Chapter 1:

Surveillance and Diagnosis

● Introduction

The efficacy of surveillance is demonstrated by increased likelihood of early detection and curative therapy, thereby improving prognosis. Because it is relatively easy to predict patients at high risk of HCC, surveillance has been widely performed for high-risk patients in Japan, especially those with viral hepatitis accompanied by cirrhosis. However, patients at high risk of liver cancer are also at high risk of recurrent cancer after curative therapy, suggesting that early detection and early treatment do not necessarily lead to complete cure. Indeed, even today, there is insufficient evidence that surveillance with ultrasonography (US) alone or a combination of US and tumor markers improves the prognosis of HCC patients, and it is unlikely from a mainly ethical standpoint that randomized controlled trials (RCTs) will be conducted in the future.

In this 2017 version (fourth edition) of the Guidelines, we begin the CQ section by asking the crucial question “Is surveillance recommended?” We then discuss the potential procedures for surveillance when it is recommended.

With recent technological advances, HCC is now diagnosed mainly by imaging, with tumor markers playing a supplementary role. In principle, definitive diagnosis is made based on histopathological findings. However, it is common to make a definitive diagnosis based on imaging findings in patients scheduled to undergo percutaneous ablation and embolization. The consensus is that the typical imaging features of HCC are intense early phase contrast enhancement and delayed phase washout. Therefore, we focused on how to diagnose atypical nodules and what the most appropriate threshold value is for tumor diameter. Also, we reviewed alternative imaging tests recommended when regular imaging is contraindicated (eg, in patients with decreased kidney or liver function) and reviewed diagnostic imaging tests recommended for extrahepatic metastasis.

Tumor markers are useful indicators of the effects of surveillance, diagnosis, and treatment. In the past, when the incidence rate of advanced HCC was at its highest, alpha-fetoprotein (AFP) was used to make the definitive diagnosis. However, as diagnostic imaging technology continues to advance, the role that tumor markers play in the diagnosis of liver cancercontinues to reduce. In Japan, the common tumor markers for HCC are AFP, PIVKA-II (a protein induced by vitamin K absence-II), and AFP-L3 fraction (a lectin-reactive fraction of AFP), and the tests are covered by the National Health Insurance system. When the cutoff values are unchanged, measuring the levels of 2 or more tumor markers categorically improves sensitivity while decreasing specificity.

When abdominal US reveals no obvious tumor, tumor marker testing is used to decide whether to repeat surveillance using a more sensitive imaging modality such as dynamic computed tomography (CT). Tumor markers used in such cases should have large positive likelihood ratios, because positive ratios, which are calculated using the equation Sensitivity / (1 – Specificity), suggest that post-test probability is high.

Absolute tumor marker levels are thought to reflect the total number of tumors in the liver or the

entire body. Therefore, pretreatment measurement of tumor marker levels enables tumor reduction after treatment to be objectively estimated.

In summary, we investigated tumor markers from the perspective of surveillance, diagnosis, and treatment effects.

Explanation of the surveillance and diagnostic algorithm for HCC

1. Target population of surveillance

The decision to start surveillance begins with risk assessment. Patients are considered at high risk for HCC when any of the following three conditions are present: cirrhosis, chronic hepatitis B, or chronic hepatitis C. The surveillance interval is determined based on the involvement of other factors such as age, sex, diabetes, body mass index, aspartate transaminase (AST), alanine transaminase (ALT), platelet count, daily alcohol consumption, and hepatitis B virus (HBV) DNA levels (in patients with hepatitis B). Among high-risk patients, those with cirrhosis type B and C are considered an extremely high-risk group. Although the incidence of HCC decreases in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment and in patients with chronic hepatitis C who achieved sustained virologic response (SVR) after anti-hepatitis C virus (HCV) therapy, these patients should remain under surveillance because the risk of developing liver cancer is still relatively high.

2. Surveillance method

The core of surveillance is screening with abdominal US as the primary measure and tumor marker tests, which is repeated every 3-6 months. This regular screening method may be combined with dynamic CT or dynamic magnetic resonance imaging (MRI) in extremely high-risk patients such as those with cirrhosis.

Theoretically, as the surveillance interval shortens, the chance of detecting tumors in the early stage increases, but the cost of surveillance also increases. It is therefore important to investigate whether exhaustive surveillance makes a clinically significant difference in tumor size and whether the difference is worth the increased cost of surveillance. Furthermore, the smallest tumor size detectable on surveillance depends on various factors such as the severity of cirrhosis, obesity, and background liver disease as well as the accuracy of the screening device. Therefore, the current version of the Guidelines recommends, as an initiative, screening with US every 6 months in high-risk patients and every 3-4 months in extremely high-risk patients. The use of dynamic CT or dynamic MRI (including gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid [Gd-EOB-DTPA]-enhanced MRI) is acceptable in patients with pathological conditions that make the detection of small HCC by US difficult, such as liver shrinkage, severe obesity, and coarse liver parenchyma.

For tumor marker tests, screening with AFP, PIVKA-II, and AFP-L3 fraction is recommended every 6 months in high-risk patients and every 3-4 months in extremely high-risk patients. However, it should be noted that, as of 2017, the National Health Insurance system covers tumor marker testing with AFP and PIVKA-II every month in high-risk and extremely high-risk patients, whereas

it covers testing with AFP-L3 fraction only when there is a high index of suspicion for HCC.

3. US findings of nodular lesions

When US findings suggest new nodular lesions, dynamic CT/MRI is done for confirmation. Contrast-enhanced US is recommended in patients for whom dynamic CT/MRI is contraindicated. In some cases, surveillance dynamic CT/MRI is performed to detect new nodules because of the difficulty with whole liver scanning by US.

Even when no tumor is detected on US, it is important to consider using dynamic CT/MRI in the following cases: persistent elevation of AFP, ≥ 200 ng/mL of AFP, ≥ 40 mAU/mL of PIVKA-II, or ≥ 15% increase in AFP-L3 fraction.

4. Assessment of hemodynamics

In contrast-enhanced imaging, typical HCC is characterized by hypervascular changes, demonstrating increased arterial blood flow in HCC compared with the surrounding liver parenchyma. Hypervascular changes are observed in the arterial (or early) phase of dynamic CT and dynamic MRI (including Gd-EOB-DTPA-enhanced MRI).

4-1. Early phase contrast enhancement

Treatment strategies for HCC should be used for lesions that are visualized as high-attenuation areas (hyperdense or hyperintense signals) in the arterial phase of dynamic CT and low-attenuation areas (hypodense or hypointense signals; i.e., washout) in the portal/equilibrium phase of dynamic MRI compared with the surrounding liver parenchyma. In Gd-EOB-DTPA-enhanced MRI, a reduction in signal intensity during the hepatobiliary phase is regarded as washout. However, because cavernous hemangioma shows as hypointense signals in the hepatobiliary phase, other MR images should be examined before excluding the possibility.

When performing Sonazoid®-enhanced US in patients for whom dynamic CT/MRI is contraindicated, contrast defects in the post-vascular (Kupffer) phase may be observed as washouts. However, it is sometimes difficult to differentiate HCC from high-flow cavernous hemangioma because the latter shows contrast enhancement in the early vascular phase and appears as a contrast defect in the Kupffer phase, necessitating exclusion based on other images.

Lesions < 1 cm not visualized as washouts in the portal/equilibrium phase of dynamic CT will require screening with US every 3 months, provided that the lesions are detectable on US. Dynamic CT/MRI is resumed on observing tumor enlargement or tumor marker elevation. Lesions not visualized on US may be followed up by performing dynamic CT/MRI every 3 months. It is not necessary to follow up lesions definitively diagnosed as benign tumors on diagnostic imaging.

Lesions ≥ 1 cm should be imaged with Gd-EOB-DTPA-enhanced MRI. An appropriate treatment

strategy should be selected for lesions definitively diagnosed as HCC. When Gd-EOB-DTPA-enhanced MRI and other imaging modalities do not clearly show whether lesions are benign or malignant, it may be necessary to perform liver biopsy, contrast-enhanced US, superparamagnetic iron oxide (SPIO)-enhanced MRI, CT during arterial portography (CTAP), or CT during hepatic arteriography (CTHA).

