact on outcomes. Hepatology 1997;26(5):1138-42.

17) LF07167　Caballeria L, Pares A, Castells A, Gines A, Bru C, Rodes J. Hepatocellular carcinoma in primary biliary cirrhosis:similar incidence to that in hepatitis C virus-related cirrhosis. Am J Gastroenterol 2001;96(4):1160-3.

18) LF07207　Mayans MV, Calvet X, Bruix J, Bruguera M, Costa J, Esteve J, et al. Risk factors for hepatocellular carcinoma in Catalonia, Spain. Int J Cancer 1990;46(3):378-81.

19) LF07204　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(4):509-14.

20) LF07203　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(4):537-41.

21) LF07193　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(4):323-31.

22) LF07194   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(2):213-6.

23) L3F05773   Loomba R, Yang HI, Su J, Brenner D, Iloeje U, Chen CJ. Obesity and alcohol synergize to increase the risk of incident hepatocellular carcinoma in men. Clin Gastroenterol Hepatol 2010;8(10):891-8, 898. e1-2.

24) L3F05761   McDonald SA, Hutchinson SJ, Bird SM, Robertson C, Mills PR, Dillon JF, et al. A record-linkage study of the development of hepatocellular carcinoma in persons with hepatitis C infection in Scotland. Br J Cancer 2008;99(5):805-10.

25) L3H00042   Lee YC, Cohet C, Yang YC, Stayner L, Hashibe M, Straif K. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. Int J Epidemiol 2009;38(6):1497-511.

26) LF12093   Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk:a Danish record-linkage study. Eur J Cancer 1994;30A(3):344-50.

27) LF12094   Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.   S. adults. N Engl J Med 2003;348(17):1625-38.

28) LF12096   Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res 2006;35(3):204-14.

29) LF12097   Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, et al. Excess risk of primary liver cancer in patients with diabetes mellitus. J Natl Cancer Inst 1996;88(20):1472-7.

30) LF12098　Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89(18):1360-5.

31) LF12099　El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126(2):460-8.

32) LF12100　Matsuo M. Association between diabetes mellitus and hepatocellular carcinoma:results of a hospital- and community-based case-control study. Kurume Med J 2003;50(3-4):91-8.

33) LF12101　Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology 2002;36(6):1349-54.

34) LF12102　Hashimoto E, Yatsuji S, Kaneda H, Yoshioka Y, Taniai M, Tokushige K, et al. The characteristics and natural history of Japanese patients with nonalcoholic fatty liver disease. Hepatol Res 2005;33(2):72-6.

CQ5　Does surveillance improve prognosis?

Recommendation

Regular screening for HCC can lead to early detection and curative treatment and may improve prognosis **(Grade B).**

- **Scientific Statement**

The results of an RCT suggested that regular surveillance for HCC may improve prognosis (LF10625[1] Level 1). HBV-infected patients underwent regular surveillance every 6 months using alpha-fetoprotein (AFP) measurement and ultrasonography. More cancers were discovered at the small nodule stage in the screened patient group compared with those in the unscreened control

group, and significantly more patients were able to undergo liver resection. Consequently, the mortality rate was improved by 37%.

Although not an RCT, a prospective study limited to patients with cirrhosis (LF01982[2] Level 2a) showed that regular surveillance using ultrasound and AFP measurement extends survival time. Furthermore, retrospective studies that were corrected for lead time bias (LF10086[3] Level 2b, LF10849[4] Level 2b, LF10274[5] Level 2b, L3F04163[6] Level2b, LF12049[7] Level 2b, L3F06012[8] Level 2b) also demonstrated that regular surveillance increased survival time.

We then examined whether the early detection of HCC by surveillance increased patients' opportunities to receive curative therapy. Patients with chronic hepatitis who were diagnosed with HCC by regular surveillance using AFP measurement and ultrasonography were able to undergo curative therapies such as liver resection, percutaneous ablation, and transcatheter arterial chemoembolization (TACE) more often than those who did not undergo surveillance and were diagnosed with HCC on the basis of presented symptoms (LF03822[9] Level 3, LF10625[1] Level 1, LF10086[3] Level 2b, LF01982[2] Level 2a, LF12049[7] Level 2b, L3F06031[10] Level 2a, L3F06018[11] Level 2a). Nevertheless, it has also been reported that regular surveillance does not increase patients' opportunities to undergo liver resection (LF03905[12] Level 2a).

- **Explanation**

To truly demonstrate the clinical utility of HCC surveillance, detection must be possible in the early stages using regular screening, and early detection must facilitate the implementation of highly curative therapies, leading to improved prognosis. Only a few published studies satisfy these conditions for HCC surveillance; therefore, it is recommended that any conclusions be drawn carefully.

There are no reports that directly compare the effectiveness of surveillance between patients with chronic hepatitis and those with cirrhosis. In addition, no studies have directly compared the effectiveness of surveillance among subgroups with various risk factors such as chronic hepatitis B and C, gender, age, and the amount of alcohol intake. The subject of surveillance differs slightly

among reports; therefore, data should be interpreted with consideration for these differences. When the annual rate of hepatocarcinogenesis was considered, studies in which a large proportion of patients with cirrhosis were included showed high incidence rates of HCC, and such studies reported that regular screening of high-risk patients for HCC increased the detection rates for solitary, small nodules and resulted in appropriate curative treatment.

■ **References**

1) LF10625　Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130(7):417-22.

2) LF01982　Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma:a cost effectiveness analysis. Gut 2001;48(2):251-9.

3) LF10086　Trevisani F, Cantarini MC, Labate AM, De Notariis S, Rapaccini G, Farinati F, et al;Italian Liver Cancer(ITALICA)group. Surveillance for hepatocellular carcinoma in elderly Italian patients with cirrhosis:effects on cancer staging and patient survival. Am J Gastroenterol 2004;99(8):1470-6.

4) LF10849　Tanaka H, Nouso K, Kobashi H, Kobayashi Y, Nakamura S, Miyake Y, et al. Surveillance of hepatocellular carcinoma in patients with hepatitis C virus infection may improve patient survival. Liver Int 2006;26(5):543-51.

5) LF10274　Yu EW, Chie WC, Chen TH. Does screening or surveillance for primary hepatocellular carcinoma with ultrasonography improve the prognosis of patients? Cancer J 2004;10(5):317-25.

6) L3F04163　Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al;Italian Liver Cancer(ITA. LI. CA)Group. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53(2):291-7.

7) LF12049　Wong GL, Wong VW, Tan GM, Ip KI, Lai WK, Li YW, et al. Surveillance

programme for hepatocellular carcinoma improves the survival of patients with chronic viral hepatitis. Liver Int 2008;28(1):79-87.

8)   L3F06012   Tong MJ, Sun HE, Hsien C, Lu DS. Surveillance for hepatocellular carcinoma improves survival in Asian-American patients with hepatitis B:results from a community-based clinic. Dig Dis Sci 2010;55(3):826-35.

9)   LF03822   Tang ZY, Yu YQ, Zhou XD, Yang BH, Ma ZC, Lin ZY. Subclinical hepatocellular carcinoma:an analysis of 391 patients. J Surg Oncol Suppl 1993;3:55-8.

10)   L3F06031   Chang KC, Lu SN, Chen PF, Hung CH, Kee KM, Yen YH, et al. Incidence and associated risk factors of hepatocellular carcinoma in a dural hepatitis B and C virus endemic area:a surveillance study. Kaohsiung J Med Sci 2011;27(3):85-90.

11)   L3F06018   Gannon CJ, Izzo F, Aloia TA, Pignata S, Nasti G, Vallone P, et al. Can hepatocellular cancer screening increase the proportion of long-term survivors? Hepatogastroenterology 2009;56(93):1152-6.

12)   LF03905   Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med 1991;325(10):675-80.

CQ6   What methods are used in surveillance?

Recommendation

HCC screening should primarily include ultrasound examination with tumor marker testing, and dynamic CT or dynamic MRI can be concurrently used for extremely high-risk patients such as those with cirrhosis **(Grade B)**.

Regular screening every 3–6 months, primarily using ultrasound examination and tumor marker testing in combination with dynamic CT or dynamic MRI, increases HCC detectability at the solitary, small nodular stage **(Grade B)**.

- **Scientific Statement**

Ultrasound is more sensitive than AFP measurement for detecting HCC during screening (cirrhosis patients: LF01982[1] Level 2a, LF02689[2] Level 2a; HBV carriers: LF03727[3] Level 2a). However, there were no obvious differences in specificity (LF02689[2] Level 2a, LF03727[3] Level 2a). There was also no significant difference in detection sensitivity between surveillance using ultrasound alone or that using ultrasound with AFP measurement (LF03727[3] Level 2a, L3F04180[4] Level 2b). A study conducted in patients with cirrhosis, however, showed that HCC is detected more frequently with ultrasound and AFP measurement combined than with ultrasound alone (LF02689[2] Level 2a).

The sensitivity and specificity of diagnostic ultrasound for HCC screening of patients with chronic hepatitis or cirrhosis are reported to be 78%–90% and 93%–93.8%, respectively (LF02689[2] Level 2a, LF03727[3] Level 2a, LF03069[5] Level 4). HCC lesions that cannot be detected on ultrasound are often present in blind spots such as the subphrenic space or are found in patients with coarse liver parenchyma (LJ03471[6] Level 1). Studies on explanted livers from liver transplant donors have shown that the detection sensitivity of ultrasound for HCC nodules is low at 20.5%–46% (LF01867[7] Level 2b, L3F03204[8] Level 1) and that nodules measuring ≤2 cm are particularly difficult to detect (LF01867[7] Level 2b, L3F03204[8] Level 1, LF12032[9] Level 1). In studies examining nodules measuring ≤2 cm, some reports claimed that ultrasound is superior to MRI or CT in detecting the nodules (LF02231[10] Level 1); however, the majority of reports have determined that the detection sensitivity of CT and MRI is superior (L3F03204[8] Level 1, LF12032[9] Level 1).

The first RCT investigating differences in HCC detection rate due to differences in screening intervals was presented in 2011. Ultrasound was performed at 3- or 6-month intervals, and the detection rate for HCC was compared between the two groups; no significant difference was found between groups (L3F06591[11] Level 1). In addition, a newly published meta-analysis of

surveillance using ultrasound concluded that ultrasound performed at 6-month intervals was able to detect early-stage HCC at a significantly higher rate compared with that performed at 12-month intervals (L3F04180[4]) Level 2b). In addition, a retrospective study conducted after correction for lead time bias (L3F04163[12]) Level 2b) showed that ultrasound examination at 6-month intervals detected HCC significantly earlier than that at 12-month intervals, thereby increasing opportunities to administer curative therapies and extend survival time.

- **Explanation**

There are no reports indicating that HCC surveillance using ultrasound combined with tumor marker testing is superior to the independent performance of each test. At the very least, screening with both tests improves sensitivity. Therefore, they are widely used in combination at present as screening procedures in Japan, even though there is no clear evidence if the combination contributes to an improvement in diagnostic performance.

Regular screening every 3–6 months using ultrasound and tumor marker testing increases HCC detectability at the single nodule stage. Therefore, a screening interval of 3–6 months is recommended in this revised edition. The first RCT to examine differences in HCC detection rate according to different screening intervals (L3F06591[11]) Level 1) did not show a significant difference in HCC diagnosis between the 3- and 6-month interval groups. However, HCC was diagnosed on the basis of EASL diagnostic criteria 2001. Therefore, the definitive diagnosis of HCC using only diagnostic imaging without biopsy-proven diagnosis was limited to tumors measuring ≥2 cm in diameter. In this study, the detectability of small nodules in the liver was superior in the 3-month interval group than in the 6-month interval group; however, because a definitive diagnosis of HCC could not be obtained using EASL diagnostic criteria 2001, it is possible that there was no significant difference in detectability between the 3- and 6-month interval groups.

During diagnostic imaging, blind spots can be present on ultrasound, and tumor detectability is less than adequate in patients with cirrhosis and a coarse echo pattern in the surrounding liver

parenchyma, particularly for tumors measuring ≤2 cm. Therefore, it is expected that the combined use of ultrasound and imaging tests such as CT or MRI may enhance the detectability of HCC. In fact, however, CT or MRI is often not considered for HCC surveillance, and no studies have investigated the intervals at which concomitant CT or MRI should be conducted to improve detection sensitivity, treatment opportunities, or survival rate. Although it remains to be determined whether the combined use of CT or MRI with ultrasound truely cost-effective, it can be expected to increase cancer detectability at the single and small nodule level in extremely high-risk groups.

- **References**

1) LF01982　Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma:a cost effectiveness analysis. Gut 2001;48(2):251-9.

2) LF02689　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(1):65-71.

3) LF03727　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(2):432-8.

4) L3F04180　Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis:surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30(1):37-47.

5) LF03069　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(1):47-51.

6) LJ03471　Saito S, Ikeda K, Koida I, Tsubota A, Arase K, Chayama K, et al. Diagnostic ability and its limitation of abdominal ultrasound and CT as tools for surveillance for

hepatocellular carcinoma. Shokakika (Japanese) ((1992;17(6):505-10.

7) LF01867 Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis:correlation of pretransplantation sonography and liver explant pathology in 200 patients. AJR Am J Roentgenol 2002;179(1):75-80.

8) L3F03204 Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW, et al. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9(2):161-7.

