Surveillance and Diagnostic Algorithm for Hepatocellular Carcinoma Proposed by the Liver Cancer Study Group of Japan: 2014 Update

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Abstract
Surveillance and diagnostic algorithms for hepatocellular carcinoma (HCC) have already been described in guidelines published by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL-EORTC), and the Japan Society of Hepatology (JSH), but the content of these algorithms differs slightly. The JSH algorithm mainly differs from the other two algorithms in that it is highly sophisticated and considers the functional imaging techniques of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI (EOB-MRI) and Sonazoid contrast-enhanced ultrasound (CEUS) to be very important diagnostic modalities. In contrast, the AASLD and EASL-EORTC algorithms are less advanced and suggest that a diagnosis be made based solely on hemodynamic findings using dynamic CT/MRI and biopsy findings. A consensus meeting regarding the JSH surveillance and diagnostic algorithm was held at the 50th Liver Cancer Study Group of Japan Congress, and a 2014 update of the algorithm was completed. The new algorithm reaffirms the very important role of EOB-MRI and Sonazoid CEUS in the surveillance and diagnosis of liver cancer and is more sophisticated than those currently used in the United States and Europe. This is now an optimized algorithm that can be used to diagnose early-stage to classical HCC easily and highly accurately.

Introduction
Unlike the surveillance and diagnostic algorithm in the guidelines by the American Association for the Study of Liver Diseases (AASLD) [1] and that in the guidelines by the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL-EORTC) [2], the Japan Society of...
Hepatology (JSH) algorithm in the JSH Consensus-Based Clinical Practice Guideline for hepatocellular carcinoma (HCC) is described in considerable detail [3]. The latter guideline recommends the following in relation to surveillance: super high-risk patients (with hepatitis B/C cirrhosis) should be screened by performing ultrasound (US) examinations and measuring the levels of 3 tumor markers (AFP, AFP L-3, and PIVKA-II) every 3–4 months and by performing dynamic CT/MRI every 6–12 months. High-risk patients (with chronic hepatitis B/C or cirrhosis of another origin) should be screened by performing US examinations and measuring the levels of the 3 tumor markers every 6 months [3–6].

The aforementioned diagnostic guidelines for HCC in the United States and Europe mention the diagnosis of HCC solely based on hemodynamic findings. However, the surveillance and diagnostic algorithms in the HCC guideline in Japan have traditionally included not only hemodynamic diagnostic methods, but also functional diagnostic methods such as superparamagnetic iron oxide MRI (SPIO-MRI), gadolinium ethoxybenzyl diethylene-triamine pentaacetic acid-enhanced MRI (EOB-MRI), and Sonazoid contrast-enhanced ultrasound (CEUS) [7, 8].

Recently, a consensus meeting has been held at the 50th Liver Cancer Study Group of Japan (LCSGJ) Congress (June 5–6, 2014, Kyoto) (Congress president: Prof. Masatoshi Kudo) to decide on an updated surveillance and diagnostic algorithm that incorporates the latest advances in the field [9]. The meeting began with a brief overview of the existing guidelines and debate over issues and was followed by a discussion of the roles and significance of EOB-MRI, dynamic CT, and Sonazoid CEUS in the diagnostic algorithm. The meeting concluded with members reaching a consensus and agreeing on an updated algorithm with the use of a voting system. The consensus process and the updated algorithm are described here.

Surveillance and Diagnostic Algorithm in the East and West

JSH Guidelines
Evidence-Based Surveillance and Diagnostic Algorithm
The surveillance and diagnostic algorithms for HCC proposed by the JSH are the surveillance and diagnostic algorithm introduced in the ‘2013 Scientific Evidence-Based Clinical Practice Guidelines for Liver Cancer’ [5], which is an evidence-based algorithm, as well as the diagnostic algorithm for hypervascular and hypovascular hepatocellular nodules [3], which is a consensus-based algorithm.