4-2. Absence of early phase contrast enhancement

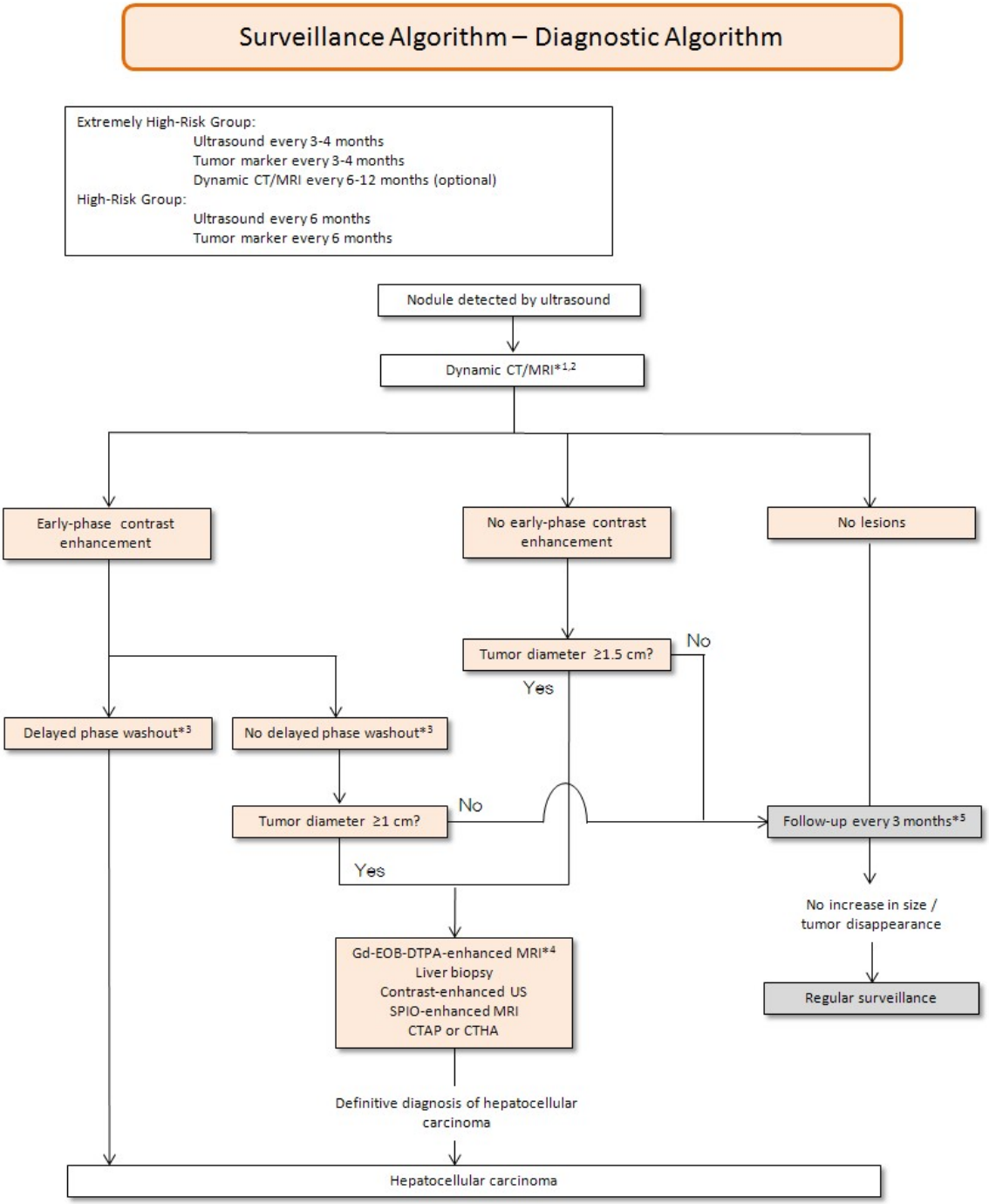
Lesions < 1.5 cm not visualized as high-attenuation areas (hyperdense or hyperintense signals) in the arterial phase of dynamic CT or dynamic MRI, respectively, will require screening with US every 3 months, provided that the lesions are detectable on US. Dynamic CT/MRI is resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US may be followed up with dynamic CT/MRI every 3 months. It is not necessary to follow up lesions that are definitively diagnosed as benign tumors on diagnostic imaging.

Lesions ≥ 1.5 cm not visualized as high-attenuation areas in the arterial phase of dynamic CT will require evaluation using Gd-EOB-DTPA-enhanced MRI. When a reduction in signal intensity is observed in the hepatobiliary phase, it may be necessary to perform liver biopsy, contrast-enhanced US, SPIO-enhanced MRI, CTAP, or CTHA. When no reduction in signal intensity is observed in the hepatobiliary phase, lesions will require screening with US every 3 months, provided that the lesions are detectable on US. Dynamic CT/MRI should be resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US may be followed up with dynamic CT/MRI.

4-3. Findings suggestive of other malignant tumors

Further examination is required of lesions most likely to be intrahepatic cholangiocarcinoma or metastatic liver cancer based on the patterns of contrast enhancement during the arterial and portal/equilibrium phase.

Surveillance Algorithm – Diagnostic Algorithm



[1] Dynamic CT/MRI are used for some patients if the nodule(s) are not visualized on US because of poor visualization and/or the tumor marker(s) are elevated.

[2] Dynamic MRI includes Gd-EOB-DTPA-enhanced MRI.

[3] On Gd-EOB-DTPA-enhanced MRI, a reduction in signal intensity during the hepatobiliary phase is regarded as washout. However, because cavernous hemangioma is visualized as hypointense signals in the hepatobiliary phase, other MR images should be examined before excluding the possibility.

[4] Gd-EOB-DTPA-enhanced MRI is recommended for patients whose first imaging modality was dynamic CT.

[5] Lesions detectable on US are followed up using US. Lesions undetectable on US may be followed up with dynamic CT/MRI.

CQ1 Is surveillance recommended?

Recommendation

Strong recommendation: Regular screening enables the early detection and curative treatment of HCC, likely improving prognosis. Therefore, surveillance is recommended.

■ Background

Surveillance for HCC is common in Japan due to the relative ease of designating high-risk patients. However, patients at high risk of liver cancer are also at high risk of recurrent cancer after curative therapy. According to a follow-up survey of primary liver cancer, liver-related mortality is the leading cause of death among HCC patients, including those with early-stage HCC[1]. Here, we reviewed the efficacy of surveillance in patients at high risk of HCC.

■ Scientific Statement

This CQ was established as a continuation of CQ5 in the third edition (2013 version). In the current revision, a literature search of articles published in the period January 1, 2012 to June 30, 2016 (ie, after the literature search period for the third edition) extracted 836 articles. This was narrowed down to 20 articles in the first screening and to 3 articles in the second screening based on the following inclusion criteria: controlled studies that were conducted in accordance with prospective surveillance protocols and analyzed all deaths. A total of 7 articles, including the 4 articles from the third edition, are cited for CQ1.

Regular surveillance for HCC improved treatment outcomes in an RCT[2]. Compared with the control group (no surveillance), patients with hepatitis B virus (HBV) infection who underwent regular surveillance with US and AFP measurement every 6 months had much smaller nodules, which significantly increased the number of hepatectomy cases and decreased the mortality rate by 37%. However, in another RCT of patients with HBV infection, surveillance based on AFP measurement alone improved the early detection rate but not the mortality rate[3].

Two RCTs have investigated the surveillance interval. The first RCT involved US surveillance every 3 or 6 months in patients with cirrhosis, but no significant difference was observed in overall survival or in the detection rate of HCC ≤ 30 mm, which was the primary endpoint of the study[4]. In the second RCT, the detection rate of early-stage HCC (≤ 2 cm) was higher among patients who underwent surveillance every 4 months than whose who underwent surveillance every 12 months, with no significant difference in 4-year survival rates[5].

In a prospective study, but not an RCT, regular surveillance with US and AFP measurement also extended survival in patients with cirrhosis[6]. In another study, a community-based clinic investigated prognosis among patients with HBV infection by comparing patients with HCC detected by

surveillance and patients who presented to the clinic with HCC, revealing the favorable effect of a mass screening program after correcting for lead-time bias[7]. In a study assessing the effect of ultrasonography mass screening of community residents in a high-risk age group for HBV infection, HCC mortality was decreased by 31% in community residents who participated in the mass screening program compared with those who did not participate[8].

■ Explanation

The most reliable evidence for determining whether to recommend surveillance for patients at high risk of HCC can be obtained from studies that compare mortality after randomly allocating participants to 2 separate groups. However, only 2 previous studies have randomly allocated clusters of patients, one in 2003 and another in 2004[2,3], and none more recently. Two other RCTs have compared short and long surveillance intervals[4,5], but these studies were clearly underpowered to examine mortality given that the estimated hazards were lower.

The second most reliable evidence can be obtained from cohort studies that compare all deaths without randomization. However, the most recent literature search extracted no studies matching this description. Studies comparing all deaths exclusively only among cancer patients after the diagnosis of cancer have inferior evidence to the former two studies[2,3], because of problems associated with lead time[6-8]. Lead time is estimated based on tumor doubling time in the natural course of a particular cancer and on the difference in tumor diameter between cancers detected through screening and those detected based on symptoms, but depending on the parameters used, estimated values may vary substantially. Studies investigating the use of surveillance at the time of diagnosing HCC were excluded from this fourth edition due to the involvement of an additional bias (referral bias).

Taken together, these findings suggest that regular screening for HCC contributes to early detection and curative treatment of HCC, likely improving prognosis. Therefore, surveillance is strongly recommended.

■ References

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a randomized trial comparing 3- and 6-month periodicities. *Hepatology* 2011; 54: 1987-97. PMID: 22144108

5) Wang JH, Chang KC, Kee KM, et al. Hepatocellular carcinoma surveillance at 4 vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. *Am J Gastroenterol* 2013; 108: 416-24. PMID: 23318478

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CQ2 What patient groups are targeted and what methods are used in surveillance?

Recommendation

Strong recommendation: Patients with chronic hepatitis C or B liver disease or nonviral cirrhosis should undergo regular HCC surveillance comprising abdominal US as the primary measure and tumor marker testing every 3-6 months. Additionally, dynamic CT/MRI should be performed in extremely high-risk patients such as those with cirrhosis.

■ Background

HCC exhibits substantial regional clustering mostly due to the involvement of HBV and hepatitis C virus (HCV) and the influence of lifestyle habits. In Japan, approximately 70% of patients with HCC have chronic hepatitis B or C liver disease[1]. Aside from viral hepatitis, risk factors for HCC include cirrhosis, male sex, older age, alcohol consumption, smoking, obesity, fatty liver, and diabetes. Here, we reviewed the targets and methods of surveillance for HCC.

■ Scientific Statement

This CQ is a combination of CQ4 (Who are eligible candidates for surveillance?) and CQ6 (What methods are used in surveillance?) in the third edition. In CQ4 in the third edition, the risk factors for HCC were investigated using a specific search query. Here in this CQ2 in the fourth edition, instead of citing the references for CQ4 in the third edition, we cite newly extracted articles, and the patients reported in these newly extracted studies are the recommended targets of surveillance in this CQ2. A literature search conducted with the search query used for CQ1 and a publication date between

January 1, 2012 and June 30, 2016 extracted 836 articles. This was narrowed down to 9 articles in the first screening based on the inclusion criterion of controlled studies that followed prospective surveillance protocols. One article from those used in the third edition was added to the 9 articles, and thus a total of 10 articles are cited for this CQ.