9) LF12032 Snowberger N, Chinnakotla S, Lepe RM, Peattie J, Goldstein R, Klintmalm GB, et al. Alpha fetoprotein, ultrasound, computerized tomography and magnetic resonance imaging for detection of hepatocellular carcinoma in patients with advanced cirrhosis. Aliment Pharmacol Ther 2007;26(9):1187-94.

10) LF02231 Horigome H, Nomura T, Saso K, Itoh M, Joh T, Ohara H. Limitations of imaging diagnosis for small hepatocellular carcinoma:comparison with histological findings. J Gastroenterol Hepatol 1999;14(6):559-65.

11) L3F06591 Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al;Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire(GRETCH). Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis:a randomized trial comparing 3- and 6-month periodicities. Hepatology(Baltimore, Md)2011;54(6):1987-97.

12) L3F04163 Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al;Italian Liver Cancer(ITA. LI. CA)Group. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53(2):291-7.

CQ7   What size (cm) of atypical liver nodules using dynamic CT or dynamic MRI should be further examined?

Recommendation

It is recommended that the lesions visualized as high-attenuation areas in the arterial phase and measuring ≥1 cm be examined carefully **(Grade B)**.

- **Background**

There is no evidence that early-stage diagnosis of HCC without typical imaging findings increases the overall survival rate. On the other hand, there is evidence that local curability increases with decreasing tumor size when percutaneous ablation is considered for therapy. In general, the smaller the nodule diameter, the lower the chances are of tumor malignancy; therefore, lowering the criteria for further testing decreases cost-effectiveness. Therefore, we examined whether there was an efficient threshold level.

- **Scientific Statement**

Byrnes et al. studied 161 nodular lesions measuring <2 cm in size in patients with cirrhosis, which showed hyperhenhancement in the arterial phase of MR imaging and were invisible in the portal venous/equilibrium phases. Then, it was determined whether tumors were benign or malignant on the basis of pathological or follow-up observations. The results showed that 16 nodules (10%) were HCCs, while the others were benign. Only one nodule out of 111 (0.6%) HCC nodules measured <1 cm, while 15 of 50 (30%) measured ≥1 cm (L3F02850[1] Level 1).

Haradome et al. compared images of 60 nodules measuring ≤3 cm in diameter obtained by triple-phase dynamic CT and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI in 52 HCC patients. The areas under the receiver operating characteristic (ROC) curve (AUROC) for both procedures were equal. However, the detectability of lesions measuring ≤1.5 cm using Gd-EOB-DTPA-enhanced MRI was significantly better than

that with CT. There were 14 out of 60 nodules that were determined to be false-negative on dynamic CT and visualized as high-attenuation areas in the arterial phase. However, the majority of nodules were found to be those without washout in the portal venous/equilibrium phases; the primary image reader found 11 such lesions, while a second reader found 10 such lesions. Of these nodules, three were detected by both the primary and secondary readers as low-signal intensity areas in the hepatobiliary phase using Gd-EOB-DTPA-enhanced MRI. This indicated that hypervascular HCC without washout in the portal venous/equilibrium phases can be diagnosed on the basis of Gd-EOB-DTPA-enhanced MRI (L3F03263[2] Level 1).

- **Explanation**

Typical findings of HCC on dynamic CT/MRI include nodules that are visualized as hyperattenuating areas in the arterial phase and hypoattenuating areas in the portal venous/equilibrium phases compared with the surrounding liver parenchyma. Nodules that do not exhibit typical findings are visualized as hyperattenuating areas in the arterial phase. However, they can appear as hyperattenuating or isoattanuating areas in the portal venous/equilibrium phases compared with the surrounding parenchyma. They may also appear as isoattanuating or hypoattenuating areas in the arterial phase or as isodense or hypoattenuating areas in the portal venous/equilibrium phases. In the former case, diagnosis must be differentiated from arterioportal (AP) shunt, focal nodular hyperplasia (FNH), and cavernous hemangioma of the liver, while in the latter case, differentiation between regenerative nodules, dysplastic nodules, and early-stage HCC may be problematic. If the tumor diameter is small, washout in the portal venous/equilibrium phase is often unclear, even in cases of hypervascular HCC. Because the biological malignancy of hypervascular nodules is thought to resemble typical HCC findings, early-stage diagnosis may be beneficial. On the other hand, if early-stage HCC is hypovascular, the degree of biological malignancy is presumably lower than that of hypervascular HCC, and the benefits of early-stage diagnosis become less clear.

- **References**

1) L3F02850　Byrnes V, Shi H, Kiryu S, Rofsky NM, Afdhal NH. The clinical outcome of small (<20 mm) arterially enhancing nodules on MRI in the cirrhotic liver. Am J Gastroenterol 2007;102(8):1654-9.

2) L3F03263　Haradome H, Grazioli L, Tinti R, Morone M, Motosugi U, Sano K, et al. Additional value of gadoxetic acid-DTPA-enhanced hepatobiliary phase MR imaging in the diagnosis of early-stage hepatocellular carcinoma:comparison with dynamic triple-phase multidetector CT imaging. J Magn Reson Imaging 2011;34(1):69-78.

Section 2　Tumor Markers

- **Introduction**

Tumor markers can be utilized for three major purposes: diagnosis, surveillance, and indication of treatment outcome. In the past, when the majority of cases were those of advanced cancer, AFP was used for the definitive diagnosis of HCC. Because of advancements in imaging diagnostics represented by the development of dynamic CT, the value of low-specificity AFP testing has diminished. On the other hand, DCP and AFP lectin fraction (AFP-L3%) are both highly specific (approximately 95%) and have come to be used broadly in Japan.

In surveillance, tumor markers are used to complement imaging tests. For instance, if tumor marker levels exceed a certain threshold value during surveillance, yet no lesion is detected by abdominal ultrasound, it has to be determined whether or not a more sensitive test such as dynamic CT should be performed. Tumor markers used to make such determinations should have a high positive likelihood ratio (the ratio that will increase post-test probability if positive).

The absolute value of a tumor marker can be thought as a substitute for the total tumor mass in the liver or the entire body. An objective evaluation of the volume-reducing effect of treatment is

possible with pre- and post-treatment tumor marker measurements, and such measurements are considered to be useful especially when used with transcatheter arterial chemoembolization (TACE). In addition, highly specific tumor markers can be used to determine the effectiveness of curative therapies such as hepatectomy and/or local therapies on the basis of the extent of tumor marker negativity. In Japan, measurement of these three tumor markers is covered by the National Health Insurance, but this is not true in all other countries. Many contributions to the scientific literature have been made by Japanese researchers in this area, and the majority of evidence has been generated in Japan.

CQ8   Is it useful to measure two or more tumor markers for diagnosing HCC?

Recommendation
It is recommended to measure two or more tumor markers when diagnosing HCC **(Grade A)**.

- **Background**

In Japan, measurement of the following three tumor markers for HCC is covered by the National Health Insurance: AFP, DCP, and AFP-L3%.

For diagnostic purposes, tumor marker measurements are used to obtain a definitive diagnosis or as the trigger for the next process during surveillance. Because of current developments in imaging diagnostics, tumor marker testing for HCC is not a requirement for definitive diagnosis. On the other hand, if a certain threshold level is exceeded during surveillance, it is important to determine how the post-test probability changes; therefore, it is recommended that the positive likelihood ratio [=sensitivity/(1 − specificity)] be used as an indicator.

- **Scientific Statement**

A systematic review was conducted using 17 research studies that examined HCC lesions measuring ≤5 cm in terms of sensitivity, specificity, the diagnostic odds ratio, and the positive

likelihood ratio. At a cut-off level of 20 ng/mL, the AFP sensitivity and specificity were 49%–71% and 49%–86%, respectively, while at a cut-off level of 200 ng/mL, they were 8%–32% and 76%–100%, respectively. The integrated diagnostic odds ratios were 4.06 and 6.99, respectively, and the positive likelihood ratios were 2.45 and 5.85, respectively. At a cut-off level of 40 mAU/mL, the DCP sensitivity and specificity were 15%–54% and 95%–99%, respectively, while at a cut-off level of 100 mAU/mL, they were 7%–56% and 72%–100%, respectively. The integrated diagnostic odds ratios were 21.31 and 6.70, respectively, and the positive likelihood ratios were 12.60 and 4.91, respectively. The AFP-L3 fraction sensitivity and specificity at a cut-off level of 10% were 22%–33% and 93%–99%, respectively, while at a cut-off level of 15%, they were 21%–49% and 94%–100%, respectively. The integrated diagnostic odds ratios were 6.43 and 10.50 each, and the positive likelihood ratios were 4.89 and 13.10.

The diagnostic odds ratio was 6.29–59.81 when two tumor markers were used in combination, which was higher than that when only one tumor marker was used (L3H00040[1] Level 1). Studies conducted after the abovementioned systematic review include a cohort study conducted in 372 patients with type C cirrhosis. During 2 years of follow-up observation in the study, HCC was observed in 34 patients. The sensitivity of AFP alone was 61% at a cut-off level of 20 ng/mL. However, in combination with AFP-L3% (cut-off level, 10%) and DCP (cut-off level, 7.5 ng/mL), this sensitivity increased to 77% (L3F05772[2] Level 1). In a study of chronic hepatitis B examining a group of 106 patients with HCC and a control group, cut-off values were set at 20 ng/mL for AFP and 40 mAU/mL forDCP, and the sensitivity was found to be 57.5% and 51.9%, respectively. However, combining the two increased the sensitivity up to 78.3%. Specificity, however, decreased from 88% for AFP and 97% forDCP to ≤85% (L3F05836[3] Level 1). Measurement of two types of tumor markers for small HCC lesions minimizes any loss in specificity and enhances test sensitivity.

- **References**

1)   L3H00040   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(1):17-30.

2) L3F05772 Sterling RK, Jeffers L, Gordon F, Venook AP, Reddy KR, Satomura S, et al. Utility of Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein and des-gamma-carboxy prothrombin, alone or in combination, as biomarkers for hepatocellular carcinoma. Clin Gastroenterol Hepatol 2009;7(1):104-13.

3) L3F05836 Yoon YJ, Han KH, Kim do Y. Role of serum prothrombin induced by vitamin K absence or antagonist-II in the early detection of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. Scand J Gastroenterol 2009;44(7):861-6.

CQ9　Is tumor marker measurement an effective post-treatment indicator for HCC?

Recommendation

Measurement of post-treatment tumor marker levels in patients with elevated tumor marker levels before treatment is an effective indicator of treatment outcome **(Grade B)**.

- **Background**

In cases of liver transplantation and hepatectomy, pathological evaluation can confirm complete tumor removal, while imaging techniques can determine the treatment outcomes of percutaneous ablation, TACE, and systemic chemotherapy, including that with molecular target drugs. Imaging techniques are also used to evaluate the presence of residual cancer outside the liver or beyond the range of resection after liver transplantation or hepatectomy. Determination of treatment outcome using imaging techniques can be occasionally difficult because of changes associated with treatment (AP shunt, lipiodol deposits, etc.). We investigated whether treatment outcomes determined on the basis of tumor marker testing complemented those determined using imaging techniques.

- **Scientific Statement**

In a study conducted for 416 patients treated with curative radiofrequency ablation (RFA, 70.7%), of the three types of markers, AFP, DCP, and AFP-L3%, elevated levels of post-treatment AFP and AFP-L3% (>100 ng/mL and >15%, respectively) were independent predictors of recurrence (LF11906[1] Level 2a). In a study of 54 patients treated with RFA (72 treatments), a decrease in AFP levels to less than the AFP half-life of 7 days served as a predictive indicator of relapse-free survival that was independent of treatment outcome evaluation by diagnostic imaging (L3F01434[2] Level 2a).

In a study of 125 patients who were treated with TACE or radioembolization therapy, a ≥50% decrease in AFP levels was a regulatory factor of overall survival independent of outcomes determined by imaging tests (L3F05802[3] Level 2a).

A study of 117 patients treated with systemic chemotherapy demonstrated that AFP responders, defined as patients who experienced an AFP reduction of ≥20%, showed a favorable prognosis, even though imaging techniques indicated stable disease (L3F01434[2] Level 2a). In a similar study that examined 107 patients treated with systemic chemotherapy or molecular targeted therapy, an AFP reduction of ≥50% was associated with a favorable prognosis (L3F00629[4] Level 2b).

- **Explanation**

The key words "liver tumor" and "tumor markers" were used in a search of the literature, and four cohort studies that examined pre- and post-treatment tumor marker levels were adopted.

- **References**

1) LF11906　Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, et al. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. Hepatology 2006;44(6):1518-27.

2) L3F01434　Tsai MC, Wang JH, Hung CH, Kee KM, Yen YH, Lee CM, et al. Favorable alpha-fetoprotein decrease as a prognostic surrogate in patients with hepatocellular carcinoma after radiofrequency ablation. J　Gastroenterol Hepatol 2010;25(3):605-12.

3) L3F05802   Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma:oncologic marker of radiologic response, progression, and survival. J Clin Oncol 2009;27(34):5734-42.

4) L3F00629   Vora SR, Zheng H, Stadler ZK, Fuchs CS, Zhu AX. Serum alpha-fetoprotein response as a surrogate for clinical outcome in patients receiving systemic therapy for advanced hepatocellular carcinoma. Oncologist 2009;14(7):717-25.