The algorithm in the JSH guidelines separates patients into a high-risk group (patients with chronic hepatitis B/C or cirrhosis) and a super high-risk group (patients with hepatitis B/C cirrhosis). For the super high-risk group, it is recommended that dynamic CT/MRI be performed every 6–12 months. If a nodule is observed on routine US, dynamic CT/MRI should be performed and the nodule classified based on presence/absence of early contrast enhancement, presence/absence of late-phase washout, and tumor diameter. The tumor diameter cutoff that indicates whether more precise testing should be performed is 1 cm if there is early contrast enhancement but no late-phase washout on dynamic CT/MRI and 1.5 cm if there is no early contrast enhancement. Additionally, if the size exceeds the relevant cutoff value, then CEUS, tumor biopsy, CT during hepatic arteriography (CTHA), and CT during arterial portography (CTAP) are recommended as optional tests [5].

Consensus-Based Diagnostic Algorithm
In the consensus-based diagnostic algorithm, dynamic CT, dynamic MRI, and CEUS is performed after detecting a nodule on US, and a diagnosis is made according to the diagnostic algorithm for hypervascular nodules if contrast enhancement is observed in the early arterial phase. If it is not observed, the diagnostic algorithm for hypovascular nodules is applied. In the diagnostic algorithm for hypovascular nodules, a diagnosis of HCC can be made when washout is observed in the portal venous phase and the equilibrium phase. When washout is not observed, the presence/absence of uptake in the hepatobiliary phase of EOB-MRI or in the Kupffer phase of Sonazoid CEUS is assessed. In the diagnostic algorithm for hypovascular nodules, EOB-MRI/Sonazoid CEUS is performed and a diagnosis of well-differentiated HCC can be made if decreased uptake is observed with both modalities. However, when decreased uptake is observed on EOB-MRI only, a tumor biopsy is performed to diagnose the nodule as either well-differentiated HCC or a precancerous or borderline lesion if the tumor diameter corresponds to the ≥1.5 cm cutoff. If the tumor diameter is <1.5 cm, intensive follow-up is recommended. When decreased uptake is observed on Sonazoid CEUS only, regardless of the tumor diameter, a tumor biopsy is typically performed to diagnose the nodule as either well-differentiated HCC or a precancerous or borderline lesion. Furthermore, if uptake is seen on both modalities, the next workup is determined based on a tumor diameter cutoff of 1.5 cm. The algo
rithms for hyper- and hypovascular nodules both suggest that for institutions capable of performing CTHA/CTAP, these should be selected as optional tests [3].

With the recent recognition that EOB-MRI is useful for diagnosing HCC, particularly hypovascular early HCC, the current HCC diagnostic algorithm needed to be updated in order to put slightly more emphasis on EOB-MRI, and thus this section was updated in the consensus meeting.

**Diagnostic Algorithm in the AASLD Practice Guidelines**

Diagnostic algorithms for HCC that have been proposed outside of Japan include the ‘AASLD Practice Guidelines’ [1] and the ‘EASL-EORTC Clinical Practice Guidelines’ [2].

The 2011 updated version of the AASLD diagnostic algorithm states that nodules found in cirrhotic patients should first be classified based on their diameter. If the nodule diameter is <1 cm, surveillance should be performed every 3 months because the diagnosis of such nodules is difficult. If the size does not change, surveillance every 3 months should be continued; if the diameter changes, the nodule should be diagnosed according to its size. If the diameter is ≥1 cm, a diagnosis of HCC is made when early enhancement is observed in the arterial phase and washout is observed in the portal venous phase on dynamic CT/MRI. If these findings are not observed, hemodynamics should be evaluated with a dynamic study that has not been used before, and a diagnosis of HCC is made if dynamic CT and dynamic MRI ultimately reveal these findings, whereas a biopsy is performed if they do not. As outlined above, this is a simple algorithm, which proposes that a diagnosis should be made based solely on hemodynamic information. Problems with this algorithm include that it does not mention functional diagnostic methods such as EOB-MRI or Sonazoid CEUS, that it requires biopsy more frequently, and that it would be difficult to make a diagnosis of early HCC by imaging [10].