Singal et al. investigated the most appropriate modality for HCC surveillance in 446 patients with cirrhosis. Among 41 patients diagnosed with HCC by abdominal US alone, AFP testing alone, or a combination of abdominal US and AFP, sensitivity was 44%, 66%, and 90% and specificity was 92%, 91%, and 83%, respectively, indicating that surveillance with abdominal US and AFP testing had better sensitivity[2]. Likewise, Chang et al. reported that surveillance with abdominal US and AFP testing improved sensitivity (99.2%) for detecting liver cancer among 1,597 patients with cirrhosis, compared with surveillance with abdominal US or AFP testing alone[3]. Also, specificity increased from 68.3% to 71.5% when the cutoff AFP level was increased by multiplying the nadir from the previous year by 2 or more. In an RCT of 163 patients with compensated cirrhosis who had a 6.6% incidence of cancer per year, Pocha et al. compared the utility of abdominal US every 6 months and contrast-enhanced CT every 12 months and found that the sensitivity and specificity of abdominal US were 71.4% and 97.5%, respectively, while those of contrast-enhanced CT were 66.7% and 94.4%, respectively, indicating superior sensitivity of abdominal US every 6 months[4]. Abdominal US is also less costly.

Two RCTs have investigated the association between screening interval and HCC diameter[5,6]. In the first RCT involving patients with cirrhosis, the detection rate of HCC ≤ 30 mm, the primary endpoint of the study, was compared between patients who underwent surveillance with abdominal US conducted at 3-month or 6-month intervals[5]. No significant difference was found in the primary endpoint or in overall survival. In the second RCT involving surveillance at 4-month or 12-month intervals, there was no significant difference in 4-year survival rates even though the detection rate of HCC ≤ 2 cm was higher in the 4-month group[6].

Han et al. compared 400 patients with HCC based on the surveillance interval at the time of diagnosis and reported significantly smaller tumor size and significantly improved prognosis (after adjusting for lead-time bias) when the interval was ≤ 6 months[7].

In a case-control study of 452 patients with HCC and cirrhosis and 676 controls, Gopal et al. investigated the diagnostic accuracy of AFP in surveillance and factors affecting the diagnostic accuracy of AFP. They found that the specificity of AFP was higher in patients with non-C hepatitis[8]. Sterling et al. investigated factors affecting tumor marker levels using data from 855 patients obtained in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) study, which measured AFP, AFP-L3, and PIVKA-II levels every 3 months. They reported mild increases in AFP and PIVKA-II levels even in patients with hepatitis C and liver fibrosis as well as HCC[9].

Furthermore, in prospective studies of patients with hepatitis B and cirrhosis, Wong et al.[10] and

Kim et al.[11] investigated the diagnostic accuracy of AFP in nucleos(t)ide analogue treatment and showed that sensitivity could be improved when the cutoff level of AFP was lowered in the drug administration group.

■ Explanation

Theoretically, the addition of AFP testing increases the sensitivity of HCC surveillance because it increases the number of patients who subsequently undergo further examination with dynamic CT/MRI. However, due to a concurrent increase in false-positive rates, the cost-effectiveness of this combined surveillance decreases. Similarly, shorter interval surveillance theoretically detects smaller tumors, but it costs more. Therefore, the question is whether exhaustive surveillance makes a clinically significant difference in terms of tumor size and whether the difference cancels out the increased surveillance costs. In addition, the smallest tumor size detectable by surveillance depends on various factors including the severity of cirrhosis, obesity, and background liver disease as well as the performance of the modality used. Also, because screening costs vary considerably among countries, it is impractical to apply data from cost-benefit analyses carried out overseas to the situation in Japan.

As such, the current tendency is to continue with the existing recommendation. However, when the typical doubling time of HCC is considered, there is insufficient rationale for the hypothesis that the most effective surveillance interval is ≤ 3 months. Also, because Gd-EOB-DTPA-enhanced MRI examination costs 8-9 times more than abdominal US screening in Japan, it seems unlikely that the additional medical cost is worth the extended survival expected. Therefore, we decided to maintain the existing “strong recommendation”, which is well established and widely used across Japan.

Today, we are able to suppress or eradicate hepatitis virus by nucleos(t)ide analogue treatment in patients with hepatitis B and by antiviral therapy in patients with hepatitis C. As a result, the specificity of AFP increases due to the decrease in AFP synthesis in the background liver. Therefore, establishing a new AFP cutoff value for surveillance of such patients is a future challenge.

■ References

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CQ3 What tumor markers are useful for diagnosing HCC?

Recommendation

Strong recommendation: It is recommended to measure AFP, PIVKA-II, and AFP-L3 fraction when diagnosing HCC.

■ Background

In Japan, measurement of the following 3 tumor markers for HCC is covered by the National Health Insurance system: AFP, PIVKA-II, 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. Here, we reviewed tumor markers that are useful when diagnosing HCC.

■ Scientific Statement

This CQ is a new addition to the current Guidelines (fourth edition). A literature search conducted with the search query created for CQ8 in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 820 articles. Among them, 8 articles are adopted based on the following inclusion criteria: studies that described sensitivity, specificity, and tumor size in detail and cohort studies that analyzed advanced tumors and involved a subanalysis based on tumor size (e.g., ≤ 2 cm, ≤ 3 cm, or ≤ 5 cm).

A systematic review was conducted using 17 research studies that examined HCC lesions ≤ 5 cm in terms of sensitivity, specificity, the diagnostic odds ratio, and the positive likelihood ratio[1]. 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 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%, 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 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%, 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.

In a systematic review of 5 studies that investigated the diagnostic accuracy of AFP in patients with hepatitis C, sensitivity was 41-65%, specificity 80-94%, positive likelihood ratio 3.1-6.8, and negative likelihood ratio 0.4-0.6 at a cutoff value of 20 ng/mL[2].

In a more recent systematic review of 49 studies, the sensitivity and specificity of AFP were 59% (95% confidence interval [CI], 54-63%) and 86% (95% CI, 82-89%) and those of PIVKA-II were 63% (95% CI, 58-67%) and 91% (95% CI, 88-93%), respectively[3]. The area under the receiver operating characteristic (AUROC) curve was 0.83 for AFP and 0.77 for PIVKA-II. However, when the number and size of tumors was limited to 3 tumors ≤ 3 cm, the sensitivity and specificity of AFP were 48% (95% CI, 39-57%) and 89% (95% CI, 79-95%) and those of PIVKA-II were 45% (95% CI, 35-57%) and 95% (95% CI, 91-97%), respectively. The AUROC curve was 0.68 for AFP and 0.84 for PIVKA-II.

In a cohort study of 734 patients with chronic hepatitis or cirrhosis, liver cancer developed in 29 patients during the mean observation period of 374.5 days[4]. The sensitivity and specificity of AFP at a cutoff value of 20 ng/mL were 61.2% and 78.3% and those of PIVKA-II at a cutoff value 60 mAU/mL were 41.4% and 90.9%, respectively. In a case-control study of 1,377 patients with HCC and 355 patients with chronic hepatitis or cirrhosis, when the cutoff value of AFP was set at 20, 100,

or 200 ng/mL for tumors < 3 cm, sensitivity was 55%, 23%, and 14% and specificity was 94%, 99%, and 100%, respectively[5]. Similarly, when the cutoff value of PIVKA-II was set at 40 or 100 mAU/mL, sensitivity was 41% and 21% and specificity was 97% and 100%, respectively. The AUROC curve was 0.887 for AFP and 0.812 for PIVKA-II. Stratification by tumor size revealed that the diagnostic accuracy of AFP was significantly higher for tumors < 3 cm, whereas the diagnostic accuracy of PIVKA-II was significantly higher for tumors > 5 cm. In a cohort study of 372 patients with HCV-related cirrhosis, liver cancer developed in 34 patients during the 2-year follow-up period[6]. The sensitivity and specificity of AFP at a cutoff value of 20 ng/mL were 61% and 71.1%; those of AFP-L3 fraction at a cutoff value of 10% were 36.5% and 91.6%; and those of PIVKA-II at a cutoff value of 7.5 ng/mL were 39.2% and 89.6%, respectively. In a different study, patients with chronic hepatitis B were divided into an HCC group (n = 106) and control group (n = 100) and underwent tumor marker testing with AFP and PIVKA-II.[7] The sensitivity and specificity of AFP at a cutoff value of 20 ng/mL were 57.5% and 88.0%, whereas those of PIVKA-II at a cutoff value of 40 mAU/mL were 51.9% and 97.0%, respectively. In a study of surveillance for HCC in 2,830 patients with chronic liver disease, 104 patients with a diagnosis of liver cancer were compared with 104 controls selected based on propensity score matching[8]. When the cutoff value of the highly sensitive AFP-L3 fraction was set at 7%, 10%, or 15%, sensitivity was 39.4%, 16.3%, and 11.5% and specificity was 77.0%, 96%, and 100%, respectively. When the cutoff value of AFP was set at 20 or 200 ng/mL, sensitivity was 41.4% and 12.5% and specificity was 90.4% and 99.0%, respectively. When the cutoff value of PIVKA-II was set at 40 mAU/mL, sensitivity was 34.6% and specificity was 94.0%.

■ Explanation

In Bayes' theorem, post-test odds are calculated by multiplying pre-test odds by a likelihood ratio. Because the incidence of HCC is only 10% per year in extremely high-risk patients, the pretest probability of detecting HCC in biannual surveillance is approximately 5% and the pre-test odds are one-nineteenth. When abdominal US findings are negative, post-test odds decrease to below one-fortieth. So, to bring the probability of having HCC up to ≥ 10% when the results of tumor marker testing are positive, the positive likelihood ratio should be at least 5. This means a sensitivity of ≥ 25% at a specificity of 95% and a sensitivity of ≥ 50% at a specificity of 90%, suggesting that the number of unnecessary confirmatory tests increases and the cost-benefit ratio decreases unless cutoff values and positive likelihood ratios are set high. Because the specificity of AFP is low in patients with chronic active hepatitis, it is necessary to set the cutoff value at ≥ 100 ng/mL. Compared with AFP, AFP-L3 fraction and PIVKA-II have excellent positive likelihood ratios because of high specificity, even though their sensitivity for small HCC is inferior to that of AFP. Recent studies have reported that the specificity of AFP increases in patients with chronic hepatitis B

who are receiving nucleos(t)ide analogue treatment and in patients with chronic hepatitis C who have achieved SVR after antiviral therapy[9-11]. Further study is needed to establish new cutoff values in these patient groups.