Section 3   Diagnostic Imaging

- **Introduction**

Diagnostic imaging is an extremely valuable tool for the diagnosis of HCC, and the majority of HCC cases can be definitively diagnosed using only diagnostic imaging.

Imaging tools used to diagnose HCC include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), angiography, and nuclear medicine imaging. Furthermore, each of these tests has their own characteristic features, and one test method can generate a large amount of variation in image quality, depending on imaging parameters such as contrast agent use, type and amount of contrast agent used, injection speed, timing of image acquisition, and slice thickness. These differences result in major differences in the diagnostic performance of HCC. When setting up the conditions for image acquisition, differences in device performance can also have a major influence.

The performance of diagnostic imaging equipment has advanced rapidly in recent years. In addition, advancements have been made in ultrasound image construction, such as Doppler and harmonic imaging, together with rapid progress in the application of contrast agents and three-dimensional (3D) data. CT imagery has advanced with the development of continuously

rotating CT (helical or spiral CT), multi-detector row CT (MDCT), and area-detector CT that can scan the entire liver in <1 s. Scan speed and spatial resolution have dramatically improved; furthermore, new applications of contrast medium by changing the X-ray tube voltage are emerging. There have been dramatic improvements in MRI equipment in addition to contrast-enhanced dynamic testing (dynamic study) using rapid MRI with parallel imaging. Density resolution and temporal resolution have also improved because of advancements in the clinical application of hepatocyte-specific contrast agents such as Gd-EOB-DTPA and diffusion-weighted imaging. In terms of angiography, techniques using digital subtraction angiography (DSA) have further increased performance levels, and new possibilities have emerged with the development of CT-like imaging and 3D images generated by rotating flat-panel detectors. In the field of nuclear medicine, tests using fluorodeoxyglucose positron emission tomography (FDG-PET) have come to play an important role in the detection and staging of malignant tumors. Combined PET and CT scanning, in particular, is increasingly viewed as being useful.

The environment surrounding diagnostic imaging has grown increasingly diverse and complicated with the rapid advancements in diagnostic imaging equipment. In this environment, we have investigated methods to effectively and accurately use diagnostic imaging. Studies related to diagnostic imaging for HCC were selected from scientific research articles published between the year of publication of the previous edition and 2011. An abstract for each high-quality article was prepared, and suggestions on how to proceed with diagnostic imaging were made on the basis of such abstracts.

CO10　What are the best tests for diagnosing early-stage HCC in patients with cirrhosis?

Recommendation

Gd-EOB-DTPA-enhanced MRI is a very accurate diagnostic tool for the detection of early-stage

HCC in patients with cirrhosis **(Grade B)**.

- **Scientific Statement**

When AFP levels gradually increase in patients with cirrhosis and a nodule/s is/are detected on ultrasound, HCC is suspected (LF10483[1] Level 3). When cirrhosis is the underlying disease, however, the sensitivity of noncontrast-enhanced ultrasound is low for differentiating hypovascular well-differentiated HCC from dysplastic nodules (LF01867[2] Level 1). Contrast-enhanced ultrasound may be implemented for screening purposes after noncontrast-enhanced ultrasound, which facilitates the procurement of real-time images and evaluation of microangiogenesis (L3F03763[3] Level 1). Dense staining in the arterial phase and washout during the portal venous/equilibrium phases are critical findings of HCC on CT and MRI using extracellular contrast agents. The sensitivity of blood flow detection in the arterial phase is higher with dynamic CT or contrast-enhanced ultrasound (LF10026[4] Level 1). However, intranodular blood flow is detected with greater sensitivity when contrast-enhanced ultrasound and dynamic CT are used together than when these modalities are used alone (L3F03080[5] Level 1). Nevertheless, the detection of small HCC during the equilibrium phase on dynamic CT is also important (L3F030376) Level 1). MRI is fundamentally an imaging technique with high tissue contrast, and despite the fact that the high tumor-to-liver contrast can be achieved with noncontrast-enhanced testing, qualitative diagnosis of liver tumors is limited. Qualitative diagnosis of the hepatic tumor is therefore required on the basis of blood flow data obtained with extracellular contrast agents and hepatocyte-specific contrast agents as well as information regarding Kupffer cell function and hepatocyte function. It has been reported that dynamic MRI using extracellular contrast agents is not very sensitive for detecting HCC lesions measuring <2 cm (LF06200[7] Level 1). On the other hand, although enhancement patterns observed on superparamagnetic iron oxide (SPIO)-enhanced MRI are useful for differentiating dysplastic nodules from HCC, it is difficult to differentiate between dysplastic nodules and hypovascular

well-differentiated HCC lesions in some cases (L3F03063[8] Level 1). The drawback of performing only SPIO-enhanced MRI is that tumor blood flow data cannot be obtained. However, double-contrast MRI (DC-MRI), which concurrently uses an extracellular contrast agent in dynamic MRI to obtain blood flow data, can be used. Nevertheless, Gd-EOB-DTPA-enhanced MRI is believed to be more beneficial for HCC detection (L3F02968[9] Level 1). Gd-EOB-DTPA-enhanced MRI is an excellent diagnostic tool for diagnosing HCC (L3F02879[10] Level 1) and is superior in detecting HCC compared with dynamic CT (L3F02939[11] Level 1). ROC analysis was performed to evaluate the diagnostic performances of dynamic CT and Gd-EOB-DTPA-enhanced MRI against 30 nodules that were histologically diagnosed as early-stage HCC in patients with cirrhosis. The results revealed that Az values, sensitivity, and negative predictive values for Gd-EOB-DTPA-enhanced MRI (0.98–0.99, 94%–97%, and 96.8%–98.1%, respectively) were significantly higher than those for dynamic CT (0.87, 58%–68%, and 80.7%–84.4%, respectively; L3F03380[12] Level 1).

In addition, definitive diagnosis cannot be made for small, hypovascular lesions that appear as low-signal intensity areas during the hepatobiliary phase on Gd-EOB-DTPA-enhanced MRI. However, a portion of these lesions occasionally develop into hypervascular HCC lesions (L3F02989[13] Level 4, L3F02995[14] Level 1, L3F02977[15] Level 3). If the diameter of the hypovascular nodule is ≥1 cm and/or contains fat, the risk of hypervascularization is high (L3F03043[16] Level 3). At present, only one study has used Gd-EOB-DTPA-enhanced MRI in patients who underwent hepatectomy to differentiate histologically identified early-stage HCC lesions from dysplastic nodules, and it demonstrated the extremely high differentiation capability of this modality (L3F03380[12] Level 1). On the basis of the above findings, Gd-EOB-DTPA-enhanced MRI can detect HCC (particularly in the early stages) and hypovascular lesions at a high risk of hypervascularization with great sensitivity. This techqniue is also more sensitive in detecting HCC compared with dynamic CT, and it may be able to differentiate between dysplastic nodules and early-stage HCC lesions. It is therefore a highly

capable diagnostic tool for detecting early-stage HCC in patients with cirrhosis.

▪ **Explanation**

To demonstrate the efficacy of surveillance for HCC, early-stage HCC must be discovered during regular screening. Consequently, it is necessary that more highly curative therapies be implemented and prognosis be improved. In general, early-stage HCC is often recognized initially as a nodular, hypovascular, well-differentiated HCC measuring ≤2 cm with unclear borders. Histologically, interstitial infiltration is considered to be critical. However, as of this time, only one study using Gd-EOB-DTPA-enahced MRI histologically verified early-stage HCC. Furthermore, the concepts of early-stage HCC imaging have yet to be unified; therefore, comparison of different studies is difficult.

Imaging techniques such as ultrasound, CT, and MRI are normally used for HCC screening. If nodules are detected by ultrasound, intranodular blood flow can be evaluated by dynamic CT/MRI. This utilizes the differences generated in arterial blood flow and portal venous blood flow between the liver nodule and surrounding liver parenchyma because of the multistage development of HCC. However, high-grade dysplastic nodules either exhibit a heterogeneous increase in hepatocyte density that is at least double that of the surrounding liver tissue or posess a slightly atypical structure. There is some overlap in the diagnosis of early-stage HCC and dysplastic nodules according to intranodular blood flow evaluation, and the ability to differentiate the two using diagnostic imaging is limited.

In these circumstances, a hepatocyte-specific contrast agent that is incorporated into hepatocytes (Gd-EOB-DTPA contrast agent) was approved for clinical use in January 2008. Blood flow data from the arterial and portal venous phases can be obtained using Gd-EOB-DTPA-enhanced MRI as a dynamic test, which is similar to testing with extracellular contrast agents. Images acquired 10–20 min after contrast agent injection, a period known as the hepatobiliary (enhanced) phase, are useful for HCC detection, including early-stage HCC detection, because such images are created on the basis of differences in contrast enhancement due to differences in hepatocyte

function. However, if patients with cirrhosis who develop marked changes in the liver parenchyma (reduced hepatocyte function), parenchymal contrast enhancement can be insufficient, leading to poor detection of HCC (false negative result). Therefore, caution is required. Because MRI has poor throughput compared with CT (longer test duration), there are limits to testing large numbers of patients with Gd-EOB-DTPA-enhanced MRI as part of an HCC screening program. On the other hand, contrast-enhanced ultrasound (Sonazoid[®] and Levovist[®]) is an imaging test that can simultaneously evaluate Kupffer cell function and blood flow in hepatic nodules. Contrast-enhanced ultrasound can be used to evaluate vascular phase (arterial phase) hemodynamics in hepatic nodules and the degree of contrast uptake during the post-vascular phase (Kupffer phase). This method is useful because of the sensitivity of blood flow evaluation and real-time determination of Kupffer cell function. However, performing the test can be complicated; therefore, a proficient operator is required. For this reason, there are a limited number of institutions that can currently conduct this test.

Therefore, effective diagnosis of early-stage HCC involves the following steps in sequence: 1) hemodynamic evaluation of hepatic nodules using conventional dynamic CT/MRI to detect early-stage HCC, 2) identifying the patient group, and evaluation of hepatocyte function in hepatic nodules using Gd-EOB-DTPA-enhanced MRI. Contrast ultrasound can be an option for diagnosis; however, a consensus regarding its effectiveness in early-stage HCC detection has not been reached till date.

- **References**

1) LF10483　He YM, Wang XY, Gao SD, Yu LY, Lin XD, Lin LW. Ultrasound-guided fine needle biopsy of intrahepatic nodules and low elevation of AFP in early diagnosis of hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2005;4(1):50-4.

2) LF01867　Bennett GL, Krinsky GA, Abitbol RJ, Kim SY, Theise ND, Teperman LW. Sonographic detection of hepatocellular carcinoma and dysplastic nodules in cirrhosis:correlation of pretransplantation sonography and liver explant pathology in 200

patients. AJR Am J Roentgenol 2002;179(1):75-80.

3) L3F03763　Isozaki T, Numata K, Kiba T, Hara K, Morimoto M, Sakaguchi T, et al. Differential diagnosis of hepatic tumors by using contrast enhancement patterns at US. Radiology 2003;229(3):798–805.

4) LF10026　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(4):1007-14.

5) L3F03080　Quaia E, Alaimo V, Baratella E, Medeot A, Midiri M, Cova MA. The added diagnostic value of 64-row multidetector CT combined with contrast-enhanced US in the evaluation of hepatocellular nodule vascularity:implications in the diagnosis of malignancy in patients with liver cirrhosis. Eur Radiol 2009;19(3):651-63.

6) L3F03037　Monzawa S, Ichikawa T, Nakajima H, Kitanaka Y, Omata K, Araki T. Dynamic CT for detecting small hepatocellular carcinoma:usefulness of delayed phase imaging. AJR Am J Roentgenol 2007;188(1):147-53.

7) LF06200　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(2):445-54.

8) L3F03063　Park HS, Lee JM, Kim SH, Chang S, Kim SJ, Han JK, et al. Differentiation of well-differentiated hepatocellular carcinomas from other hepatocellular nodules in cirrhotic liver:value of SPIO-enhanced MR imaging at 3.0 Tesla. J Magn Reson Imaging 2009;29(2):328-35.

9) L3F02968　Kim YK, Kim CS, Han YM, Park G. Detection of small hepatocellular carcinoma:can gadoxetic acid-enhanced magnetic resonance imaging replace combining gadopentetate dimeglumine-enhanced and superparamagnetic iron oxide-enhanced magnetic resonance imaging? Invest Radiol 2010;45(11):740-6.

10) L3F02879　Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al.

Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 2010;256(3):806-16.

11) L3F02939 Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, et al. Detection and characterization of focal liver lesions:a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol 2010;45(3):133-41.

12) L3F03380 Sano K, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, et al. Imaging study of early hepatocellular carcinoma:usefulness of gadoxetic acid-enhanced MR imaging. Radiology 2011;261(3):834-44.

13) L3F02989 Kumada T, Toyoda H, Tada T, Sone Y, Fujimori M, Ogawa S, et al. Evolution of hypointense hepatocellular nodules observed only in the hepatobiliary phase of gadoxetate disodium-enhanced MRI. AJR Am J Roentgenol 2011;197(1):58-63.

14) L3F02995 Lee MH, Kim SH, Park MJ, Park CK, Rhim H. Gadoxetic acid-enhanced hepatobiliary phase MRI and high-b-value diffusion-weighted imaging to distinguish well-differentiated hepatocellular carcinomas from benign nodules in patients with chronic liver disease. AJR Am J Roentgenol 2011;197(5):W868-75.