**Diagnostic Algorithm in the EASL-EORTC Clinical Practice Guidelines**

The EASL-EORTC diagnostic algorithm proposes a fundamentally similar one to the AASLD algorithm for nodules <1 cm in diameter. However, it differs in that it proposes a different diagnostic flow for nodules ≥1 cm, namely, for nodules of 1–2 cm and >2 cm. If the nodule diameter is 1–2 cm, early enhancement in the arterial phase and washout in the portal venous phase must be seen on both dynamic CT and dynamic MRI (except if one imaging technique only is recommended in centers of excellence with high-end radiological equipment). If the nodule diameter is >2 cm, a diagnosis of HCC is made when these findings are seen on one of the two modalities. However, as it is actually still possible to diagnose a nodule as HCC if arterial enhancement with portal venous washout is observed on one modality even without high-end radiological equipment, the abovementioned annotation appears to have no meaning. This is a very simple algorithm because, as described above, it essentially considers radiologic hallmarks on one modality as an index that allows for a diagnosis of HCC to be made. Furthermore, neither the AASLD diagnostic algorithm nor the EASL-EORTC diagnostic algorithm is appropriate for diagnosing early HCC, and these algorithms are also problematic in that they do not actively promote the use of noninvasive diagnostic methods since they state that a biopsy must be performed for all nodules when early enhancement in the arterial phase and washout in the portal venous phase are not observed [2].


The diagnostic algorithm for hepatocellular carcinoma proposed by the Arii Research Group as part of a research project funded by a 2008–2010 grant from the Japanese Ministry of Health, Labour and Welfare (principal investigator: Prof. Shigeki Arii) is an algorithm that was mainly compiled by Prof. Osamu Matsui as the group’s final report. This is an easy-to-use algorithm centered on EOB-MRI [11, 12], which can detect and diagnose hyper- and hypovascular HCC with high performance, has strong diagnostic performance for differentiating between liver masses, and which has excellent objectivity and reproducibility. Minor updates were made to this algorithm at a consensus meeting held at the 48th LCSGJ Congress in 2012 [13].

Before the 2014 consensus meeting, HCC experts gathered to create an updated version of the diagnostic algorithm for HCC that was used to spark a discussion at the meeting. First, after surveillance with US and tumor markers, it is recommended that dynamic EOB-MRI should be performed (or dynamic CT for institutions unable to use MRI as the first-line modality) and that nodules are classified as ‘hypervascular with washout’, ‘hypervascular without washout’, or ‘hypovascular’. Nodules that are hypervascular with washout are diagnosed as HCC. However, although cavernous hemangiomas usually do not exhibit washout in the equilibrium phase of dynamic CT, they can exhibit findings resembling washout (pseudo-washout) in

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the equilibrium phase (transitional phase) of dynamic EOB-MRI. Thus, this possibility must be ruled out using another imaging modality or diagnostic method. Furthermore, nodules that are hypervascular without washout are diagnosed as HCC if they are hypointense in the hepatobiliary phase of EOB-MRI. However, the abovementioned issue with hemangiomas necessitates the cautionary notation that cavernous hemangiomas are usually hypointense in the hepatobiliary phase of EOB-MRI and thus should be ruled out using other sequences of MRI and/or other imaging modalities. Nodules that are hypovascular and hypointense in the hepatobiliary phase of EOB-MRI are further evaluated with Sonazoid CEUS and diagnosed as classical HCC if they are hypervascular on that modality. Furthermore, nodules that show a defect in the Kupffer phase of Sonazoid CEUS, it is recommended that a biopsy be performed to differentiate between early HCC and dysplastic nodules (DN) or borderline lesions if the diameter is ≥1 cm, and that intensive follow-up with EOB-MRI be performed every 6 months if the diameter is <1 cm. During the 2014 consensus meeting, LCSGJ experts discussed the updated Ariii Research Group algorithm to form a consensus for the new LCSGJ algorithm.