In the approximately 20 years since AFP-L3 fraction was approved as a tumor marker for HCC in Japan (and was the last approved), many new tumor markers have been reported, including glypican-3, Golgi protein 73, osteopontin, and microRNAs. However, none of these seem to be clinical applicable at this point. On this basis, it was decided that the use of the three current tumor markers continue to be strongly recommended because their roles have been established and they are covered by the National Health Insurance system.

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CQ4 Is measuring the levels of 2 or more tumor markers useful for diagnosing HCC?

Recommendation

Strong recommendation: Measuring the levels of 2 or more tumor markers is recommended when diagnosing small HCCs.

■ Background

In Japan, AFP, PIVKA-II, and AFP-L3 fraction are covered by the National Health Insurance system for use as tumor markers for HCC.

Tumor markers for HCC are used in definitive diagnosis or in surveillance to determine the need for the next step in the diagnostic process. Today, technological advances in diagnostic imaging mean that tumor marker testing is not always required to make a definitive diagnosis of HCC. However, when tumor marker levels exceed the threshold values in HCC surveillance, it is important to be fully aware of changes in the post-test probability, using the positive likelihood ratio, calculated with the equation Sensitivity / (1 – Specificity), as an indicator. Here, we reviewed the validity of measuring the levels of 2 or more tumor markers for the definitive diagnosis of HCC.

■ Scientific Statement

This CQ is identical to CQ8 in the third edition. A literature search conducted with the search query created for CQ8 in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 688 articles. Among these, 4 articles were carefully selected based on the following inclusion criteria: studies that used 2 or more tumor markers and analyzed sensitivity, specificity, and tumor size in detail. A total of 7 articles, including the 3 articles from the third edition, are thus cited for CQ4.

In a systematic review of 17 studies that analyzed sensitivity, specificity, diagnostic OR, and positive likelihood ratio in patients with HCC ≤ 5 cm, the sensitivity and specificity of AFP were 49-71% and 49-86%, respectively, when the cutoff value was set at 20 ng/mL[1]. At a cutoff value of 200 ng/mL, the sensitivity and specificity were 8-32% and 76-100%, respectively. At the cutoff values of 20 and 200 ng/mL, integrated diagnostic ORs were 4.06 and 6.99 and positive likelihood ratios were 2.45 and 5.85, respectively. For PIVKA-II, the sensitivity and specificity at a cutoff value

of 40 mAU/mL were 15-54% and 95-99% and those at a cutoff value of 100 mAU/mL were 7-56% and 72-100%, respectively. At the cutoff values of 40 and 100 mAU/mL, integrated diagnostic ORs were 21.31 and 6.70 and positive likelihood ratios were 12.60 and 4.91, respectively. The sensitivity and specificity of AFP-L3 fraction at a cutoff value of 10% were 22-33% and 93-99% and those at a cutoff value of 15% were 21-49% and 94-100%, respectively. At the cutoff values of 10% and 15%, integrated diagnostic ORs were 6.43 and 10.50 and positive likelihood ratios were 4.89 and 13.10, respectively. When two tumor markers were used in combination, the diagnostic OR was 6.29-59.81, which was higher than the value obtained from using each tumor marker alone.

However, in a more recent systematic review of 49 studies, the sensitivity and specificity of AFP were 59% (95% CI, 54-63%) and 86% (95% CI, 82-89%) and those of PIVKA-II were 63% (95% CI, 58-67%) and 91% (95% CI, 88-93%), respectively[2]. The AUCs were 0.83 for AFP, 0.77 for PIVKA-II, and 0.88 for their combination, showing that diagnostic accuracy improved when the two markers were used in combination. However, when the number and size of tumors were limited to 3 tumors and ≤ 3 cm, the sensitivity and specificity of AFP were 48% (95% CI, 39-57%) and 89% (95% CI, 79-95%) and those of PIVKA-II were 45% (95% CI, 35-57%) and 95% (95% CI, 91-97%), respectively. The AUCs were 0.68 for AFP, 0.84 for PIVKA-II, and 0.83 for both, showing that diagnostic accuracy was unchanged by using 2 markers.

In a cohort study of 734 patients with chronic hepatitis or cirrhosis, HCC developed in 29 patients during the mean observation period of 374.5 days[3]. Sensitivity and specificity were 65.5% and 85.5%, respectively, in an analysis with cutoff values of AFP and PIVKA-II set at 40 ng/mL and 80 mAU/mL, respectively. In a case-control study of 1,377 HCC patients and 355 patients with chronic hepatitis or cirrhosis, sensitivity and specificity were 82% and 91%, respectively, in an analysis with cutoff values of AFP and PIVKA-II set at 20 ng/mL and 40 mAU/mL, respectively[4].

In a cohort study of 372 patients with HCV-related cirrhosis, HCC developed in 34 patients during the 2-year follow-up period. At a cutoff value of 20 ng/mL, the sensitivity of AFP alone was 61%, but when used in combination with AFP-L3 fraction (at a cutoff value of 10%) and PIVKA-II (at a cutoff value of 7.5 ng/mL), sensitivity increased up to 77%[5]. In a study comparing patients with chronic hepatitis B with HCC (n=106) and without HCC (n=100), the sensitivities of AFP (at a cutoff value of 20 ng/mL) and PIVKA-II (at a cutoff value of 40 mAU/mL) were 57.5% and 51.9%, respectively. However, when the markers were used in combination, sensitivity increased up to 78.3%, while specificity decreased slightly from 88% and 97%, respectively, to just 85%[6]. In a surveillance study of 2,830 patients with chronic liver disease, which compared 104 HCC patients with 104 controls selected based on the propensity score matching method, sensitivity was 60.6% and specificity was 76% when the cutoff values of the highly sensitive AFP-L3 fraction and of AFP and PIVKA-II were set at 7%, 200 ng/mL, and 40 mAU/mL, respectively[7].

■ Explanation

In the surveillance of small HCCs, the use of two types of tumor markers improves sensitivity while minimizing loss of specificity. When measuring 2 or more tumor markers in combination, the result of the tumor marker testing is normally determined to be positive when the level of one of the markers surpasses the cutoff value. Therefore, as the number of tumor markers used in one test increases, sensitivity increases, while specificity inevitablely declines. Because the positive likelihood ratio is defined by the equation Sensitivity / (1 – Specificity), specificity loss has a greater impact, which increases the use of unnecessary confirmatory tests in the case of surveillance or leads to only a negligible increase in post-test probability, even when positive, in the case of definitive diagnosis. To avoid loss of specificity, the cutoff values of tumor markers used in combination should be set higher than the cutoff values when used alone. It is especially important to set the cutoff value of AFP above 20 ng/mL because of low specificity. It is also desirable to combine tumor markers that are complementary to each other. From this standpoint, the combination of AFP and PIVKA-II is ideal because of their low association, which suggests the complementary roles of AFP and PIVKA-II for HCC diagnosis.

In the approximately 20 years since AFP-L3 fraction was approved as a tumor marker for HCC in Japan (the last to be approved), numerous novel tumor markers have been reported, including glypican-3, Golgi protein 73, osteopontin, and microRNAs. However, none of these seem to be clinically applicable at this point. Therefore, it was decided that the use of 2 or more of the 3 conventional tumor markers should continue to be strongly recommended because their roles are well accepted and their use is are currently approved in the diagnosis of HCC in Japan.

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CQ5 Are tumor markers effective indicators of treatment response in patients with HCC?

Recommendation

Strong recommendation: Post-treatment tumor marker levels are effective indicators of clinical response in patients with high tumor marker levels prior to treatment.

■ Background

While the completeness of tumor resection can be evaluated by pathological examination after liver transplantation and hepatectomy, imaging is used to assess clinical response after percutaneous ablation, transcatheter arterial chemoembolization (TACE), systemic chemotherapy, and radiation therapy. Even after liver transplantation and hepatectomy, imaging is used to assess for residual tumor outside the resection margins and the liver. However, imaging-based assessment of clinical tumor response is often problematic due to treatment-related changes such as arterioportal (AP) shunt and Lipiodol accumulation. Here, we reviewed the possibility of using tumor markers to supplement imaging-based assessment of clinical tumor response.

■ Scientific Statement

This CQ is identical to CQ9 in the third edition. A literature search conducted with the search query created for CQ3-5 in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 688 articles. Among these, 3 articles were carefully selected based on the inclusion criterion of studies that used tumor markers to evaluate clinical tumor response. A total of 8 articles, including the 5 articles from the third edition, are thus cited for CQ5.

A previous study investigating whether AFP, PIVKA-II, and AFP-L3 fraction predicted treatment outcome in 416 patients who underwent curative percutaneous ablation (radiofrequency ablation [RFA], 70.7%; PEIT, 24.0%; PMCT, 5.2%) revealed that high post-treatment levels of AFP (> 100 ng/mL) and AFP-L3 fraction (> 15%) were independent factors predicting tumor recurrence[1]. In a

study of 54 patients with HCC treated with RFA (a total of 72 treatment sessions), decrease in AFP levels within 7 days (i.e., the half-life of AFP) was a predictive factor for recurrence-free survival independent of treatment outcome assessed by diagnostic imaging[2]. In a study of 714 HCC patients who underwent hepatectomy, post-hepatectomy normalization rates of tumor markers were 80.3% with AFP and 99.6% with PIVKA-II when the cutoff level was set at 20 ng/mL and 40 mAU/mL, respectively[3]. The pre-treatment levels of AFP and PIVKA-II were correlated with recurrence in ≤ 6 months but not after 2 years. In another study of 165 patients who underwent hepatectomy, non-AFP normalization was likely to be observed especially in recurrent HCCs. Multivariate analysis revealed an association between HCC recurrence and the lowest AFP levels observed after surgery[4].