15) L3F02977 Kobayashi S, Matsui O, Gabata T, Koda W, Minami T, Ryu Y, et al. Gadolinium ethoxybenzyl diethylenetriamine pentaacetic Acid-enhanced magnetic resonance imaging findings of borderline lesions at high risk for progression to hypervascular classic hepatocellular carcinoma. J Comput Assist Tomogr 2011;35(2):181-6.

16) L3F03043 Motosugi U, Ichikawa T, Sano K, Sou H, Onohara K, Muhi A, et al. Outcome of hypovascular hepatic nodules revealing no gadoxetic acid uptake in patients with chronic liver disease. J Magn Reson Imaging 2011;34(1):88-94.

CO11 What are the best tests for diagnosing typical HCC in high-risk patients?

Dynamic CT, dynamic MRI, or contrast-enhanced ultrasound is recommended to diagnose typical HCC **(Grade A)**.

- **Background**

Noncontrast-enhanced ultrasound used for screening high-risk patients tend to have low sensitivity [60.5% (95% confidence interval: 44%–76%)] and high specificity [96.9% (95% confidence interval: 95%–98%)] (LF10092[1] Level 1). If a 1–2-cm nodule is detected by ultrasound in a patient with cirrhosis, and if contrast-enhanced ultrasound, CT, or MRI reveals a pattern typical of HCC, then the diagnosis of HCC is definitive (L3F03095[2] Level 2a). Within the scope of our literature search, there are no reports that comprehensively compared the diagnostic performance of these methods; therefore, we have described the diagnostic performance of each test.

- **Scientific Statement**

The sensitivity of dynamic CT using MDCT is 73% at a slice thickness of 5 mm, and the positive predictive value is 69%. Changing the thickness to 2.5 mm does not significantly improve the detection sensitivity (LF05711[3] Level 1).

Diagnostic performance was improved with Gd-EOB-DTPA (EOB/Primovist®)-enhanced MRI when the hepatobiliary phase was added to dynamic studies (L3F03216[4] Level 1). The resulting sensitivity exceeded that of dynamic CT (L3F03310[5] Level 1, L3F03125[6] Level 1, L3F02879[7] Level 1) and noncontrast-enhanced MRI (L3F02939[8] Level 1). No differences in positive predictive values, negative predictive values, and reproducibility of results were observed between Gd-EOB-DTPA-enhanced MRI and dynamic CT. However, Gd-EOB-DTPA-enhanced MRI demonstrated excellent performance in detecting HCC lesions measuring ≤1 cm (L3F03434[9]

Level 1, L3H00001[10] Level 1).

When SPIO-enhanced MRI using ferucarbotran (Resovist®), a type of SPIO agent, was compared with dynamic CT, there was no significant difference when a 1.5-T MRI scanner was used (LF10045[11] Level 1, LF10956[12] Level 1), although SPIO-enhanced MRI was slightly superior (L3H00013[13] Level 1). When a 3.0-T MRI scanner is used, the sensitivity of SPIO-enhanced MRI is high because it is more capable of detecting small HCC lesions measuring 1 cm or less (L3F03306[14] Level 1). When SPIO-enhanced MRI and Gd-EOB-DTPA-enhanced MRI were compared, the sensitivity achieved with Gd-EOB-DTPA-enhanced MRI was higher when 1.5-T MRI scanners were used (L3F03312[15] Level 1). Moreover, the results were identical when a 3.0-T MRI scanner was used (L3F03323[16] Level 1). The sensitivity of diffusion-weighted MRI is 45%–55%; therefore, diagnosis using this technique alone is difficult. However, because the specificity is 92%–100% (L3F03264[17] Level 1), pairing the test with Gd-DTPA-enhanced MRI (L3F03186[18] Level 1), Gd-EOB-DTPA-enhanced MRI (L3F03350[19] Level), or SPIO-enhanced MRI (L3F03355[20] Level 1) is useful for differentiating between benign and malignant lesions. Sonazoid® contrast-enhanced ultrasound can detect tumor blood flow in the early vascular phase in 88% lesions exhibiting early-phase staining on dynamic CT and 28% lesions without early-phase staining. Kupffer imaging can detect 83% lesions with washout on dynamic CT; however, the detection rates decrease for lesions measuring ≤ 2 cm and/or lesions located 9 cm or deeper from the body surface (L3F03341[21] Level 3).

Studies using SonoVue®, a second-generation contrast agent (not yet approved in Japan) that is similar to Sonazoid®, have shown that the sensitivity is 80% when HCC is diagnosed on the basis of early-phase staining and washout (L3F03184[22] Level 1). This sensitivity is higher than the 29% achieved with noncontrast-enhanced ultrasound, and this technique is useful regardless of lesion size or location depth (L3F03184[22] Level 1). When dynamic CT is combined with contrast-enhanced ultrasound, the sensitivity is 97%, which is better than that of dynamic CT alone (87%–88%) or contrast-enhanced ultrasound alone (71%–74%) (L3F03080[23] Level 1).

- **Explanation**

When comparing the pros and cons of imaging techniques for lesion detection, specificity as well as sensitivity must be considered; however, the results must be interpreted with caution because these terms are defined differently depending upon the study. What we would like to know at this time is the sensitivity and specificity per nodule. However, a true negative result cannot be uniquely defined when examining at the per-nodule level; therefore, the specificity inevitably changes depending on arbitrary definitions set by the authors, making it difficult to perform an objective comparison. On the other hand, although per-patient analysis is more sensitive than per-nodule analysis, specificity can be uniquely defined and the pros and cons can be compared between tests. Recently, articles using per-segment analysis occupying the middle ground between either method have been occasionally encountered. However, one should be aware that sensitivity is lower and specificity is higher with per-segment analysis than with per-patient analysis.

In recent years, both CT and MRI capable of performing high-quality dynamic studies have come to be widely used. This CQ cited the study results of dynamic CT scans using MDCT scanners and the results of dynamic MRI using 1.5- or 3.0-T scanners. Both dynamic CT and dynamic MRI are typically highly sensitive in detecting hypervascular HCC; therefore, both techniques should be used for diagnosis. At present, comparisons of MRI and CT have shown that both are nearly equivalent or that MRI is superior. Considering that HCC patients require repeated testing and that both techniques have nearly equivalent detection capabilities, dynamic MRI is preferred because of the decreased radiation exposure. Furthermore, Gd-EOB-DTPA-enhanced MRI hepatobiliary phase imaging and diffusion-weighted imaging can be performed using the same test, contributing greatly to lesion detection and qualitative diagnosis. On the other hand, CT has the benefit of simultaneous examination of extrahepatic organs and evaluation of ascites. Because patients with decreased renal function should not receive iodinated contrast agents or Gd-based contrast agents, SPIO-enhanced MRI is valuable to a certain extent. Abdominal ultrasound cannot thoroughly assess the entire hepatic region, resulting in low sensitivity. However, it can certainly be useful as

a highly specific supplemental test. The second-generation ultrasound contrast agent Sonazoid®

can be used independent of renal impairment, and serious pseudoallergic reactions develop less

frequently with this agent than with iodinated contrast agents and Gd-based contrast agents

(L3F03411[24] Level 6). Although contrast-enhanced ultrasound is objectively inferior to CT and

MRI, information on blood flow and hepatocyte function can be obtained; therefore, it is useful

for qualitative diagnosis of pre-existing space-occupying lesions in the liver.

- **References**

1) LF10092   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(3):513-23.

2) L3F03095   Sangiovanni A, Manini MA, Iavarone M, Romeo R, Forzenigo LV, Fraquelli M, et al. The diagnostic and economic impact of contrast imaging techniques in the diagnosis of small hepatocellular carcinoma in cirrhosis. Gut 2010;59(5):638-44.

3) LF05711   Kawata S, Murakami T, Kim T, Hori M, Federle MP, Kumano S, et al. Multidetector CT:diagnostic impact of slice thickness on detection of hypervascular hepatocellular carcinoma. AJR Am J Roentgenol 2002;179(1):61-6.

4) L3F03216   Ahn SS, Kim MJ, Lim JS, Hong HS, Chung YE, Choi JY. Added value of gadoxetic acid-enhanced hepatobiliary phase MR imaging in the diagnosis of hepatocellular carcinoma. Radiology 2010;255(2):459-66.

5) L3F03310   Kim YK, Kim CS, Han YM, Kwak HS, Jin GY, Hwang SB, et al. Detection of hepatocellular carcinoma:gadoxetic acid-enhanced 3-dimensional magnetic resonance imaging versus multi-detector row computed tomography. J Comput Assist Tomogr 2009;33(6):844-50.

6) L3F03125   Sun HY, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular

carcinomas(<or=2 cm in diameter)from arterial enhancing pseudolesions:special emphasis on hepatobiliary phase imaging. Invest Radiol 2010;45(2):96-103.

7) L3F02879   Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 2010;256(3):806-16.

8) L3F02939   Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, et al. Detection and characterization of focal liver lesions:a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol 2010;45(3):133-41.

9) L3F03434   Akai H, Kiryu S, Matsuda I, Satou J, Takao H, Tajima T, et al. Detection of hepatocellular carcinoma by Gd-EOB-DTPA-enhanced liver MRI:comparison with triple phase 64 detector row helical CT. Eur J Radiol 2011;80(2):310-5.

10) L3H00001   Baek CK, Choi JY, Kim KA, Park MS, Lim JS, Chung YE, et al. Hepatocellular carcinoma in patients with chronic liver disease:a comparison of gadoxetic acid-enhanced MRI and multiphasic MDCT. Clin Radiol 2012;67(2):148-56.

11) LF10045   Kim SH, Choi D, Lim JH, Lee WJ, Kim MJ, Lim HK, et al. Ferucarbotran-enhanced MRI versus triple-phase MDCT for the preoperative detection of hepatocellular carcinoma. AJR Am J Roentgenol 2005;184(4):1069-76.

12) LF10956   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(2):531-41.

13) L3H00013   Hori M, Murakami T, Kim T, Tsuda K, Takahashi S, Okada A, et al. Detection of hypervascular hepatocellular carcinoma:comparison of SPIO-enhanced MRI with dynamic helical CT. J Comput Assist Tomogr 2002;26(5):701-10.

14) L3F03306   Kim SJ, Kim SH, Lee J, Chang S, Kim YS, Jeon YH, et al. Ferucarbotran-enhanced 3.0-T magnetic resonance imaging using parallel imaging technique compared with triple-phase multidetector row computed tomography for the preoperative detection of hepatocellular carcinoma. J Comput Assist Tomogr 2008;32(3):379-85.

15) L3F03312   Kim YK, Kim CS, Han YM, Park G, Hwang SB, Yu HC. Comparison of gadoxetic acid-enhanced MRI and superparamagnetic iron oxide-enhanced MRI for the detection of hepatocellular carcinoma. Clin Radiol 2010;65(5):358-65.

16) L3F03323   Lee JY, Kim SH, Jeon YH, Lee J, Kim MJ, Choi D, et al. Ferucarbotran-enhanced magnetic resonance imaging versus gadoxetic acid-enhanced magnetic resonance imaging for the preoperative detection of hepatocellular carcinoma:initial experience. J Comput Assist Tomogr 2010;34(1):127-34.

17) L3F03264   Hardie AD, Kizziah MK, Boulter DJ. Diagnostic accuracy of diffusion-weighted MRI for identifying hepatocellular carcinoma with liver explant correlation. J Med Imaging Radiat Oncol 2011;55(4):362-7.

18) L3F03186   Xu PJ, Yan FH, Wang JH, Shan Y, Ji Y, Chen CZ. Contribution of diffusion-weighted magnetic resonance imaging in the characterization of hepatocellular carcinomas and dysplastic nodules in cirrhotic liver. J Comput Assist Tomogr 2010;34(4):506-12.

19) L3F03350   Motosugi U, Ichikawa T, Sou H, Sano K, Tominaga L, Muhi A, et al. Distinguishing hypervascular pseudolesions of the liver from hypervascular hepatocellular carcinomas with gadoxetic acid-enhanced MR imaging. Radiology 2010;256 (1):151-8.

20) L3F03355   Nishie A, Tajima T, Ishigami K, Ushijima Y, Okamoto D, Hirakawa M, et al. Detection of hepatocellular carcinoma (HCC)using super paramagnetic iron oxide(SPIO)-enhanced MRI:Added value of diffusion-weighted imaging (DWI). J Magn Reson Imaging 2010;31(2):373-82.

21) L3F03341　Mandai M, Koda M, Matono T, Nagahara T, Sugihara T, Ueki M, et al. Assessment of hepatocellular carcinoma by contrast-enhanced ultrasound with perfluorobutane microbubbles:comparison with dynamic CT. Br J Radiol 2011;84(1002):499-507.

22) L3F03184　Xu HX, Xie XY, Lu MD, Liu GJ, Xu ZF, Zheng YL, et al. Contrast-enhanced sonography in the diagnosis of small hepatocellular carcinoma <or=2 cm. J Clin Ultrasound 2008;36(5):257-66.

23) L3F03080　Quaia E, Alaimo V, Baratella E, Medeot A, Midiri M, Cova MA. The added diagnostic value of 64-row multidetector CT combined with contrast-enhanced US in the evaluation of hepatocellular nodule vascularity:implications in the diagnosis of malignancy in patients with liver cirrhosis. Eur Radiol 2009;19(3):651-63.