**Diagnostic Algorithm**

**Role of Sonazoid CEUS**

Sonazoid CEUS serves two roles in the diagnostic algorithm for HCC. First, it can be used to evaluate hypervascularity even in nodules that dynamic EOB-MRI or dynamic multidetector CT (MDCT) cannot determine to be hypervascular because CEUS can capture arterial blood flow within the nodule with high sensitivity without missing the timing of arterial blood flow due to its excellent real-time imaging capabilities. Therefore, CEUS should be performed to actively evaluate the arterial vascularity within the nodule, even for nodules determined to be hypovascular by dynamic EOB-MRI or dynamic MDCT. Second, it has been discovered that hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and show decreased uptake in the Kupffer phase of Sonazoid CEUS are at high risk of malignancy and have a high rate of progression to hypervascular typical HCC. Therefore, hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and hypoechoic in the Kupffer phase of Sonazoid CEUS can almost always be diagnosed as early HCC even without biopsy.

**Role of Dynamic CT and CT Angiography**

Findings of early enhancement in the arterial phase and washout in the portal venous phase on CT have been considered typical of HCC and have been widely used in its diagnosis [14]. However, some types of HCC such as ‘moderately differentiated HCC with fat deposition’ and ‘highly malignant poorly differentiated HCC’ do not show clear early enhancement in the arterial phase, and thus are considered difficult to diagnose with dynamic CT [14]. Furthermore, the lag in scan timing in the arterial phase of dynamic CT may decrease its ability to detect hypervascular lesions, and it is therefore necessary to either improve time resolution or strictly control scan timing. In addition, the enhancing effect of iodine contrast medium used in dynamic CT is weaker than that of gadolinium used in dynamic MRI, which means that it may not depict lesions detected by dynamic MRI.

However, dynamic CT has high spatial resolution and thus can also depict portal vein tumor thrombi that are not depicted in the hepatobiliary phase of EOB-MRI. In addition, EOB-MRI is actually more prone to artifacts with proper scan timing, whereas artifacts appear relatively infrequent on dynamic CT. Dynamic CT is also more reliable than EOB-MRI for differentiating HCC from hemangiomas. Therefore, dynamic CT plays a complementary role to EOB-MRI as it compensates for the shortcomings of EOB-MRI in diagnosing HCC.

The malignancy of hepatocellular nodules in multistep hepatocarcinogenesis has been shown to be correlated with the composition of arterial and portal vein blood flow, so an examination of that composition on CTAP and CTHA images has become the gold standard diagnostic method for estimating the malignancy grade [15, 16]. This diagnostic method can be used to evaluate the malignancy grade of hepatocellular nodules in the process of multistep hepatocarcinogenesis from DN to moderately differentiated HCC based on CTAP and CTHA findings.

In addition, although a nodule that shows enhancement in the early phase of CTHA could be an arterioporal (AP) shunt rather than HCC, HCC can be confirmed if corona enhancement is shown in the late phase [17]. Therefore, it is possible to differentiate HCC from AP shunts by taking late-phase CTHA images and determining whether there is corona enhancement.

These characteristics give CT angiography excellent diagnostic performance for HCC, and it can also reduce the risk of overlooking lesions when used to screen for hepatic lesions before surgery, making it a useful preoperative test as well. However, CT angiography is highly invasive as it requires arterial puncture and therefore is
categorized as an optional test in the JSH diagnostic algorithm for HCC. Actually, the need to perform diagnostic CTHA and CTAP in the routine clinical setting has decreased considerably since the emergence of EOB-MRI.

**Role of EOB-MRI**

**Ability of EOB-MRI to Detect HCC**

The sensitivity and Az values from alternative free-response receiver operating characteristic (AFROC) analysis of EOB-MRI for detecting HCC are significantly higher than those for MDCT, and the ability of EOB-MRI to detect small hypervascular HCC is particularly superior. It has actually become common to encounter cases where hypervascular HCC or nodule-in-nodule HCC that is undetectable by MDCT is detected in a routine screening by EOB-MRI because of early enhancement in the arterial phase or clear hypointensity in the hepatobiliary phase [10, 21]. Furthermore, studies comparing the diagnostic performance of EOB-MRI and MDCT for hypervascular HCC have shown that EOB-MRI is superior or, at the very least, that the two are equivalent.