A study of 146 HCC patients treated with RFA reported an association between the levels of AFP and alanine transaminase in patients with elevated AFP levels despite no tumor recurrence[5]. In contrast, patients without elevated AFP levels and HCC recurrence had normal ALT levels. At the cutoff value of 20 ng/mL, AFP elevation after RFA at HCC recurrence was found in 72.2% in patients with pre-treatment AFP elevation compard with 12.2% in patients with pre-treatment normalized AFP.

In a study of 125 patients who underwent TACE or radioembolization, a decrease of ≥ 50% in AFP levels was a prognostic factor dependent on imaging-based assessment of treatment outcome[6].

In a study of 72 patients who underwent systemic chemotherapy (including molecular-targeted therapy), prognosis was particularly favorable in patients who had stable disease determined based on imaging findings and were AFP responders (i.e., had a 20% or more reduction in AFP levels), compared with patients who had stable disease and were non-AFP responders[7]. Similarly, a study of 107 patients who received systemic chemotherapy or molecular-targeted therapy showed an association between favorable prognosis and a ≥ 50% decrease in AFP levels[8].

■ Explanation

Disease severity, especially for hepatitis, in the background liver is significantly correlated with AFP levels and this often presents problems in HCC surveillance. When AFP test results remain positive in patients with complete response on imaging, it may suggest AFP elevation related to inflammation in the background liver. When using AFP-L3 fraction or PIVKA-II, however, both of which are highly specific tumor markers and are less susceptible to disease activity in the background liver, persistently positive test results strongly indicate the presence of residual tumor.

From the perspective of tumor progression, there is a significant correlation between tumor differentiation and tumor marker production. A linear correlation between tumor size and tumor marker levels can be observed in general, and thus tumor marker levels can be useful indicators of response in advanced HCC. In summary, the use of the 3 types of tumor markers should continue to be strongly recommended because their roles have been well accepted and their use is currently

approved in the diagnosis of HCC in Japan.

To be truly valuable in the assessment of clinical tumor response, tumor marker testing should be incorporated into clinical decision-making processes (e.g., deciding when to perform imaging tests or to change treatment modalities). However, no articles reporting this issue could be found in the current literature search.

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CQ6 What imaging modalities help to accurately diagnose typical HCC in high-risk patients?

Recommendation

Strong recommendation: Dynamic CT, dynamic MRI, and contrast-enhanced US are recommended when diagnosing typical HCC.

■ Background

Most HCCs demonstrate rapid contrast enhancement in the arterial dominant phase and are detected as washouts in the portal venous-dominant phase or equilibrium phase of dynamic CT/MRI. As such, HCCs with this typical contrast enhancement pattern on images are termed typical HCC. When US findings show nodules 1-2 cm in patients with cirrhosis, contrast-enhanced US, CT, or MRI is performed to make a diagnosis of HCC based on the typical contrast enhancement pattern[1].

Here, we reviewed the utility of individual imaging modalities in making a diagnosis of typical HCC.

■ Scientific Statement

This CQ was established by combining CQ11 and CQ15 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 1,193 articles. This was narrowed down to 47 in the first screening and to 25 in the second screening based on the inclusion criterion of studies that accurately assessed the diagnostic accuracy of imaging modalities for typical HCC. A total of 46 articles, including 21 articles (out of 42) with high-quality evidence from the third edition, are cited for CQ6.

The sensitivity and positive predictive value of dynamic CT using multidetector CT (MDCT) scanners is 73% and 69%, respectively, when performed at 5-mm slice thickness, with no significant improvement in detection sensitivity at 2.5-mm slice thickness[2].

Several meta-analyses have shown that the diagnostic accuracy of dynamic MRI with the hepatobiliary-specific contrast agent Gd-EOB-DTPA (trade name, EOB-Primovist) is extremely high for HCC, with a sensitivity of 0.91-0.93 and specificity of 0.94-0.96[3-6]. In Gd-EOB-DTPA-enhanced MRI, the hepatobiliary phase plays an important role in improving diagnostic accuracy[6-10]. However, it should be noted that the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI decreases in patients with decreased liver function and in patients who require liver transplantation[10-12].

The detection sensitivity of diffusion-weighted MRI in detecting HCC is reported to be 45-55%[13] or 57%[14]. It may[15,16] or may not[17] be useful to combine Gd-EOB-DTPA-enhanced MR images with diffusion-weighted images.

Previous studies have compared the accuracy of dynamic MRI and dynamic CT (both with Gd-EOB-DTPA) for HCC detection. Some studies reported the superiority of MRI to CT[18-24], while others showed no significant difference between the two modalities[25-28]. However, 2 meta-analyses have also shown the superior diagnostic accuracy of MRI[10,29]. MRI was also superior in a comparative study involving patients with typical HCC only[30] and was useful for staging HCC and planning treatment[31-33].

SPIO-enhanced MRI is not[34,35] or is slightly[36] superior to dynamic CT when 1.5 T MRI scanners are used, whereas with 3.0 T MRI scanners, the sensitivity of SPIO-enhanced MRI increases and is

superior at detecting small HCCs ≤ 1 cm[37]. Comparison of SPIO-enhanced MRI and Gd-EOB-DTPA-enhanced MRI has shown that the sensitivity of Gd-EOB-DTPA-enhanced MRI is higher with 1.5 T MRI scanners[38] but is comparable with 3.0 T MRI scanners[39].

A meta-analysis of conventional contrast-enhanced US in patients with HCC ≤ 2 cm revealed that sensitivity, specificity, and the Az value on the summary ROC curve were 0.81 (95% CI, 0.78-0.85), 0.86 (95% CI, 0.82-0.89), and 0.93, respectively[40]. Only a limited number of studies have investigated the diagnostic accuracy of contrast-enhanced US with perfluorobutane microbubbles (trade name, Sonazoid®), with even fewer number of studies reporting evidence and levels compared with CT and MRI. In a comparative study of Sonazoid®-enhanced US, dynamic CT, and Gd-EOB-DTPA-enhanced MRI, diagnostic accuracy was 72%, 74%, and 86%, respectively, with no significant difference between the modalities[41]. The early vascular phase of Sonazoid®-enhanced US detects blood flow in 88% of lesions with early contrast enhancement and 28% of HCC with no early phase contrast enhancement on dynamic CT. The Kupffer phase of Sonazoid®-enhanced US detects approximately 83% of lesions visualized as washouts on dynamic CT, but the detection rate decreases for lesions ≤ 2 cm and those located ≥ 9 cm from the body surface[42]. However, in a study of 138 nodular HCCs detected in 123 of 400 areas examined using dynamic CT, the detection sensitivity in the Kupffer phase with Sonazoid®-enhanced US was 73.2-83.1%, which was inferior to the detection sensitivity of non-contrast B-mode US (83.7-84.6%)[43].

The accuracy of detecting HCC before treatment is higher with Gd-EOB-DTPA-enhanced MRI than with CTAP + CTHA using 4-slice MDCT scanners[44], but the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI may[21] or may not[45] be superior to CTAP + CTHA using 16-slice MDCT scanners.

■ Explanation

Today, most institutions use MDCT scanners to perform dynamic CT, rapidly generating clear images compared with MRI. Because one scan takes only a few seconds, the quality of CT images remains high even in patients who cannot breath-hold for the required period of time. In addition, the diagnostic accuracy of CT for typical HCC ≥ 1 cm is satisfactory[25,30].

Remarkable technological advances in MRI scanners has resulted in outstanding diagnostic accuracy of Gd-EOB-DTPA-based dynamic MRI in recent years. However, the high costs of incorporating, maintaining, and operating MRI scanners and the long scan time required mean it may be impractical for some institutions to screen all patients at high risk for HCC using MRI. It is also important to keep in mind that despite the high specificity of Gd-EOB-DTPA-enhanced MRI for HCC, differential diagnosis may be necessary for lesions that show similar early phase contrast enhancement, such as small hemangioma and mass-forming hypervascular intrahepatic cholangiocarcinoma[30].

SPIO-enhanced MRI may be a viable choice for patients with kidney failure for whom iodinated contrast agents and Gd-based agents such as Gd-EOB-DTPA are contraindicated.

Even though CT and MRI are more objective modalities, contrast-enhanced US enables the hemodynamics and reticuloendothelial system of the liver to be examined and it has excellent diagnostic accuracy when second-generation contrast agents are used. Sonazoid® is used in patients with or without kidney failure and is associated with far fewer cases of severe anaphylactoid reactions compared with iodinated contrast agents and Gd-based contrast agents[46]. However, a greater number of comparative studies should investigate the diagnostic accuracy of Sonazoid®-enhanced US in patients with HCC.

Angiography has long been used for the diagnosis of HCC. In recent years, CT scanner systems with interventional radiology features (IVR-CT) have been increasingly used, where MDCT is combined with a flat-panel detector angiography system. Angiography, such as CTAP and CTHA, is an extremely useful diagnostic modality for typical HCC, but it is invasive compared with other imaging modalities because of the catheterization of the hepatic artery or superior mesenteric artery. For this reason and also functional improvement of other diagnostic modalities, CTHA and CTAP are performed less frequently for diagnosing HCC. Lately, they are mostly used in combination with other therapeutic techniques such as TACE.

In conclusion, Sonazoid®-enhanced US, dynamic CT, and Gd-EOB-DTPA-enhanced MRI are all useful imaging modalities for typical HCC. It is important to choose the most appropriate of these based on the condition of individual patients and institutional circumstances. All of the modalities are supported by sufficient scientific evidence, and their clinical application has been well established in Japan. Therefore, the Revision Committee has decided by majority vote to recommend them strongly.

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CQ7 What size (cm) of liver nodules showing atypical HCC enhancement pattern on dynamic CT/MRI warrants further examination?

Recommendation

Strong recommendation: Further examination is recommended for hypervascular lesions ≥ 1 cm.

■ Background

There is no definitive evidence that early detection of HCCs with atypical imaging patterns improves overall survival. However, in the case of percutaneous ablation, there is now evidence supporting the increasing possibility that local cure can be achieved as the size of the tumor decreases. Because smaller nodules generally have a lower probability of malignancy, lowering the threshold values during examinations increases the number of unnecessary confirmatory tests and also decreases cost-effectiveness. Here, we reviewed effective threshold values.