24) L3F03411　Wilson SR, Burns PN. Microbubble-enhanced US in body imaging:what role? Radiology 2010;257(1):24-39.

CQ12　Is angiography necessary before HCC treatment?

Recommendation

Angiography is not recommended for HCC diagnosis **(Grade D)**.

- **Scientific Statement**

The diagnostic performances of angiography, CT, and MRI were compared on a per-lesion basis for hypervascular HCC, and the sensitivity of lesion detection by angiography was determined to be 33-77% (LF12103[1] Level 1, LF00474[2] Level 1, LF10030[3] Level 1), and by size was > 2 cm; 100%, 1-2 cm; 38%, 1 cm; 12% (LF121031) Level 1).

The detection sensitivity of dynamic CT was 53.8-78.6% (LF02001[4] Level 1, LF10546[5] Level 1, LF10371[6] Level 1, LF10023[7] Level 1, LF05773[8] Level 1, LF10051[9] Level 1), and that of Gd

dynamic MRI was nearly identical at 55-76.9% (LF06200[10]Level 1, LF10023[7]Level 1, LF10546[5]Level 1, LF02001[4]Level 1), with a slightly higher sensitivity compared with that of angiography. For lesions measuring >2 cm, the sensitivities of both modalities were increased, with that of CT being 82-100% (LF05773[8]Level 1, LF10371[6]Level 1, LF10023[7]Level 1, LF10546[5]Level 1) and that of MRI being 80-100% (LF06200[10]Level 1, LF10023[7]Level 1, LF10546[5]Level 1). For lesions measuring 1-2 cm, the sensitivity of CT was 33.3-65% (LF10371[6]Level 1, LF10546[5]Level 1) and that of MRI was 50-89% (LF06200[10]Level 1, LF10546[5]Level 1). Therefore, the sensitivity of MRI was equivalent to or higher than that of CT. For lesions measuring <1 cm, CT findings varied greatly at 0-45.1% (LF10371[6]Level 1, LF10546[5]Level 1, LF10051[9]Level 1). Therefore, a comparison of sensitivity between CT and MRI (33-34%) (LF06200[10]Level 1, LF10546[5]Level 1) was difficult.

- **Explanation**

In recent years, with advancements in CT and MRI, the diagnostic performance of dynamic CT and dynamic MRI for cases of hypervascular HCC have surpassed that of angiography. Therefore, considering the invasive nature of angiography, it is recommended that angiography should not be performed for the locational diagnosis of HCC. In addition, vascular anatomy prior to surgery can be easily visualized using 3D vascular reconstructed images obtained with the latest MDCT scanner; therefore, angiography is rarely needed.

- **References**

1) LF12103   Krinsky GA, Nguyen MT, Lee VS, Rosen RJ, Goldenberg A, Theise ND, et al. Dysplastic nodules and hepatocellular carcinoma:sensitivity of digital subtraction hepatic arteriography with whole liver explant correlation. J Comput Assist Tomogr 2000;24(4):628-34.

2) LF00474   Spreafico C, Marchianò A, Mazzaferro V, Frigerio LF, Regalia E, Lanocita R, et al. Hepatocellular carcinoma in patients who undergo liver transplantation:sensitivity of CT with iodized oil. Radiology 1997;203(2):457-60.

3) LF10030 Steingruber IE, Mallouhi A, Czermak BV, Waldenberger P, Gassner E, Offner F, et al. Pretransplantation evaluation of the cirrhotic liver with explantation correlation:accuracy of CT arterioportography and digital subtraction hepatic angiography in revealing hepatocellular carcinoma. AJR Am J Roentgenol 2003;181(1):99-108.

4) LF02001 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(3):327-36.

5) LF10546 Burrel M, Llovet JM, Ayuso C, Iglesias C, Sala M, Miquel R, et al;Barcelona Clínic Liver Cancer Group. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation:an explant correlation. Hepatology 2003;38(4):1034-42.

6) LF10371 Bhattacharjya S, Bhattacharjya T, Quaglia A, Dhillon AP, Burroughs AK, Patch DW, et al. Liver transplantation in cirrhotic patients with small hepatocellular carcinoma:an analysis of preoperative imaging, explant histology and prognostic histologic indicators. Dig Surg 2004;21(2):152-9.

7) LF10023 Noguchi Y, Murakami T, Kim T, Hori M, Osuga K, Kawata S, et al. Detection of hepatocellular carcinoma:comparison of dynamic MR imaging with dynamic double arterial phase helical CT. AJR Am J Roentgenol 2003;180(2):455-60.

8) LF05773 Lim JH, Kim CK, Lee WJ, Park CK, Koh KC, Paik SW, et al. Detection of hepatocellular carcinomas and dysplastic nodules in cirrhotic livers:accuracy of helical CT in transplant patients. AJR Am J Roentgenol 2000;175(3):693-8.

9) LF10051 Kim YK, Kim CS, Chung GH, Han YM, Lee SY, Chon SB, et al. Comparison of gadobenate dimeglumine-enhanced dynamic MRI and 16-MDCT for the detection of hepatocellular carcinoma. AJR Am J Roentgenol 2006;186(1):149-57.

10) LF06200 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(2):445-54.

CO13　Is CTAP/CTHA necessary before HCC treatment?

Recommendation

Lesions are more easily detected with CT during arterial portography (CTAP)/CT during hepatic arteriography (CTHA) than with noninvasive imaging tests such as dynamic CT and dynamic MRI. These methods should be considered when more accurate staging is desired **(Grade B)**.

- **Scientific Statement**

Articles comparing the combination of CTAP and CTHA with combinations of non-invasive test methods such as MDCT and SPIO-enhanced MRI demonstrated that the lesion detection capability of combined CTAP/CTHA testing was equivalent to or greater than that of noninvasive test methods (L3F03313[1] Level 1, L3F03470[2] Level 1). CTAP and CTHA were particularly better at detecting small lesions measuring ≤1.5 cm (L3F03470[2] Level 1, L3F03538[3] Level 1, L3F03494[4] Level 2a). However, angiography must be performed in order to conduct CTAP and CTHA, and because of its invasive nature, some believe that this procedure should be considered only when microlesions need to be detected and accurate staging is required (L3F0315[35] Level 1, L3F03055[6] Level 3).

The combination of CTAP and CTHA exhibited the most effective detection of nodule-in-nodule type (hypovascular nodules with hypervascular foci) early-stage HCC, followed by dynamic MDCT. Dynamic MDCT is therefore recommended for follow-up monitoring of nodule-in-nodule type early-stage HCC (L3F03110[7] Level 1).

- **Explanation**

Compared with a combined noninvasive test using MDCT or SPIO-enhanced MRI, the combined CTAP/CTHA test shows superior detection of small HCC lesions measuring ≤1.5 cm, such as nodule-in-nodule type, early-stage HCC. Because invasive testing such as angiography is necessary, one must determine whether testing is indicated.

Angiographic equipment with C-arm CT function has come to be widely used in recent years, and detectors in such angiography equipment rotate around the patient to generate a CT-like cross-sectional image. The applications of C-arm CTHA (L3F03291[8] Level 1) and CTAP (L3F03520[9] Level 2a) have also been examined. In the future, when angiography is performed for TACE or hepatic arterial infusion, C-arm built-in CT devices may easily enable the acquisition of cross-sectional images that are equivalent to those obtained by conventional CTAP/CTHA.

- **References**

1) L3F03313   Kim YK, Kwak HS, Han YM, Kim CS. Usefulness of combining sequentially acquired gadobenate dimeglumine-enhanced magnetic resonance imaging and resovist-enhanced magnetic resonance imaging for the detection of hepatocellular carcinoma:comparison with computed tomography hepatic arteriography and computed tomography arterioportography using 16-slice multidetector computed tomography. J Comput Assist Tomogr 2007;31(5):702-11.

2) L3F03470   Imai Y, Murakami T, Hori M, Fukuda K, Kim T, Marukawa T, et al. Hypervascular hepatocellular carcinoma:Combined dynamic MDCT and SPIO-enhanced MRI versus combined CTHA and CTAP. Hepatol Res 2008;38(2):147-58.

3) L3F03538   Pugacheva O, Matsui O, Kozaka K, Minami T, Ryu Y, Koda W, et al. Detection of small hypervascular hepatocellular carcinomas by EASL criteria:comparison with double-phase CT during hepatic arteriography. Eur J Radiol 2011;80(3):e201-6.

4) L3F03494   Kim SR, Ando K, Mita K, Fuki S, Ikawa H, Kanbara Y, et al. Superiority of CT arterioportal angiography to contrast-enhanced CT and MRI in the diagnosis of hepatocellular carcinoma in nodules smaller than 2 cm. Oncology 2007;72(Suppl 1):58-66.

5) L3F03153   Tsurusaki M, Sugimoto K, Fujii M, Fukuda T, Matsumoto S, Sugimura K. Combination of CT during arterial portography and double-phase CT hepatic arteriography with multi-detector row helical CT for evaluation of hypervascular hepatocellular carcinoma. Clin Radiol 2007;62(12):1189-97.

6) L3F03055　Ohnishi H, Sakaguchi K, Nouso K, Kobayashi Y, Nakamura S, Tanaka H, et al. Outcome of small liver nodules detected by computed tomographic angiography in patients with hepatocellular carcinoma. Hepatol Int 2010;4(3):562-8.

7) L3F03110　Shinmura R, Matsui O, Kadoya M, Kobayashi S, Terayama N, Sanada J, et al. Detection of hypervascular malignant foci in borderline lesions of hepatocellular carcinoma:comparison of dynamic multi-detector row CT, dynamic MR imaging and superparamagnetic iron oxide-enhanced MR imaging. Eur Radiol 2008;18(9):1918-24.

8) L3F03291　Iwazawa J, Ohue S, Hashimoto N, Abe H, Hamuro M, Mitani T. Detection of hepatocellular carcinoma:comparison of angiographic C-arm CT and MDCT. AJR Am J Roentgenol 2010;195(4):882-7.

9) L3F03520　Miyayama S, Matsui O, Yamashiro M, Ryu Y, Takata H, Takeda T, et al. Detection of hepatocellular carcinoma by CT during arterial portography using a cone-beam CT technology:comparison with conventional CTAP. Abdom Imaging 2009;34(4):502-6.

CQ14　What test methods are useful for diagnosing liver tumors in patients with decreased kidney and liver functions?

Recommendation

Noncontrast MRI with diffusion-weighted imaging and ultrasound using Sonazoid® are useful techniques that can be safely performed in patients with impaired kidney or liver function and are therefore recommended **(Grade B)**.

When conducting dynamic CT and dynamic MRI in patients with renal impairment, if the eGFR is 30–60 mL/min/1.73 m^2, Gd-EOB-DTPA-enhanced MRI can be performed. For an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2, MRI with SPIO can be considered, and dialysis patients may undergo MRI with SPIO or dynamic CT **(Grade C1)**.

There is an insufficient amount of research on the selection of appropriate test methods and

contrast agents for contrast-enhanced CT/MRI in patients with liver impairment equivalent to Child–Pugh class C.

- **Scientific Statement**

Although diffusion-weighted images cannot surpass dynamic MRI, some of their applications have been shown (L3F03161[1] Level 1, L3F03185[2] Level 1). The ultrasound contrast agent known as perfluorobutane microbubbles (Sonazoid®) and the liver-specific MRI contrast agent, SPIO (Resovist®), do not affect renal function and are not known to exacerbate the adverse effects associated with renal dysfunction (see attached document).

In dialysis patients, the clearance of Gd-EOB-DTPA (EOB; Primovist®) is significantly decreased; at the same time, enhancement is also decreased (L3F03750[3] Level 2b). Therefore, its use is not recommended. There is an insufficient amount of research on the selection of appropriate contrast agents and test methods on the basis of eGFR for dynamic CT or dynamic MRI in patients with decreased renal function.

Enhancement is decreased in the hepatobiliary phase when Gd-EOB-DTPA is used in patients with decreased liver function (L3F03774[4] Level 1, L3F03811[5] Level 3), and enhancement is also diminished during the so-called Kupffer phase with SPIO (L3H00032[6] Level 3). There is an insufficient amount of research on the selection of dynamic CT or MRI for patients with decreased liver function categorized as Child–Pugh class C; therefore, it is difficult to make even a provisional recommendation.

- **Explanation**

The use of iodinated contrast agents and Gd contrast agents is restricted in patients with decreased renal function, and the enhancement effects of Gd-EOB-DTPA and SPIO are decreased in patients with decreased liver function. Therefore, testing options are limited and diagnostic performance is decreased in patients with decreased kidney or liver function.

An itemized discussion of the risks associated with the use of iodinated and Gd contrast agents in

patients with decreased renal function detracts from the purpose of these guidelines; therefore, other guidelines are merely cited. Patients with decreased renal function and an eGFR of <60 mL/min/1.73 m^2 are at an increased risk of developing contrast-induced nephropathy from the use of iodinated contrast agents (http://www.esur.org/guidelines/en/index.php). When risk factors such as diabetes mellitus, dehydration, congestive heart failure, gout, age ≥ 70 years, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) are added, the risk is thought to increase even further.