EOB-MRI is also considered useful for diagnosing early HCC because hypovascular and well-differentiated HCC that cannot be detected by CTHA, CTAP, MDCT, or SPIO-MRI are depicted as hypointense in the hepatobiliary phase of EOB-MRI [10, 75, 76, 84, 89]. In a study of the diagnostic performance of various modalities for early HCC, Sano et al. [89] found that among the many findings with 100% specificity, the only finding with close to 100% sensitivity was hypointensity in the hepatobiliary phase of EOB-MRI (97%); this and other findings have now made it clear that the hepatobiliary phase of EOB-MRI is the superior modality for the diagnosis of early HCC [10, 21].

Moreover, when comparing the detection rates of progressed HCC, early HCC, and DN in the hepatobiliary phase of EOB-MRI with those in the Kupffer phase of Sonazoid CEUS, T1-, T2-, and diffusion-weighted images, the detection rate of progressed HCC with EOB-MRI was 93%; the remaining 7% were hyperintense typical HCC, so the actual detection rate was 100%. Furthermore, the detection rate of early HCC was also as high as 95%. In addition, 33% of DN were detected as faintly hypointense. The detection rate in the Kupffer phase of Sonazoid CEUS was 100% for progressed HCC but just 11% for early HCC, which indicates that the hepatobiliary phase of EOB-MRI is the superior modality for detecting early HCC. Furthermore, the EOB-MRI protocol also includes T1-, T2-, and diffusion-weighted images, so another advantage of EOB-MRI is that it can obtain these findings.

**Risk Factors for Hypervascular Change of Hypovascular Nodules**

In many Japanese studies that have discussed the risk of hypervascular change of hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI [23, 25, 32, 36, 37, 51, 55, 56, 69, 70, 74, 100, 104–110], tumor diameter and nodule growth speed have been reported as risk factors for hypervascularization; these characteristics are therefore important in predicting the hypervascularization of hypovascular nodules. It should be noted that the tumor diameter cutoff in these studies was often around 1 cm. Actually, intensive follow-up of hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI has shown that nodules with a higher growth speed are more prone to develop into hypervascular nodules [56], which suggests that nodule growth speed might be included in the algorithm as well. However, intensive follow-up by EOB-MRI should ensure that hypervascularization is detected at an early stage. In addition, the median tumor diameter of hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI but become hypervascular during the course of intensive follow-up is 1.2 cm, and many hypovascular nodules become hypervascular when they are ≤1 cm.

EOB-MRI has high diagnostic performance for both hypervascular HCC and early HCC compared with other modalities, so it should be considered the first choice for use after US screening in the HCC diagnostic algorithm.
saw <5 patients per month, 44% saw 6–25 patients, 13% saw 26–50 patients, 14% saw 51–100 patients, and 11% saw ≥101 patients per month.

**HCC Surveillance**

The responses to questions regarding the use of imaging diagnostics for HCC were as follows: in answer to the question ‘Following the JSH guideline, is dynamic CT/MRI performed 1–2 times per year for virus-related cirrhotic patients at your institution?’, 84% responded affirmatively and 15% responded negatively, revealing that institutions are following the guideline and actively performing dynamic CT/MRI screening of super high-risk patients (fig. 1). When asked about the frequency of screening, 84% indicated that they performed screening 1–2 times a year (45% once a year and 39% twice a year; fig. 2).