■ Scientific Statement

This CQ is identical to CQ7 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 705 articles. This was narrowed down to 9 articles based on the following inclusion criteria: studies that described atypical imaging patterns, tumor size, and pathological assessments of liver nodules. A total of 11 articles, including the 2 articles from the third edition, are cited for CQ7.

In a study involving 54 patients with cirrhosis, Byrnes et al. performed histopathological examination and follow-up observation to determine the malignant or benign potential of 161 nodules < 2 cm that showed early enhancement and subsequently had iso- or hyperintense signals in the portal and equilibrium phases of dynamic MRI[1]. The results showed that 16 (10%) of the 161 nodules were HCC and the rest were benign nodules. When the 161 nodules were classified by size into 111 nodules < 1 cm and 50 nodules ≥ 1 cm, the proportion of HCC was 0.6% (1) and 30% (15), respectively.

Haradome et al. compared dynamic CT and Gd-EOB-DTPA-enhanced MR image findings of 60 HCC nodules ≤ 3 cm in 52 patients[2]. Even though AUROC curves from the two modalities were similar, visualization of nodules ≤ 1.5 cm was significantly better with Gd-EOB-DTPA-enhanced MRI than with dynamic CT. With the latter, 14 of the 60 nodules were false-negatives, and as many as 11 and 10 of the 14 nodules were read by readers 1 and 2, respectively, as nodules with early enhancement but no washout. However, both readers reported hypointense signals in 3 of the nodules with no washout during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. This suggests that Gd-EOB-DTPA-enhanced MRI enables the diagnosis of hypervascular HCCs that do

not show washout.

In a study conducted by Sersté et al., 74 patients with chronic liver disease and nodules 1-2 cm on abdominal US underwent dynamic CT, dynamic MRI, and biopsy[3]. Nodules were visualized on the CT or MR images in 60 of the 74 patients and classified based on histopathological findings into 47 HCCs, 6 high-grade dysplastic nodules, 1 cholangiocarcinoma, and 1 hepatic angiomyolipoma. Subsequently, the 6 high-grade dysplastic nodules were all treated as HCC because of changes in imaging patterns and tumor enlargement during follow-up. Also, on CT and MRI of the 47 HCCs, early enhancement and washout were observed in 37 (79%) and 38 (81%) HCCs and early enhancement without washout was observed in 2 (4%) and 6 (13%) HCCs, respectively. On CT and MRI of the 27 nodules that were diagnosed as lesions other than HCC, early enhancement and washout were observed in 5 (18%) and 4 (15%) nodules and early enhancement without washout was seen in 14 and 13 nodules, respectively.

Using Gd-EOB-DTPA-enhanced MRI, Golfieri et al. examined 111 nodules that did not show typical imaging patterns (ie, early enhancement and washout in the portal and equilibrium phases) in 77 patients with cirrhosis[4]. With histopathological diagnosis as the benchmark, 60 of the 111 nodules were diagnosed as benign and the remaining 51 nodules as malignant or borderline lesions. The classification of malignant lesions was as follows: 31 (94%) Class IA nodules (isovascular in the arterial phase and hypointense in the hepatobiliary phase) and 1 (3%) Class IB nodule (isovascular in the arterial phase and isointense in the hepatobiliary phase). All class IC nodules (isovascular in the arterial phase and hyperintense in the hepatobiliary phase) were benign, and all IIA nodules (hypervascular in the arterial phase, no washout, and hypointense in the hepatobiliary phase) were malignant. Three (37.5%) Class IIB nodules (hypervascular in the arterial phase, no washout, and isointense in the hepatobiliary phase) were malignant and 2 (28.5%) Class IIC nodules (hypervascular in the arterial phase, no washout, and hyperintense in the hepatobiliary phase) were malignant. Hypointensity in the hepatobiliary phase of Gd-EOB-DTPA enhanced MRI (Class IA and IIA nodules) had a sensitivity of 88%, negative predictive value of 91%, and diagnostic accuracy of 93% for the diagnosis of malignant or premalignant lesions, values which were significantly higher than for any other MR imaging feature alone or combined ($p < 0.05$, $p < 0.006$, and $p < 0.05$, respectively).

Performing abdominal US every 3 months and dynamic CT every 6 months, Iavarone et al. followed up 36 patients with cirrhosis and histologically proven dysplastic nodules (21 low-grade and 15 high-grade dysplastic nodules)[5]. During the median 36-month observation period (range, 6-128 months), HCC developed in 21 patients (converted to a rate of 13.8% per year). During the follow-up period, 8.7% of the nodules underwent malignant transformation per year, while the incidence of HCC in the area of the liver parenchyma that was nodule-free was 7.1% per year. The rate of malignant transformation was higher in high-grade dysplastic nodules than in low-grade

dysplastic nodules (32.2% vs. 9.3% per year, respectively; p = 0.0039).

DiMartino et al. investigated the diagnostic accuracy of Gd-BOPTA-enhanced MRI in 140 patients with 163 HCCs, performing Gd-BOPTA-enhanced MRI along with abdominal US and dynamic CT and using histopathological diagnosis or tumor diameter ≥ 5 mm as the benchmark[6]. Among 83 nodules 1-2 cm, the diagnostic confidence of malignancy increased for 21 (25.3%) nodules based on the imaging patterns in the hepatobiliary phase, whereas 10 (12.0%) nodules showed imaging patterns indicative of malignancy only in the hepatobiliary phase.

Using Gd-EOB-DTPA-enhanced MRI in 216 patients with 304 pathologically proven HCCs, Choi et al. showed that HCCs with atypical patterns of contrast enhancement were small (52.8% in HCCs ≤ 1 cm), lower histologic grade (38.8% in well-differentiated HCC), and associated with worse Child-Pugh class (57.1% in class C) and that HCCs with iso- to hyperintensity in the hepatobiliary phase were smaller (30.6% in HCCs ≤ 1 cm), had lower histologic grade (20.4% in well-differentiated HCCs), and were associated with worse Child-Pugh class (34.3% in class C)[7].

Manini et al. performed contrast-enhanced US, dynamic CT, and dynamic MRI in 98 patients with cirrhosis and 119 liver nodules (7 nodules < 1 cm, 67 nodules 1-2 cm, and 45 nodules > 2 cm) detected during US surveillance, making a diagnosis of HCC in 84 nodules (70%)[8]. Among 43 HCCs 1-2 cm, typical imaging features were seen in 23 (53%) on contrast-enhanced US and CT, in 5 (12%) on CT and MRI, in 2 (5%) on CT only, and in 4 (9%) on MRI only. Biopsy was needed for definitive diagnosis in 35 (53%) nodules.

In a study involving 60 patients with HCC (146 lesions; 70 > 1 cm and 76 ≤ 1 cm), Yu et al. showed that mean sensitivity of Gd-EOB-DTPA-enhanced MRI was 46% for HCCs ≤ 1 cm[9].

Forner et al. performed contrast-enhanced US and dynamic MRI in 168 patients with cirrhosis and nodules 5-20 mm detected during US surveillance, followed by biopsy in patients whose imaging findings were inconclusive[10]. They found that 18 of 55 nodules that did not appear as hypervascular lesions on contrast-enhanced US were HCC, leading them to conclude that HCC should not be excluded even when hypervascular lesions are not detected on contrast-enhanced US.

In accordance with the Liver Imaging Reporting and Data System (LI-RADS), which was established to standardize CT and MR imaging features for the diagnosis of HCC, Darnell et al. evaluated 133 nodules visualized on MRI in 159 patients with liver nodules ≤ 20 mm, which were detected during US surveillance for HCC[11]. On the LI-RADS, category 1 and 2 nodules indicate definitely and probably benign lesions, respectively. Category 4 and 5 nodules indicate probable and definitive HCC, respectively. Among 42 category 3 lesions (intermediate probability of HCC), none of the 4 lesions < 10 mm were HCCs, whereas 65% (17/26) of nodules 10-15 mm and all 12 lesions 16-20 mm were HCCs.

■ Explanation

Typical features of HCC on dynamic CT/MRI are nodules visualized as high signal intensity areas in the arterial phase (early enhancement) and low-signal intensity areas relative to the surrounding liver parenchyma in the portal and/or equilibrium phase (washout). Nodules with atypical findings are defined as those showing high signal intensity in the arterial phase and high- or iso-signal intensity relative to the surrounding liver parenchyma in the portal and equilibrium phases; or those showing iso- or low-signal intensity in the arterial phase and iso- or low-signal intensity in the portal and/or equilibrium phase. The differential diagnosis includes arterioportal shunt, focal nodular hyperplasia, and cavernous hemangioma for the former; and regenerative nodules, dysplastic nodules, and early-stage HCC for the latter. Washouts are often unclear in small nodules even if they are hypervascular HCCs. Hypervascular nodules may benefit from early diagnosis because their biological malignancy is thought to conform to HCCs with typical imaging features. In contrast, the beneficial effect of early diagnosis is less clear in early-stage hypovascular HCCs because they are thought to be well differentiated compared with hypervascular HCCs. In the case of nodules < 1 cm, imaging findings are often insufficient to make a definitive diagnosis, and biopsy is associated with a high incidence of sampling error. For these reasons, and because it generally takes a relatively long time for lesions < 1 cm to double in size (growing into lesions > 2 cm), follow-up observation may be appropriate. The above findings suggest there is sufficient evidence to recommend thorough examination for hypervascular lesions ≤ 1 cm even when they are atypical nodules. Therefore, the Revision Committee has decided by majority vote to strongly recommend further examination for liver nodules ≥ 1 cm showing high signal intensity in the arterial phase and high- or iso-signal intensity relative to the surrounding liver parenchyma in the portal and equilibrium phases on dynamic CT/MRI.

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CQ8 What imaging modalities help to accurately diagnose early-stage HCC in patients with cirrhosis?