The risk of developing Gd-induced nephrogenic systemic fibrosis (NSF) is increased in patients with decreased renal function ("Guidelines for the use of gadolinium contrast agents in patients with kidney impairment;" http://www.radiology.jp/modules/news/article.php?storyid=773). Therefore, dialysis patients, acute renal failure patients, and patients with chronic kidney disease and an eGFR of <30 mL/min/1.73 m^2 are, as a general rule, not administered extracellular Gd contrast agents or Gd-EOB-DTPA. After investigating the risks and benefits, if Gd contrast agents must be used by necessity, the use of gadopentetate dimeglumine (Magnevist®) and gadodiamide (Omniscan®) should be avoided because they have often been associated with NSF onset.

An insufficient amount of research has been conducted on the use of eGFR for the appropriate selection of contrast agents and test methods during dynamic CT or dynamic MRI for further liver testing in patients with renal impairment. Therefore, the recommendation given in these guidelines is only provisional. Considering that patients with an eGFR of 30–60 mL/min/1.73 m^2 are not at a very high risk of developing NSF, Gd-EOB-DTPA-enhanced MRI is recommended for these patients because of its high diagnostic performance. In patients with an eGFR of <30 mL/min/1.73 m^2, the risk of developing NSF increases, and it is difficult to determine whether Gd-EOB-DTPA- or SPIO-enhanced MRI should be recommended. However, because the Gd-EOB-DTPA package insert states "avoid using this drug," and because it is likely to be frequently administered, SPIO-enhanced MRI is recommended. It is recommended that dialysis patients avoid Gd contrast agents and that SPIO-enhanced MRI or dynamic CT be selected depending upon the situation at

the medical institution. It is thought that diffusion-weighted and T2-weighted imaging will become more important than usual for patients with decreased kidney and liver function.

- **References**

1) L3F03161   Vandecaveye V, De Keyzer F, Verslype C, Op de Beeck K, Komuta M, Topal B, et al. Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. Eur Radiol 2009;19(10):2456-66.

2) L3F03185   Xu PJ, Yan FH, Wang JH, Lin J, Ji Y. Added value of breathhold diffusion-weighted MRI in detection of small hepatocellular carcinoma lesions compared with dynamic contrast-enhanced MRI alone using receiver operating characteristic curve analysis. J Magn Reson Imaging 2009;29(2):341-9.

3) L3F03750   Gschwend S, Ebert W, Schultze-Mosgau M, Breuer J. Pharmacokinetics and imaging properties of Gd-EOB-DTPA in patients with hepatic and renal impairment. Invest Radiol 2011;46(9):556-66.

4) L3F03774   Katsube T, Okada M, Kumano S, Hori M, Imaoka I, Ishii K, et al. Estimation of liver function using T1 mapping on Gd-EOB-DTPA-enhanced magnetic resonance imaging. Invest Radiol 2011;46(4):277-83.

5) L3F03811   Motosugi U, Ichikawa T, Sou H, Sano K, Tominaga L, Kitamura T, et al. Liver parenchymal enhancement of hepatocyte-phase images in Gd-EOB-DTPA-enhanced MR imaging:which biological markers of the liver function affect the enhancement? J Magn Reson Imaging 2009;30(5):1042-6.

6) L3H00032   Chung YE, Park MS, Kim MS, Kim E, Park J, Song HT, et al. Quantification of superparamagnetic iron oxide-mediated signal intensity change in patients with liver cirrhosis using T2 and T2* mapping:a preliminary report. J Magn Reson Imaging 2010;31(6):1379-86.

CQ15   How should contrast media be used for the diagnostic imaging of HCC?

Recommendation

When evaluating hypervascular HCC, rapid injection of the contrast agent and optimal timing of image acquisition are recommended **(Grade A).**

When evaluating hypovascular nodules, it is recommended that images be obtained during the hepatobiliary phase using a hepatocyte-specific contrast agent **(Grade A)**.

- **Scientific Statement**

It has long been known that studies using CTHA showed increased arterial blood flow in clinically malignant HCC lesions compared with that in the surrounding liver tissue (LF06209[1] Level 3). Furthermore, ultrasound angiography using CO_2 has shown that nodules with increased arterial blood flow have a mean tumor volume doubling time of 70 days. In contrast, nodules with poor arterial blood flow have a mean tumor volume doubling time of 370 days; therefore, hypovascular tumors grow slower (LJ03368[2] Level 3). Furthermore, studies using CTHA and CTAP have shown that the degree of histological differentiation, from dysplastic nodules to well-differentiated HCC and moderately to poorly differentiated HCC, was correlated with changes in tumor blood flow, reflecting the multistage development of HCC (LF06204[3] Level 2a, LF05724[4] Level 2a). Such HCC lesions with increased arterial blood flow will likely be a major target of diagnosis and treatment in the future.

The increased diagnostic rate for hypervascular HCC has been achieved in dynamic studies using iodinated contrast agents with CT and extracellular Gd contrast agents with MRI. In a study based on initial-stage angiography findings, 88% patients were diagnosed using a combination of precontrast and arterial phase CT (LF02538[5] Level 1). A subsequent study revealed that addition of the delayed phase to the arterial phase increased the diagnostic rate of CT (LF05710[6] Level 1). Among the multitude of imaging methods that can possibly be used with MRI, the clinical

application of dynamic studies remain high, and the arterial phase is extremely important for the detection of hypervascular HCC (LF05839[7] Level 1).

It is recommended that the required injection time for all contrast agents be fixed in order to minimize individual variations in the ideal timing of arterial phase image acquisition (LF12082[8] Level 2a). Some reports mentioned that the bolus tracking method and double arterial phase imaging performed during the early and late arterial phases were useful for improving the detection rate of hypervascular HCC (LF06201[9] Level 1, LF10959[10] Level 3).

Gd-EOB-DTPA became available for use in Japan in January 2008, and it is characteristically incorporated in hepatocytes. Therefore, information about hepatocyte function can be obtained in addition to blood flow data acquired with conventional, extracellular Gd-based contrast.

Gd-EOB-DTPA-enhanced MRI imaging during the hepatobiliary phase is an excellent assessment method for early-stage HCC, including hypovascular nodules (L3F03380[11] Level 1, L3F02914[12] Level 2a).

SPIO used in MRI is taken up by reticuloendothelial cells, which results in decreased signal intensity in the liver parenchyma. Diagnosis is determined when reticuloendothelial cells are absent in the tumor area and when there is no decrease in signal intensity. This SPIO-enhanced MRI reportedly shows that differentiation of HCC is strongly correlated with SPIO uptake (LF06202[13] Level 3).

Outside Japan, double-contrast-enhanced MRI is used to acquire images with simultaneous administration of SPIO and Gd-EOB-DTPA, and it is reportedly very useful. However, it is rarely used in Japan (L3F01625[14] Level 3, L3F02082[15] Level 1).

The applications of microbubble contrast-enhanced ultrasound testing have been demonstrated. Contrast-enhanced ultrasound testing significantly improves the diagnostic performance of HCC lesions measuring ≤2 cm compared with noncontrast-enhanced ultrasound (L3F03184[16] Level 1).

- **Explanation**

Excluding early-stage disease, the majority of HCC lesions exhibit increased arterial blood flow

within the tumor, and contrast agents are required during CT or MRI diagnosis. Knowledge of lesion dynamics and contrast agents is essential, with the arterial phase being particularly critical. The delayed phase also contributes to increasing diagnostic performance. Images are generally acquired before contrast is administered and during three phases with contrast (arterial phase, portal venous phase, and delayed phase). Of these phases, the portal venous phase contributes the least to diagnosis. When performing such dynamic studies, rapid dynamic CT or high-speed MRI scanners are the standard equipment. Autoinjectors must also be equipped for rapid injection of contrast agents at 3 mL/s. In order to minimize individual variation in arterial phase image quality, the total amount of contrast agent as determined by body weight must be injected for a set time period, and images should be acquired 15 seconds after completing the injection. Alternatively, a trigger mechanism may be used when the contrast reaches the [abdominal] aorta. When using these contrast agents, on the assumption that contrast allergies may occur, it is required that tests be thoroughly explained to the patient in advance and consent be obtained. Furthermore, emergency procedures must be fully prepared in the event of a sudden change in the patient's condition.

Gd-EOB-DTPA became available for use in Japan in January 2008. Information about hepatocyte function can be obtained when this contrast agent is used in combination with blood flow data acquired in conventional dynamic studies. In general, 20 min after Gd-EOB-DTPA is intravenously injected, Gd-EOB-DTPA particles are taken up by hepatocytes and increase the signal intensity in the liver parenchyma, thereby improving contrast against the vessel interior and the spleen. This temporal phase is known as the hepatobiliary phase, which has high detection sensitivity for HCC, and its applications have been widely reported. Furthermore, advances in MRI imaging technology led to the development of high-resolution 3D images in dynamic liver studies and may have contributed to the application of Gd-EOB-DTPA-enhanced MRI. Gd-EOB-DTPA-enhanced MRI is equivalent or superior to dynamic MDCT in terms of HCC detection capability (L3F02879[17] Level 1, L3F02939[18] Level 1, L3F03305[19] Level 1,

L3F03310[20] Level 1). Even in comparison with SPIO-enhanced MRI, HCC diagnosis by

Gd-EOB-DTPA-enhanced MRI is superior (L3F03312[21] Level 1, L3F03323[22] Level 1).

Furthermore, the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI is useful for

differentiating between HCC and hypervascular pseudolesions (AP shunts, etc.; L3F03125[23]

Level 1).

When parallel imaging was performed with a 3.0-T MRI scanner, the diagnostic performance of

SPIO-enhanced MRI was superior to that of dynamic MDCT, while the sensitivity of SPIO-enhanced

MRI was particularly high for HCC lesions measuring ≤1 cm (L3F03306[24] Level 1).

Contrast-enhanced ultrasound is superior to dynamic MDCT for the detection and qualitative

diagnosis of HCC tumor thrombi (L3F03375[25] Level 1). Moreover, contrast-enhanced ultrasound

has greater sensitivity and diagnostic accuracy for detecting malignant lesions compared with

dynamic MDCT (L3F03267[26] Level 1).

- **References**

1) LF06209　Matsui O, Kadoya M, Kameyama T, Yoshikawa J, Takashima T, Nakanuma Y, et al. Benign and malignant nodules in cirrhotic livers:distinction based on blood supply. Radiology 1991;178(2):493-7.

2) LJ03368　Tochio H, Tomita S, Kudo M, Mimura J, Hamada M, Minowa K, et al. Growth Rate of Hepatocellular Carcinoma. Relationship with arterial vascularity evaluated by US angiography. Acta Hepatologica Japonica 1992;33(10):758-65.

3) LF06204　Hayashi M, Matsui O, Ueda K, Kawamori Y, Kadoya M, Yoshikawa J, et al. Correlation between the blood supply and grade of malignancy of hepatocellular nodules associated with liver cirrhosis:evaluation by CT during intraarterial injection of contrast medium. AJR Am J Roentgenol 1999;172(4):969-76.

4) LF05724　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(1):143-9.

5) LF02538   Ueda K, Kitagawa K, Kadoya M, Matsui O, Takashima T, Yamahana T. Detection of hypervascular hepatocellular carcinoma by using spiral volumetric CT:comparison of US and MR imaging. Abdom Imaging 1995;20(6):547-53.

6) LF05710   Lim JH, Choi D, Kim SH, Lee SJ, Lee WJ, Lim HK, et al. Detection of hepatocellular carcinoma:value of adding delayed phase imaging to dual-phase helical CT. AJR Am J Roentgenol 2002;179(1):67-73.

7) LF05839   Fujita T, Ito K, Honjo K, Okazaki H, Matsumoto T, Matsunaga N. Detection of hepatocellular carcinoma:comparison of T2-weighted breath-hold fast spin-echo sequences and high-resolution dynamic MR imaging with a phased-array body coil. J Magn Reson Imaging 1999;9(2):274-9.

8) LF12082   Awai K, Hiraishi K, Hori S. Effect of contrast material injection duration and rate on aortic peak time and peak enhancement at dynamic CT involving injection protocol with dose tailored to patient weight. Radiology 2004;230(1):142-50.

9) LF06201   Murakami T, Kim T, Takamura M, Hori M, Takahashi S, Federle MP, et al. Hypervascular hepatocellular carcinoma:detection with double arterial phase multi-detector row helical CT. Radiology 2001;218(3):763-7.

10) LF10959   Sultana S, Awai K, Nakayama Y, Nakaura T, Liu D, Hatemura M, et al. Hypervascular hepatocellular carcinomas:bolus tracking with a 40-detector CT scanner to time arterial phase imaging. Radiology 2007;243(1):140-7.

11) L3F03380   Sano K, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, et al. Imaging study of early hepatocellular carcinoma:usefulness of gadoxetic acid-enhanced MR imaging. Radiology 2011;261(3):834-44.

12) L3F02914   Golfieri R, Renzulli M, Lucidi V, Corcioni B, Trevisani F, Bolondi L. Contribution of the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI to Dynamic MRI in the detection of hypovascular small(</=2 cm)HCC in cirrhosis. Eur Radiol

2011;21(6):1233-42.

13) LF06202　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(2):205-12.

14) L3F01625　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(7):538-46.

15) L3F02082　Lee DH, Kim SH, Lee JM, Park HS, Lee JY, Yi NJ, et al. Diagnostic performance of multidetector row computed tomography, superparamagnetic iron oxide-enhanced magnetic resonance imaging, and dual-contrast magnetic resonance imaging in predicting the appropriateness of a transplant recipient based on Milan criteria:correlation with histopathological findings. Invest Radiol 2009;44(6):311-21.