When asked ‘Which modality is the first-line tool for surveillance of HCC by dynamic CT/MRI every 6–12 months for virus-related cirrhotic patients at your institution?’, 58% responded dynamic CT, 40% responded dynamic EOB-MRI, and 1% responded conventional dynamic MRI (with extracellular contrast medium) (fig. 3). Dynamic CT was the most common modality used, but it appears that dynamic EOB-MRI is becoming more commonly used as well. Next, when asked ‘Is it possible to perform dynamic EOB-MRI every 6–12 months for surveillance of HCC in patients with virus-related cirrhosis at your institution?’, 54% responded it was possible and now routinely performed, while 39% responded it was possible but not performed at present, indicating that the majority of institutions are currently capable of routinely performing EOB-MRI (fig. 4). In answer to the
question ‘What is the second-line modality when nodular lesions are detected by US at your institution?’, 60% responded dynamic CT, 32% dynamic EOB-MRI, 8% CEUS, and 0% conventional dynamic MRI (with extracellular contrast medium) or CT angiography (CTHA + CTAP) (fig. 5). As expected, it appears that clinicians find dynamic CT to be an easier test than EOB-MRI to perform after US, due to throughput issues among other reasons. It was also confirmed that dynamic MRI with extracellular contrast medium has been completely replaced with dynamic EOB-MRI. When asked ‘Is it possible to routinely perform Sonazoid-enhanced US (Sonazoid CEUS) when necessary at your institution?’, 92% responded affirmatively, 4% responded negatively, and 4% responded ‘rarely yes’ (fig. 6). The respondents were all physician members of the LCSGJ, so it is likely that many of their institutions were actively engaged in the diagnosis and treatment of HCC. These findings reveal that institutions across Japan are becoming equipped to perform CEUS.

**Role of CEUS and Need for Biopsy**

The next item discussed at the consensus meeting was the ‘2014 Updated Diagnostic Algorithm for Hepatocellular Carcinoma’ proposed by the LCSGJ. In this algorithm, hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI are evaluated with Sonazoid CEUS and those found to be hypervascular and/or those which show a defect in the Kupffer phase of Sonazoid CEUS should be diagnosed as HCC without performing a biopsy. Therefore, when asked ‘Do you think Sonazoid CEUS should be performed if a nodule is not hypervascular in the arterial phase of EOB-MRI or on dynamic CT, especially when it is hypointense in the hepatobiliary phase of EOB-MRI, and shows a defect in the Kupffer phase of Sonazoid CEUS?’, the vast majority (75%) were of the opinion that CEUS should be performed (fig. 7). Next, participants were asked ‘Is it possible to confirm a nodule is HCC without biopsy if the nodule is hypovascular, hypointense in the hepatobiliary phase of EOB-MRI, and shows a defect in the Kupffer phase of Sonazoid CEUS?’. The majority (58%) responded it is possible, but 27% responded that biopsy is mandatory (fig. 8). Although such nodules are uncommon, hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and are hypervascular and/or show a defect in the Kupffer phase of Sonazoid CEUS may also be liver metastases or granulomatous nodules; thus, biopsy is considered necessary to rule out these possibilities. In addition, the current diagnostic algorithm for HCC recommends biopsy for nodules determined to be hypervascular without washout on dynamic EOB-MRI and isointense to hyperintense in the hepatobiliary phase of EOB-MRI. However, in clinical practice, most HCC that are hyperintense in the hepatobiliary phase of EOB-MRI have a capsule or mosaic structure and show radiologic hallmarks on dynamic CT, so biopsy is rarely necessary. This implicates that biopsy should be an optional test. At the same time, although it is possible to diagnose...
hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and hypervascular and/or show a defect in the Kupffer phase of Sonazoid CEUS as HCC with almost complete certainty based on their appearance (e.g., capsule or mosaic structure) and dynamic CT findings, the need for biopsy still cannot be denied. Therefore, the consensus was to recommend biopsy as an optional test on a case-by-case basis.

**Tumor Diameter Cutoff Used to Determine Whether Biopsy Should Be Performed**

The 2012 surveillance and diagnostic algorithm for hepatocellular carcinoma (updated version of the Arii Research Group algorithm) states that hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI should be evaluated with Sonazoid CEUS and sets 1 cm as the tumor diameter cutoff that determines whether biopsy or intensive follow-up should be chosen when a nodule is not hypervascular and shows no defect in the Kupffer phase. The evidence for this is based on the data presented below.

When the data from the pathological diagnoses of 147 nonhypervascular nodules that were hypointense in the hepatobiliary phase of EOB-MRI were analyzed separately by tumor diameter, the percentage of HCC (early to poorly differentiated) was found to be 82% among nodules ≥1.5 cm and 87% among nodules <1.5 cm when using a cutoff size of 1.5 cm. When using a cutoff size of 1 cm, 86% of nodules ≥1 cm and 81% of nodules <1 cm were HCC. Essentially, over 80% of nonhypervascular nodules that were hypointense in the hepatobiliary phase of EOB-MRI were HCC, regardless of the tumor diameter. Therefore, a tumor diameter cutoff of 1 cm was chosen because the risk of HCC is high even when the tumor diameter is 1 cm and in consideration of data indicating that the tumor doubling time rapidly rises when the diameter is 1–1.5 cm.