Recommendation

Strong recommendation: Gd-EOB-DTPA-enhanced MRI has a high detection rate for early-stage HCC.

■ Background

With improvements in the performance of diagnostic imaging modalities and with the introduction of novel contrast agents and diffusion-weighted imaging, it is now often possible to detect small or hypovascular nodules, including early-stage HCCs, in patients with chronic liver disease. Early-stage HCCs, which are generally ill-defined hypovascular nodules and well-differentiated HCCs, are less likely to be malignant and are highly unlikely to cause intrahepatic metastasis or vascular invasion. Because HCC presents with various imaging features during a multistage development process, it is important to manage early-stage HCC differently from typical HCC. Here, we reviewed imaging modalities for accurate diagnosis of early-stage HCC in patients with cirrhosis.

■ Scientific Statement

This CQ was established by combining CQ10, 15, and 17 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1,

2012 and June 30, 2016 extracted 467 articles. This was narrowed down to 73 articles in the first screening and 15 articles in the second screening based on the following inclusion criteria: preferably RCTs but also non-RCTs that investigated the ability and accuracy of detecting early-stage HCC by Sonazoid®-enhanced US, Gd-EOB-DTPA-enhanced MRI, and contrast-enhanced CT conducted following an appropriate protocol designed to diagnose HCC. A total of 26 articles, including the 11 articles from CQ10 in the third edition, are cited for CQ8.

HCC is suspected when serum AFP levels increase gradually and nodules are detected on US in patients with cirrhosis[1], but because of cirrhosis in the background liver, conventional unenhanced US is often not sensitive enough to distinguish between well-differentiated hypovascular HCC and dysplastic nodule in this group of patients[2]. As with unenhanced US used for screening, Sonazoid®-enhanced US enables microvessels and defects in the Kupffer phase to be examined[3] and is useful for distinguishing early-stage HCC and borderline lesions[4,5].

In dynamic CT, the equilibrium phase is essential for small HCC detection[6]. MRI provides superior tissue contrast, clearly delineating between the liver and tumor even without the use of a contrast agent. However, a contrast agent is needed for qualitative diagnosis of liver tumors. Gd-EOB-DTPA-enhanced MRI is an excellent diagnostic modality for HCC[7], detecting HCC more effectively than dynamic MDCT[8]. In a study comparing the diagnostic accuracy of dynamic MDCT and Gd-EOB-DTPA-enhanced MRI in ROC analysis of 30 nodules that were histologically diagnosed as early-stage HCC after hepatectomy, Gd-EOB-DTPA-enhanced MRI was superior to dynamic MDCT in terms of Az value (0.98-0.99 vs 0.87, respectively), sensitivity (94-97% vs 58-68%, respectively), and negative predictive value (96.8-98.1% vs 80.7-84.4%, respectively)[9]. The diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI and dynamic MDCT was also compared for 86 nodules histopathologically diagnosed as HCC and dysplastic nodule. Gd-EOB-DTPA-enhanced MRI had a significantly better diagnostic accuracy for hypervascular HCCs ≤ 2 cm than dynamic MDCT, and Gd-EOB-DTPA-enhanced MRI had significantly higher sensitivity (95%) in detecting hypovascular nodules than MDCT (61%)[10]. Similarly, in other studies, the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI (hepatobiliary phase) was superior to dynamic MDCT for small HCC (especially HCC ≤ 2 cm), hypovascular HCC, and early-stage HCC, even though the diagnostic accuracy for typical HCC is comparable to or slightly better than dynamic MDCT[11-16].

In a study comparing the diagnostic accuracy of Sonazoid®-enhanced US and Gd-EOB-DTPA-enhanced MRI for nodules histopathologically diagnosed as advanced HCC (n = 40), well-differentiated hypovascular HCC (n = 33), or dysplastic nodules (n = 9), while 0% of dysplastic nodules and 9% of well-differentiated hypovascular HCCs were visualized as hypoechoic signals in the Kupffer phase of Sonazoid®-enhanced US, 33% and 94%, respectively, were visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI[17]. This suggests that Gd-EOB-DTPA-enhanced MRI is more effective than Sonazoid®-enhanced US at

detecting hypovascular and well-differentiated HCCs.

Some small hypovascular nodules with hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI undergo transformation to hypervascular HCCs[18-20], and nodules ≥ 1 cm and fat-containing nodules are at high risk of hypervascularization[21]. Gd-EOB-DTPA-enhanced MRI was reported to extremely useful in differentiating early-stage HCCs from dysplastic nodules in one study[9], but in another study it was difficult to use[10].

Taken together, the findings from these studies suggest that Gd-EOB-DTPA-enhanced MRI is superior to dynamic MDCT and contrast-enhanced US in detecting early-stage HCC.

■ Explanation

The validity of surveillance for HCC is demonstrated by improved prognosis, by detecting early-stage HCC on regular screening and then providing highly curative treatment. In general, ill-defined, hypovascular nodules ≤ 2 cm and well-differentiated HCCs are early-stage HCCs, and no stromal invasion is also an important histopathological feature.

US, CT, and MRI are common screening modalities for HCC. When nodules are visualized on US, they are then evaluated on dynamic MDCT using contrast agents. This is because the dynamics of arterial and portal blood flow changes between liver nodules and the surrounding liver parenchyma during multistep hepatocarcinogenesis. However, in the case of high-grade dysplastic nodules with ≥ 2-fold cell density in some areas or with mild structural atypia, there is a limit to differentially diagnosing early-stage HCC and dysplastic nodules based on intranodular blood flow because of overlapping imaging features. Therefore, Sonazoid®-enhanced US and Gd-EOB-DTPA-enhanced MRI are more often used of late. Sonazoid®-enhanced US allows for the assessment of blood flow in nodules during the arterial phase and the uptake of contrast agent during the post-vascular (or Kupffer) phase, so is very useful for real-time assessment of hemodynamics in liver nodules and Kupffer cell function. Early-stage HCCs, which are hypovascular due to reduced intratumoral arterial/portal blood flow, are expected to show hypoechoic signals on Sonazoid®-enhanced US compared with non-tumor areas; however, at present, there is no consensus about US findings or diagnostic accuracy presumably due to very subtle changes in blood flow. Also, few early-stage HCCs are visualized as defects in the Kupffer phase of Sonazoid®-enhanced US because even the Kupffer cells have comparable or slightly reduced signals compared with non-tumor areas.

Similar to dynamic CT/MRI using contrast agents, Gd-EOB-DTPA-enhanced MRI provides information about hemodynamics in the arterial and portal venous phases, and the hepatobiliary phase, which begins approximately 10-20 min after the injection of contrast agent, is thought to be useful for detecting HCC, including early-stage HCC, because of differences in contrast enhancement due to functional variability in liver cells. Signal intensity in the hepatobiliary phase of

Gd-EOB-DTPA-enhanced MRI correlates with the malignant potential of borderline lesions, and due to clear hypointense signals, the detection rate is high for early-stage HCC compared with that for dysplastic nodule. The consensus on Gd-EOB-DTPA-enhanced MRI is that, compared with other conventional diagnostic modalities, the hepatobiliary phase more distinctly visualizes changes occurring in the early stage of multistep oncogenesis (e.g., from dysplastic nodule to early-stage HCC) and is therefore useful for distinguishing HCCs from borderline lesions[22]. However, it should be kept in mind that HCC may be poorly detected in patients with cirrhosis and severe hepatocellular dysfunction, which increases false negatives, because of insufficient contrast enhancement of the liver parenchyma. An increasing number of institutions are now able to produce high-quality diffusion-weighted MRI images. In studies that investigated the findings and accuracy of diagnostic imaging in HCC and hypovascular HCC ≤ 2 cm, diagnostic reliability was improved by combining hypointense signals from the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI and hyperintense signals from diffusion-weighted MRI[23,24]. However, in another study, the addition of diffusion-weighted images to Gd-EOB-DTPA-enhanced MR images did not increase the diagnostic accuracy rate for HCC ≤ 2 cm[25], suggesting that there is currently insufficient evidence to support using diffusion-weighted imaging for the detection of early-stage HCC. Hypovascular nodules visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI are sometimes visualized as hypervascular nodules on contrast-enhanced US, resulting in a diagnosis of HCC. For this reason, contrast-enhanced US may be used to complement Gd-EOB-DTPA-enhanced MRI[26].

According to the articles selected for this CQ, the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI is high for early-stage HCC compared with dynamic MDCT and contrast-enhanced US, provided that the MRI scanner is equipped for high-quality dynamic scanning. Low-field MRI scanners and those with insufficient diagnostic accuracy are not suited for detection of early-stage HCC. Compared with US and MDCT devices, MRI scanners equipped for high-quality dynamic scanning are not yet widespread in Japan. Also, there are limits to the number of patients who can undergo HCC screening with Gd-EOB-DTPA-enhanced MRI because, unlike CT, the scanning time is long and patient throughput is poor. As for contrast-enhanced US, the number of institutions offering this service is limited at this point because of cumbersome steps and skill requirements. In Japan, the large number of patients with chronic liver disease has rendered conventional US and dynamic MDCT the main diagnostic modalities for screening HCC.

Because the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI for small and hypovascular HCCs has been proven in many studies, in this CQ the Revision Committee strongly recommends this imaging modality for the accurate diagnosis of early-stage HCC in patients with cirrhosis.

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CQ9 What imaging modalities effectively detect liver cancer in patients with decreased kidney or liver function?

Recommendations

Weak recommendation: Contrast-enhanced CT or MRI may be performed in patients with decreased kidney function in accordance with the following criteria: Gd-EOB-DTPA-enhanced MRI with estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73 m^2, SPIO-enhanced MRI with eGFR < 30 mL/min/1.73 m^2, and SPIO-enhanced MRI or dynamic CT when undergoing dialysis.

Weak recommendation: Noncontrast-enhanced MRA (including diffusion-weighted MRI) and US (including Sonazoid®-enhanced US) are safe and effective in patients with kidney failure for whom contrast-enhanced CT or MRI is contraindicated.