16) L3F03184　Xu HX, Xie XY, Lu MD, Liu GJ, Xu ZF, Zheng YL, et al. Contrast-enhanced sonography in the diagnosis of small hepatocellular carcinoma<or=2 cm. J Clin Ultrasound 2008;36(5):257-66.

17) L3F02879　Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the Detection of hepatocellular carcinoma in patients with cirrhosis. Radiology 2010;256(3):806-16.

18) L3F02939　Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, et al. Detection and characterization of focal liver lesions:a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol 2010;45(3):133-41.

19) L3F03305　Kim SH, Lee J, Kim MJ, Jeon YH, Park Y, Choi D, et al. Gadoxetic acid-enhanced MRI versus triple-phase MDCT for the preoperative detection of

hepatocellular carcinoma. AJR Am J Roentgenol 2009;192(6):1675-81.

20) L3F03310   Kim YK, Kim CS, Han YM, Kwak HS, Jin GY, Hwang SB, et al. Detection of hepatocellular carcinoma:gadoxetic acid-enhanced 3-dimensional magnetic resonance imaging versus multi-detector row computed tomography. J Comput Assist Tomogr 2009;33(6):844-50.

21) L3F03312   Kim YK, Kim CS, Han YM, Park G, Hwang SB, Yu HC. Comparison of gadoxetic acid-enhanced MRI and superparamagnetic iron oxide-enhanced MRI for the detection of hepatocellular carcinoma. Clin Radiol 2010;65(5):358-65.

22) L3F03323   Lee JY, Kim SH, Jeon YH, Lee J, Kim MJ, Choi D, et al. Ferucarbotran-enhanced magnetic resonance imaging versus gadoxetic acid-enhanced magnetic resonance imaging for the preoperative detection of hepatocellular carcinoma:initial experience. J Comput Assist Tomogr 2010;34(1):127-34.

23) L3F03125   Sun HY, Lee JM, Shin CI, Lee DH, Moon SK, Kim KW, et al. Gadoxetic acid-enhanced magnetic resonance imaging for differentiating small hepatocellular carcinomas(<or=2 cm in diameter)from arterial enhancing pseudolesions:special emphasis on hepatobiliary phase imaging. Invest Radiol 2010;45(2):96-103.

24) L3F03306   Kim SJ, Kim SH, Lee J, Chang S, Kim YS, Jeon YH, et al. Ferucarbotran-enhanced 3.0-T magnetic resonance imaging using parallel imaging technique compared with triple-phase multidetector row computed tomography for the preoperative detection of hepatocellular carcinoma. J Comput Assist Tomogr 2008;32(3):379-85.

25) L3F03375   Rossi S, Ghittoni G, Ravetta V, Torello Viera F, Rosa L, Serassi M, et al. Contrast-enhanced ultrasonography and spiral computed tomography in the detection and characterization of portal vein thrombosis complicating hepatocellular carcinoma. Eur Radiol 2008;18(8):1749-56.

26) L3F03267   Hatanaka K, Kudo M, Minami Y, Maekawa K. Sonazoid-enhanced

ultrasonography for diagnosis of hepatic malignancies:comparison with contrast-enhanced CT. Oncology 2008;75(Suppl 1):42-7.

CQ16　Are brain MRI, chest CT, bone scintigraphy, and FDG-PET necessary for determining the stage of HCC?

Recommendation

Chest CT, bone scintigraphy, and FDG-PET scans can be recommended for HCC patients with risk factors for extrahepatic metastases **(Grade B)**.

It is worth considering a brain CT/MRI to search for brain metastasis in HCC patients with neurological findings and lung metastasis **(Grade C1)**.

- **Scientific Statement**

The frequency of extrahepatic metastasis from HCC at initial onset is low at 1.0%–2.3% (L3F05972[1] Level 2b, L3F00784[2] Level 2b). However, the frequency of extrahepatic metastasis increases to 21% during post-therapy follow-up (L3F05944[3] Level 2a). The frequencies according to site of metastasis are 6%–29% in the lungs, 5%–20% in the lymph nodes, 2%–10% in the bones, 1%–10% in the adrenal glands, and 0.2%–0.6% in the brain (L3F05944[3] Level 2a, L3F00784[2] Level 2b, L3H00004[4] Level 2a). Risk factors for extrahepatic metastasis are reported to be advanced intrahepatic lesions, portal venous tumor thrombus, DCP levels ≥ 300 mAU/mL, AFP levels > 100 ng/mL, platelet count $\leq 130\times10^3/\mu L$, no esophageal varix, and viral hepatitis (L3F05955[5] Level 2b, L3F05944[3] Level 2a, L3F04055[6] Level 2b).

New metastasis that develops from a single HCC nodule measuring ≤5 cm or 2–3 HCC nodules measuring ≤3 cm is rarely detected even when chest CT or bone scintigraphy are performed to search for metastasis. As a more likely outcome, the loss resulting from false positive results can pose a problem (LF11146[7] Level 2b).

Bone metastasis from HCC is generally osteolytic, and approximately half the metastasis sites are located in the vertebrae (L3F05972[1] Level 2b). When conducting a systemic evaluation for HCC bone metastasis, bone scintigraphy (LF105068) Level 1) and FDG-PET (L3F01371[9] Level 1, L3F04193[10] Level 1) are useful. FDG-PET is also useful for the systemic evaluation of other types of extrahepatic metastasis (L3F03364[11] Level 1) however, the sensitivity for the detection of brain metastasis is low (L3F01371[9] Level 1, L3F04193[10] Level 1).

The frequency of brain metastasis from HCC is low (L3F05944[3] Level 2a, L3F03968[12] Level 5, L3F00784[2] Level 2b, L3H00004[4] Level 2a), and nearly all brain metastases are concomitant with lung metastasis (L3F05972[1] Level 2b).

- **Explanation**

The presence or absence of extrahepatic metastasis is a critical factor for determining whether local therapy is indicated for HCC. There is little significance of an aggressive search for extrahepatic metastases from single HCC lesions measuring ≤5 cm or 2–3 lesions measuring ≤3 cm. If one is treating an HCC patient with risk factors for extrahepatic metastasis, however, it does appear valid to search for metastases before administering local therapy to common sites of metastases.

Chest CT is the standard method for evaluating liver metastasis. If chest CT is used in addition to abdominal dynamic CT, not only can intrahepatic lesions be evaluated, but also nearly all the common sites of extrahepatic metastases can be covered.

Bone scintigraphy is useful for the systemic evaluation of bone metastases from HCC. However, a known shortcoming is the occasional low accumulation of tracer with bone metastases. It is hoped that FDG-PET will be useful for the evaluation of bone metastases with low tracer accumulation. With PET-CT, it may be possible to evaluate the risk of compression fracture and spinal stenosis in addition to liver metastases. Evidence is insufficient, however, for a direct comparison of the diagnostic performances of bone scintigraphy and FDG-PET in terms of bone metastases from HCC. FDG-PET is an excellent diagnostic tool for detecting extrahepatic metastasis from HCC,

including bone metastases, and it may be appropriate to proactively perform FDG-PET in patients with elevated tumor marker levels that cannot be accounted for by the presence of abdominal lesions and/or lung metastasis alone.

Contrast-enhanced brain CT or MRI may be considered for the evaluation of brain metastasis in patients with symptoms, neurological signs, or lung metastasis.

- **References**

1) L3F05972　Natsuizaka M, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol 2005;20(11):1781-7.

2) L3F00784　Uchino K, Tateishi R, Shiina S, Kanda M, Masuzaki R, Kondo Y, et al. Hepatocellular carcinoma with extrahepatic metastasis:clinical features and prognostic factors. Cancer 2011;117(19):4475-83.

3) L3F05944　Bae HM, Lee JH, Yoon JH, Kim YJ, Heo DS, Lee HS. Protein induced by vitamin K absence or antagonist-II production is a strong predictive marker for extrahepatic metastases in early hepatocellular carcinoma:a prospective evaluation. BMC Cancer 2011;11:435.

4) L3H00004　Kudo M, Arii S, Ikai I, Omata M, Kojiro M,Sakamoto M, et al. Report of the 18th Follow-Up Survey of Primary Liver Cancer in Japan(2004-2005) (Liver Cancer Study Group of Japan, Follow-Up Survey Committee)(Commentary).Acta Hepatologica Japonica 2010;51(8):460-84.

5) L3F05955　Addario L, Tritto G, Cavaglià E, Amodio F, Giannelli E, Di Costanzo GG. Preserved liver function, portal thrombosis and absence of oesophageal varices are risk factors for metastasis of hepatocellular carcinoma. Dig Liver Dis 2011;43(4):319-24.

6) L3F04055　Kanda M, Tateishi R, Yoshida H, Sato T, Masuzaki R, Ohki T, et al. Extrahepatic metastasis of hepatocellular carcinoma:incidence and risk factors. Liver Int 2008;28(9):1256-63.

7) LF11146   Koneru B, Teperman LW, Manzarbeitia C, Facciuto M, Cho K, Reich D, et al. A multicenter evaluation of utility of chest computed tomography and bone scans in liver transplant candidates with stages I and II hepatoma. Ann Surg 2005;241(4):622-8.

8) LF10506   Lee KH, Park JM, Yoon JK, Koh KC, Paik SW, Kim BT. Bone scintigraphy of skeletal metastasis in hepatoma patients treated by TAE. Hepatogastroenterology 2003;50(54):1983-6.

9) L3F01371   Kim YK, Lee KW, Cho SY, Han SS, Kim SH, Kim SK, et al. Usefulness 18F-FDG positron emission tomography/computed tomography for detecting recurrence of hepatocellular carcinoma in posttransplant patients. Liver Transpl 2010;16(6):767-72.

10) L3F04193   Sugiyama M, Sakahara H, Torizuka T, Kanno T, Nakamura F, Futatsubashi M, et al. 18F-FDG PET in the detection of extrahepatic metastases from hepatocellular carcinoma. J Gastroenterol 2004;39(10):961-8.

11) L3F03364   Park JW, Kim JH, Kim SK, Kang KW, Park KW, Choi JI, et al. A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J Nucl Med 2008;49(12):1912-21.

12) L3F03968   Chen SF, Tsai NW, Lui CC, Lu CH, Huang CR, Chuang YC, et al. Hepatocellular carcinoma presenting as nervous system involvement. Eur J Neurol 2007;14(4):408-12.

CO17   Does contrast-enhanced ultrasound improve the ability to diagnose HCC?

Recommendation

Contrast-enhanced ultrasound is useful for the differential diagnosis of liver tumors and the differential and locational diagnoses of HCC **(Grade B)**.

- **Background**

The Japanese Society of Ultrasonics in Medicine has revised its "Ultrasound Diagnostic Criteria for Hepatic Tumors" (L3H00050[1)]), and it is now recommended that Doppler and contrast enhancement findings in addition to B-mode findings be examined for the qualitative diagnosis of liver tumors.

As of January 2013, Sonazoid® is the only ultrasound contrast agent that is clinically available in Japan. The first-generation contrast agent known as Levovist® (not currently manufactured) is composed of air-filled microbubbles covered with palmitic acid, with no shell. Because Levovist® is easily broken down during ultrasonography, an intermittent transmission method using high acoustic pressure was generally used to enhance images. However, real-time imaging proved to be difficult. Moreover, Kupffer images can only be acquired in one sweep scan in the post-vascular phase. Sonazoid® is a second-generation contrast agent composed of insoluble gas (perfluorobutane) microbubbles enclosed in a phospholipid shell, which became available for clinical use in January 2007 in Japan. With low acoustic pressure ultrasound, the gas bubbles are not easily broken, allowing for continuous image transmission, resulting in improved real-time observation. With contrast-enhanced ultrasound, vascular images acquired immediately after contrast administration are combined with Kupffer images generated when Sonazoid® is phagocytosed by reticuloendothelial cells; these images are then used for liver tumor diagnosis. However, although SonoVue® and Definity®, the second-generation contrast agents, are used overseas (neither has been approved in Japan), they are used only for vascular imaging because they are not phagocytosed by reticuloendothelial cells.

- **Scientific Statement**

Contrast-enhanced ultrasound can be used to diagnose HCC with a sensitivity of 94%–100% and a specificity of 91%–97% (L3F05344[2)] Level 1, L3F05345[3)] Level 1, L3F03901[4)] Level 1, L3F05389[5)] Level 1, L3F05397[6)] Level 1, L3F05398[7)] Level 1, L3F03082[8)] Level 1). Compared with the diagnostic performance of dynamic CT, dynamic MRI, and SPIO-enhanced MRI, that of

contrast-enhanced ultrasound is not considered inferior. Furthermore, it has been reported for surveillance in patients with cirrhosis, and the contrast-enhanced group was found to be more useful for diagnosing HCC compared with the B-mode-only group and the B-mode + AFP measurement group [diagnostic accuracy was 72.0%, 90.3%, and 96.6%, respectively (p < 0.05); L3F05383[9] Level 1]. In addition, Sonazoid® was found to be excellent for the detection and diagnosis of intrahepatic lesions, even with intraoperative contrast-enhanced ultrasound. Not only was staging determined correctly, but also diagnostic accuracy was improved (L3F05339[10] Level 1, L3F05343[11] Level 2a). Nevertheless, the diagnostic performance of contrast-enhanced ultrasound tends to decrease as the depth of lesions increases and the size of lesions decreases to <1 cm (L3F05346[12] Level 1).