The conventional morphological cutoff for malignancy, however, was 1.5 cm; thus, many members were opposed to the 1-cm cutoff in the 2012 surveillance and diagnostic algorithm for hepatocellular carcinoma (updated version of the Arii Research Group algorithm). This issue was therefore included as a topic for debate at the consensus meeting this year. When asked ‘What size of nodule should be biopsied when it is hypovascular, hypointense in the hepatobiliary phase of EOB-MRI, and shows no defect in the Kupffer phase of Sonazoid CEUS?’, 55% responded ≥1 cm, 35% responded ≥1.5 cm, 7% answered ≥2 cm, and 0% answered all nodules regardless of size (including <1 cm). The majority of participants responded ≥1 cm, but this was less than the 67% needed to reach a consensus (fig. 9).

The reason for supporting the tumor diameter cutoff of 1.5 cm was that it is difficult to accurately collect tissue from a 1-cm nodule by biopsy, and thus the possibility of sampling errors would increase if nodules ≥1 cm were considered candidates for biopsy. It was noted that neglecting intensive follow-up due to overlooking HCC that was too small to collect tissue from by biopsy would be more likely to delay diagnosis than if biopsy were only performed on nodules ≥1.5 cm. It was also suggested that different tumor diameter cutoffs should be set for hypo- and hypervascular...
nodules because it is not as urgent to treat the former compared to the latter. As biopsy is invasive, its use should be carefully considered even when there is diagnostic evidence for choosing it. There is certainly a problem with tumor doubling time, but some members felt that this could probably be monitored by intensive follow-up to a certain extent. When using data collected by the LCSGJ for 6 years until 2005 to determine the percentage of hypovascular nodules among single new nodules with \( \leq 3 \) cm diameter divided into groups by diameter (at 5-mm intervals), it was found that the percentage of hypervascular nodules drastically increased around 1.5 cm. Furthermore, some members commented that a cutoff of 1.5 cm may not be appropriate as they had observed many hypovascular lesions \( \leq 1.5 \) cm becoming hypervascular once they reached exactly 1.5 cm during follow-up. Therefore, since agreement with the cutoff points of \( \geq 1 \) cm and \( \geq 1.5 \) cm totaled over 90%, the cutoff of ‘small nodules (1–1.5 cm)’ was proposed to the members. Almost all members agreed by voting with a show of hands, so it was decided to adopt this cutoff size. Whether biopsy should actually be performed when nodules are in the 1–1.5 cm stage is left to the institutions themselves on a case-by-case basis.

**Intensive Follow-Up**

Participants were first asked ‘How do you conduct follow-up for a hypovascular nodule that is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS?’. The most frequent response was periodic EOB-MRI at 60%, followed by alternating dynamic CT and EOB-MRI at 25%, and routine surveillance similar to other cirrhotic patients at 6%. More than two-thirds of the respondents responded periodic EOB-MRI and alternating dynamic CT and EOB-MRI (fig. 10). Next, when asked about the frequency of follow-up with EOB-MRI a hypovascular nodule, which is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS or malignancy on biopsy?’, the most frequent response was periodic EOB-MRI at 60%, followed by alternating dynamic CT and EOB-MRI at 25%, and routine surveillance similar to other cirrhotic patients at 6%. More than two-thirds of the respondents responded periodic EOB-MRI and alternating dynamic CT and EOB-MRI (fig. 10). Next, when asked about the frequency of follow-up with EOB-MRI for this type of nodule, 56% of participants answered every 3–4 months, 43% every 6 months, and 1% every 12 months. The majority answered every 3–4 months, but the percentage was lower than the 67% required to reach a consensus (fig. 11), and thus every 3–6 months was se-

**Fig. 9.** Question and answers on the adequate nodular size for biopsy.

Q9. What size of nodule should be biopsied when it is hypovascular, hypointense in the hepatobiliary phase of EOB-MRI, and shows no defect in the Kupffer phase on Sonazoid CEUS?