(Very few studies have investigated the effect of contrast-enhanced CT and MRI and the appropriate contrast agents to be used in patients with decreased liver function equivalent to Child-Pugh C.)

■ Background

There are limited options for testing and diagnostic imaging in patients with kidney and liver failure because the use of iodinated contrast agents and Gd-based contrast agents is contraindicated for patients with decreased kidney function and the enhancement effect of hepatobiliary-specific contrast agents decreases in patients with liver dysfunction. Here, we reviewed imaging modalities useful for the diagnosis of liver tumors in this group of patients.

■ Scientific Statement

This CQ was established based on CQ14 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 257 articles. This was narrowed down to 31 articles after the first screening and to 9 articles after the second screening based on the following inclusion criteria: studies that involved a large number of patients and reported higher evidence levels than cross-sectional studies. Of the 6 articles used in the third edition, 1 article that used a special technique was excluded and was replaced with a new article. Therefore, a total of 16 articles are cited for CQ9.

Diffusion-weighted imaging does not outweigh contrast-enhanced MRI, but it is useful in certain aspects[1-5]. The US contrast agent perfluorobutane microbubbles (Sonazoid®) and hepatocyte-specific MRI contrast agent SPIO (Resovist®) do not adversely affect kidney function and their side effects are not amplified in patients with decreased kidney function (as stated in the package inserts).

Administration of Gd-EOB-DTPA (EOB-Primovist®) for patients on dialysis is not recommended because these patients show reduced contrast enhancement of the liver parenchyma and significantly reduced clearance of the agent[6]. To date, only a few studies have investigated the appropriate

combinations of contrast agents and imaging methods when performing dynamic CT/MRI in patients with various levels of estimated glomerular filtration rate (eGFR).

Some utility of Gd-EOB-DTPA-enhanced MRI has been shown in patients with decreased liver function[7], but the contrast enhancement of tissues decreases in the hepatobiliary phase[8-11] and diagnostic accuracy decreases as liver function deteriorates[7,12]. In addition, patients with decreased liver function show decreased contrast enhancement in the Kupffer phase of SPIO-enhanced MRI[13] and contrast-enhanced US[14]. Also, the diagnostic accuracy of diffusion-weighted MRI for HCC is decreased in this group of patients with decreased liver function[7]. To date, only a few studies have investigated the appropriate combinations of contrast agents and imaging methods in patients with liver failure regarded as Child-Pugh C, preventing us from making even a tentative recommendation for such cases.

■ Explanation

When explaining the risks associated with the use of iodinated contrast agents and Gd-based contrast agents in patients with decreased kidney function, we need to cite other guidelines because it is outside the scope of the current Guidelines. In patients with eGFR < 60 mL/min/1.73 m^2, iodinated contrast agents are associated with the risk of contrast nephropathy (http://www.esur.org/guidelines/en/index.php), and the risk is thought to increase in the presence of other risk factors such as diabetes, dehydration, congestive heart failure, gout, age ≥ 70 years, and administration of nonsteroidal anti-inflammatory drugs.

Gd-based contrast agents are associated with nephrogenic systemic fibrosis (NSF) in patients with decreased kidney function (see guidelines on the administration of Gd-based contrast agents in patients with kidney failure; http://www.radiology.jp/content/files/649.pdf). Therefore, in principle, extracellular Gd-based contrast agents and Gd-EOB-DTPA are contraindicated in patients undergoing dialysis, patients with chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), and patients with acute kidney failure. However, when the use of Gd-based contrast agents is inevitable even after weighing benefits and risks, gadodiamide (Omniscan®) and gadopentetate dimeglumine (Magnevist®) should be avoided because of the high incidence of NSF.

Only a few studies have investigated the appropriate combinations of contrast agents and imaging methods when performing dynamic CT/MRI for the thorough examination of patients with decreased kidney function and variable ranges of eGFR. For this reason, only a tentative recommendation is made in the Guidelines: Gd-EOB-DTPA-enhanced MRI is recommended based on the assumption that patients with eGFR 30-60 mL/min/1.73 m^2 have a relatively small risk of NSF. In contrast, the risk of NSF increases in patients with eGFR < 30 mL/min/1.73 m^2, so it was difficult to decide whether Gd-EOB-DTPA-enhanced MRI or SPIO-enhanced MRI was to be recommended. However, SPIO-enhanced MRI is recommended because the package insert of

Gd-EOB-DTPA states “Avoid using this agent” and because the need for frequent administration is highly likely. Gd-based contrast agents are contraindicated for patients undergoing dialysis. Each institution may choose SPIO-enhanced MRI or dynamic CT depending on its circumstances.

Although some utility of Gd-EOB-DTPA-enhanced MRI has been shown in patients with decreased liver function, the liver parenchyma does not show a clear time-dependent increase in contrast enhancement during the hepatobiliary phase, especially in patients with Child-Pugh C liver function and high ICGR15 rates[9,11].

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CQ10 Are head MRI, thoracic CT, bone scintigraphy, and FDG-PET required for staging HCC?

Recommendations

Weak recommendation: Thoracic CT and FDG-PET are recommended for HCC patients with risk factors for extrahepatic metastasis.

Weak recommendation: Bone scintigraphy may be performed when the patient's condition is unfavorable for FDG-PET.

Weak recommendation: Head CT/MRI may be used as a screening modality for brain metastasis in HCC patients with neurological findings or lung metastasis.

■ Background

The presence or absence of extrahepatic metastasis is an important indication to consider when selecting locoregional therapy for HCC. Therefore, HCC patients with risk factors for extrahepatic metastasis should undergo examination of anatomical sites with a high propensity for metastasis before starting treatment for intrahepatic lesions. Here, we reviewed previous studies that investigated the association between different groups of patients and different imaging modalities for extrahepatic metastasis.

■ Scientific Statement

This CQ is the same as CQ16 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 287 articles. This was narrowed down to 32 articles after the first screening and to 9 articles after the

second screening based on the following inclusion criteria: studies that involved ≥ 50 patients and assessed the staging of HCC based on head MRI, thoracic CT, bone scintigraphy, and FDG-PET. A total of 21 articles, including the 12 articles from the third edition, are cited for CQ10.

The frequency of occurrence of extrahepatic metastasis is thought to be low, at around 1.0-2.3%, in patients with new onset HCC[1,2]. However, one study conducted overseas has shown that 15.4% of HCC patients have asymptomatic extrahepatic metastasis[3]. The frequency of extrahepatic metastasis that appears during follow-up after treatment of intrahepatic lesions is 21-24%[4,5]. The frequency of metastasis by site is 6-29% in the lungs, 5-20% in the lymph nodes, and 0.2-0.6% in the brain[2,5,6]. The risk factors that have been reported for extrahepatic metastasis are progression of intrahepatic lesions, portal vein tumor thrombus, PIVKA-II ≥ 300 mAU/mL, AFP > 100 ng/mL, platelet count ≤ $13 \times 10^4/\mu L$, the absence of esophageal varices, and viral hepatitis[6-8].

Thoracic CT and bone scintigraphy for screening metastasis seldom detect new metastatic lesions in patients with solitary HCC ≤ 5 cm or 3 or more HCCs ≤ 3 cm, but what is worse is the loss associated with false-positive results[9-11].

Bone metastasis from HCC is primarily osteolytic, and approximately 50% of bone metastases occur in the vertebral bodies[1]. Bone scintigraphy[12] and FDG-PET[13-16] are useful whole-body screening modalities for bone metastasis in HCC patients. Bone scintigraphy has a relatively high false-negative rate[11], and FDG-PET is superior to bone scintigraphy in terms of sensitivity and specificity for bone metastasis[15,16].

The detection rate of lung metastasis is higher with thoracic CT than with FDG-PET[16]. FDG-PET is also useful in detecting other extrahepatic metastasis[17], but sensitivity for brain metastasis is reported to be low[13,14]. One study reported that FDG-PET for staging HCC detected extrahepatic metastasis in 9.8% of the patients[18]. A meta-analysis has revealed that the sensitivity and specificity of FDG-PET for extrahepatic metastasis was 76.6% and 98.0%, respectively[19].

The accumulation of FDG in intrahepatic lesions during FDG-PET is an independent prognostic factor for HCC[20].

Because HCC rarely causes brain metastasis[2,5,6,21], most brain metastasis is accompanied by lung metastasis in patients with HCC[1].

■ Explanation

Thoracic CT is the standard screening modality for lung metastasis. Combined abdominal dynamic CT and thoracic CT is used for examining intrahepatic lesions as well as detecting the majority of common extrahepatic metastases.

Bone scintigraphy is useful for whole-body screening, but it does not always demonstrate increased radiotracer accumulation in bone metastasis from HCC. Compared with bone scintigraphy, FDG-PET is an excellent diagnostic imaging modality for bone metastasis from HCC and it even

allows for information related to bone fracture, such as compression fracture, to be evaluated from CT images generated in PET/CT. Because FDG-PET also detects extrahepatic metastasis other than bone metastasis, institutions equipped for FDG-PET may prefer it over bone scintigraphy. FDG-PET has excellent diagnostic accuracy for extrahepatic metastasis from HCC, such as bone metastasis, so proactive use of FDG-PET is reasonable when the abdominal lesion and lung metastasis do not fully explain elevated tumor marker levels.

However, given that only a limited number of institutions are performing FDG-PET imaging at present due to high system costs and the need for a radionuclide with a short half-life, bone scintigraphy may be performed as an alternative to FDG-PET.

Based on these findings, the Revision Committee has concluded that thoracic CT, bone scintigraphy, and FDG-PET are useful for staging HCC and are therefore also useful for screening extrahepatic metastasis. However, the recommendation is rated weak because of insufficient scientific evidence currently reported by large-scale RCTs and meta-analyses. There is also insufficient evidence to support their utility for screening brain metastasis. However, in Japan, these modalities are commonly used for screening brain metastasis in patients with neurological symptoms and those at high risk of brain metastasis based on existing metastasis to other organs such as the lungs. Consequently, the Revision Committee has decided by majority vote on a weak recommendation.

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