Defect reperfusion imaging is possible with contrast-enhanced ultrasound using Sonazoid®. Defect reperfusion imaging is a method in which tumors appear as defects that are targeted for repeat administration of Sonazoid®, which results in detailed visualization of tumor hemodynamics. This method is useful for liver tumors that are difficult to identify in B-mode (L3F03791[13] Level 1).

It has been reported that new applications of contrast-enhanced ultrasound images, such as 3D and real-time 3D (so-called "4D") images, for the diagnosis of liver tumors and the relevant treatment guidelines are underway (L3F05403[14] Level 1, L3F03339[15] Level 1).

- **Explanation**

In this investigation, we examined studies on second-generation contrast agents, including Sonazoid®, that could not be included in the previous edition (2009 edition) because they were conducted beyond the specified search period.

Differential diagnosis of liver tumors using contrast-enhanced ultrasound is relatively easy when typical hemodynamics are presented. Contrast-enhanced ultrasound using Sonazoid®, in particular, is beneficial. Nevertheless, it is not easy to differentially diagnose low-grade dysplastic nodules (LGDNs) that are thought to be hypovascular hepatic nodules, high-grade dysplastic nodules

(HGDNs), and early-stage HCC. Portal venous blood flow is preserved in approximately two-third of early-stage HCC patients, and Gd-EOB-DTPA-enhanced MRI is thought to capture pathological changes in liver tumors earlier than contrast-enhanced ultrasound.

Although image quality and arithmetic processing capability have improved in both 3D and 4D contrast-enhanced ultrasound, there remains room for improvement in terms of resolution and real-time imaging. For this reason, these devices must be improved further before they can be used widely in clinical settings.

- **References**

1) L3H00050 Kumada T, Matsuda Y, Iijima H, Ogawa M, Kudo N, Kohara K, et al. ; Sub-Committee for the Revision of Ultrasound Diagnostic Criteria for Liver Tumors. C Ultrasound Diagnostic Criteria for Liver Tumors. Japanese Journal of Medical Ultrasonics 2012;39 (3):317-26.

2) L3F05344 Giorgio A, De Stefano G, Coppola C, Ferraioli G, Esposito V, Di Sarno A, et al. Contrast-enhanced sonography in the characterization of small hepatocellular carcinomas in cirrhotic patients:comparison with contrast-enhanced ultrafast magnetic resonance imaging. Anticancer Res 2007;27(6C):4263-9.

3) L3F05345 Giorgio A, Calisti G, di Sarno A, Farella N, de Stefano G, Scognamiglio U, et al. Characterization of dysplastic nodules, early hepatocellular carcinoma and progressed hepatocellular carcinoma in cirrhosis with contrast-enhanced ultrasound. Anticancer Res 2011;31(11):3977-82.

4) L3F03901 Korenaga K, Korenaga M, Furukawa M, Yamasaki T, Sakaida I. Usefulness of Sonazoid contrast-enhanced ultrasonography for hepatocellular carcinoma:comparison with pathological diagnosis and superparamagnetic iron oxide magnetic resonance images. J Gastroenterol 2009;44(7):733-41.

5) L3F05389 Hatanaka K, Kudo M, Minami Y, Maekawa K. Sonazoid-enhanced ultrasonography for diagnosis of hepatic malignancies:comparison with contrast-enhanced

CT. Oncology 2008;75(Suppl 1):42-7.

6) L3F05397   Seitz K, Bernatik T, Strobel D, Blank W, Friedrich-Rust M, Strunk H, et al. Contrast-enhanced ultrasound(CEUS)for the characterization of focal liver lesions in clinical practice(DEGUM Multicenter Trial):CEUS vs. MRI—a prospective comparison in 269 patients. Ultraschall Med 2010;31(5):492-9.

7) L3F05398   Bernatik T, Seitz K, Blank W, Schuler A, Dietrich CF, Strobel D. Unclear focal liver lesions in contrast-enhanced ultrasonography—lessons to be learned from the DEGUM multicenter study for the characterization of liver tumors. Ultraschall Med 2010;31(6):577-81.

8) L3F03082   Quaia E, D'Onofrio M, Cabassa P, Vecchiato F, Caffarri S, Pittiani F, et al. Diagnostic value of hepatocellular nodule vascularity after microbubble injection for characterizing malignancy in patients with cirrhosis. AJR Am J Roentgenol 2007;189(6):1474-83.

9) L3F05383   D'Onofrio M, Faccioli N, Zamboni G, Malagò R, Caffarri S, Fattovich G, et al. Focal liver lesions in cirrhosis:value of contrast-enhanced ultrasonography compared with Doppler ultrasound and alpha-fetoprotein levels. Radiol Med 2008;113(7):978-91.

10) L3F05339   Arita J, Hasegawa K, Takahashi M, Hata S, Shindoh J, Sugawara Y, et al. Correlation between contrast-enhanced intraoperative ultrasound using Sonazoid and histologic grade of resected hepatocellular carcinoma. AJR Am J Roentgenol 2011;196(6):1314-21.

11) L3F05343   Arita J, Takahashi M, Hata S, Shindoh J, Beck Y, Sugawara Y, et al. Usefulness of contrast-enhanced intraoperative ultrasound using Sonazoid in patients with hepatocellular carcinoma. Ann Surg 2011;254(6):992-9.

12) L3F05346   Mandai M, Koda M, Matono T, Nagahara T, Sugihara T, Ueki M, et al. Assessment of hepatocellular carcinoma by contrast-enhanced ultrasound with perfluorobutane microbubbles:comparison with dynamic CT. Br J Radiol

2011;84(1002):499-507.

13) L3F03791　Kudo M, Hatanaka K, Maekawa K. Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78(Suppl 1):40-5.

14) L3F05403　Luo W, Numata K, Morimoto M, Nozaki A, Ueda M, Kondo M, et al. Differentiation of focal liver lesions using three-dimensional ultrasonography:retrospective and prospective studies. World J Gastroenterol 2010;16(17):2109-19.

15) L3F03339　Luo W, Numata K, Morimoto M, Oshima T, Ueda M, Okada M, et al. Role of Sonazoid-enhanced three-dimensional ultrasonography in the evaluation of percutaneous radiofrequency ablation of hepatocellular carcinoma. Eur J Radiol 2010;75(1):91-7.

CQ18　Is contrast-enhanced ultrasound useful for determining the outcomes of percutaneous ablation therapy and TACE?

Recommendation

Contrast-enhanced ultrasound is useful for visualizing areas with residual tumors **(Grade B)**.

- **Background**

The Response Evaluation Criteria in Solid Tumors (RECIST; L3H00051[1], L3H00052[2]) is widely used as criteria for determining the treatment outcomes for solid cancers. However, it is difficult to use RECIST during the determination of treatment outcomes for HCC because lesions may remain after treatment with curative therapies such as ablative therapy and TACE. For this reason, modified RECIST (mRECIST) (L3H00046[3], L3F00487[4]), which incorporates tumor necrosis evaluation, have been proposed in western countries for determining the treatment outcomes for HCC. Meanwhile, the Response Evaluation Criteria in Cancer of the Liver (2009 revised edition; L3H00047[6]) have been published in Japan as RECICL (L3H00028[7]), together with the "General

Rules for the Clinical and Pathological Study of Primary Liver Cancer (5th edition)"

(L3H00055[5)]).

- **Scientific Statement**

In this investigation, studies on second-generation ultrasound contrast agents, including Sonazoid[®],

were examined.

*Determination of RFA outcome:

According to Ricci et al., a comparative study of contrast-enhanced ultrasound using SonoVue[®]

and dynamic CT as the gold standard revealed that the sensitivity, specificity, negative predictive

value, and positive predictive value of SonoVue[®] were 92.3%, 100%, 97.4%, and 100%,

respectively (L3F03373[8)] Level 1). Kudo et al. reported that residual cancer can be easily indicated

by the defect reperfusion imaging procedure, and diagnosis of HCC was possible even for small

nodules that were not indicated on dynamic CT (L3F03791[9)] Level 1).

Another study examined changes in tumor margins over time after RFA using B-mode imaging

(L3F03724[10)] Level 1), and the tumor margin detection rates at 1, 3, 4, and 5 days after RFA were

65.2%, 54.3%, 43.5%, and 39.1%, respectively. Tumors ablated by RFA tend to appear less clear

over time, and the timing for clearest detection was the following day. Even then, however, tumor

margins could be observed in only two-thirds of the patients, that is, safety margins were difficult

to evaluate in the remaining one-third patients.

*Determination of TACE treatment outcome:

Contrast-enhanced ultrasound has good sensitivity for the detection of remaining vascularity

within liver tumors and is useful for determining treatment outcomes and predicting recurrence

(LF07130[11)] Level 1, LF10810[12)] Level 1, L3F00262[13)] Level 1).

- **Explanation**

Contrast-enhanced CT is generally used to determine treatment outcomes because the objective

evaluation of images, including tumor margins, and assessment of multiple nodules for treatment

are required for the assessment of treatment outcomes. Contrast-enhanced ultrasound, however,

has many benefits, such as the absence of radiation exposure, and it can be used safely in patients with iodine allergies or renal impairment. Therefore, depending on patient and tumor conditions, contrast-enhanced ultrasound will continue to be selected for the evaluation of treatment outcome. Because contrast-enhanced ultrasound offers excellent spatial, contrast, and temporal resolution, even a small residual area of HCC will be well visualized as a hypervascular spot. For this reason, small lesions that cannot be detected by CT because of the partial volume effect, such as residual tumors after percutaneous ablation therapy, can be detected by contrast-enhanced ultrasound. Furthermore, when additional therapies are performed, imaging procedures can become more effective because lesions can be monitored during ablation with contrast enhancement. Moreover, contrast-enhanced ultrasound can be used to assess the treatment outcome within a month of completing treatment (LF10810[12] Level 1, L3F00262[13] Level 1), and although treatment outcome assessment using TACE is conventionally recommended 1 month or more after treatment completion, it is essential that treatment outcomes are assessed in the early stages in order to continue aftercare without losing time.

- **References**

1) L3H00051 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205-16.

2) L3H00052 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours:revised RECIST guideline(version 1.1). Eur J Cancer 2009;45(2):228-47.

3) L3H00046 Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al;Panel of Experts in HCC-Design Clinical Trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100(10):698-711.

4) L3F00487 Lencioni R, Llovet JM. Modified RECIST(mRECIST)assessment for

hepatocellular carcinoma. Semin Liver Dis 2010;30(1):52-60.

5) L3H00055 Edited by the Liver Cancer Study Group of Japan. The General Rules for the Clinical and Pathological Study of Primary Liver Cancer. 5th Edition, Tokyo, Kanehara Shuppan, 2009;p102.

6) L3H00047 Kudo M, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, et al.; Committee for Response Evaluation Criteria in Cancer of the Liver, Liver Cancer Study Group of Japan. Response Evaluation Criteria in Cancer of the Liver (2009 revised edition). Acta Hepatologica Japonica 2010;51(5):261-6.

7) L3H00028 Kudo M, Kubo S, Takayasu K, Sakamoto M, Tanaka M, Ikai I, et al;Liver Cancer Study Group of Japan(Committee for Response Evaluation Criteria in Cancer of the Liver, Liver Cancer Study Group of Japan). Response Evaluation Criteria in Cancer of the Liver(RECICL)proposed by the Liver Cancer Study Group of Japan(2009 Revised Version). Hepatol Res 2010;40(7):686-92.

8) L3F03373 Ricci P, Cantisani V, Drudi F, Pagliara E, Bezzi M, Meloni F, et al. Is contrast-enhanced US alternative to spiral CT in the assessment of treatment outcome of radiofrequency ablation in hepatocellular carcinoma? Ultraschall Med 2009;30(3):252-8.

9) L3F03791 Kudo M, Hatanaka K, Maekawa K. Newly developed novel ultrasound technique, defect reperfusion ultrasound imaging, using sonazoid in the management of hepatocellular carcinoma. Oncology 2010;78(Suppl 1):40-5.

10) L3F03724 Zhou P, Kudo M, Minami Y, Chung H, Inoue T, Fukunaga T, et al. What is the best time to evaluate treatment response after radiofrequency ablation of hepatocellular carcinoma using contrast-enhanced sonography? Oncology 2007;72(Suppl 1):92-7.

11) LF07130 Minami Y, Kudo M, Kawasaki T, Kitano M, Chung H, Maekawa K, et al. Transcatheter arterial chemoembolization of hepatocellular carcinoma:usefulness of coded phase-inversion harmonic sonography. AJR Am J Roentgenol 2003;180(3):703-8.

12) LF10810 Kono Y, Lucidarme O, Choi SH, Rose SC, Hassanein TI, Alpert E, et al.

Contrast-enhanced ultrasound as a predictor of treatment efficacy within 2 weeks after transarterial chemoembolization of hepatocellular carcinoma. J Vasc Interv Radiol 2007;18(1 Pt 1):57-65.

13) L3F00262　Xia Y, Kudo M, Minami Y, Hatanaka K, Ueshima K, Chung H, et al. Response evaluation of transcatheter arterial chemoembolization in hepatocellular carcinomas:the usefulness of sonazoid-enhanced harmonic sonography. Oncology 2008;75(Suppl 1):99-105.