1. \( \geq 1 \) cm 54.8%
2. \( \geq 1.5 \) cm 35.5%
3. \( \geq 2 \) cm 6.5%
4. All nodules regardless of the size (including \(< 1 \) cm) 0.0%
5. Other 3.2%

**Fig. 10.** Question and answers on intensive follow-up for a hypointense nodule in the hepatobiliary phase of EOB-MRI (1).

Q10. How do you follow up a hypovascular nodule, which is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS or malignancy on biopsy?

1. Routine surveillance similar to other cirrhotic patients 8.0%
2. Periodic EOB-MRI 59.8%
3. Conventional dynamic MRI 1.1%
4. Alternating dynamic CT and EOB-MRI 25.3%
5. Contrast-enhanced US (to depict early vascularization) 5.7%
6. Other 0.0%

**Fig. 11.** Question and answers on intensive follow-up for a hypointense nodule in the hepatobiliary phase of EOB-MRI (2).
lected (99%). When asked about the frequency of follow-up with dynamic CT for this type of nodule, most respondents (54%) answered every 6 months, followed by every 3–4 months (41%) and every 12 months (6%) (fig. 12). In addition, when asked about the frequency of performing each modality when using alternating dynamic CT and EOB-MRI for follow-up of this type of nodule, most respondents (57%) again answered every 6 months, followed by every 3–4 months (37%) and every 12 months (6%) (fig. 13). Therefore, follow-up every 3–6 months was also recommended for this method (94%).

Finally, when asked how often this type of nodule was followed up by Sonazoid CEUS to evaluate hypervascularity in its early stages, most respondents (50%) again answered every 6 months, followed by every 3–4 months (42%), CEUS is not performed (6%), and every 12 months (1%) (fig. 14). In addition, almost all participants agreed that follow-up every 3–6 months with EOB-MRI or dynamic CT should be performed for hypovascular small nodules <1–1.5 cm that are hypointense in the hepatobiliary phase.

Summary

The following updates to the 2012 surveillance and diagnostic algorithm for hepatocellular carcinoma (updated version of the Arii Research Group algorithm) are included in the latest 2014 updated algorithm (fig. 15):

- The need for biopsy is mentioned as an optional test for hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and are hypervascular and/or show a defect in the Kupffer phase of Sonazoid CEUS.
- ‘Small nodules (1–1.5 cm)’ is defined as the cutoff size that determines whether biopsy or intensive follow-up should be performed for hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and are hypovascular with no defect in the Kupffer phase of Sonazoid CEUS.
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- Intensive follow-up ‘every 3–6 months’ with EOB-MRI (or dynamic CT) should be performed for hypovascular nodules that are hypointense in the hepatobiliary phase of EOB-MRI and show no defect in the Kupffer phase of Sonazoid CEUS when malignancy cannot be ruled out by biopsy.

**Diagnostic Algorithm Updated by the Consensus Reached among the LCSGJ Members**

**Consensus Statements (≥67% Agreement)**

(1) Dynamic CT or dynamic MRI is routinely performed 1–2 times per year for surveillance of HCC in patients with Child-Pugh A or B liver function (84%; percentages indicate the agreement ratio among 350 participants).

(2) Dynamic CT and dynamic EOB-MRI carried out 1–2 times per year are the most frequently performed modalities in the surveillance of HCC in patients with Child-Pugh A or B liver function (98%).

(3) Conventional dynamic MRI has been completely replaced by dynamic EOB-MRI for confirmation of HCC when nodules are detected by US (100%).

(4) Sonazoid CEUS can be performed whenever necessary in the majority of institutions in Japan (92%).

(5) When arterial hypervascularity is not depicted on dynamic EOB-MRI or dynamic CT, CEUS should be performed since the sensitivity of CEUS in detecting intranodular arterial vascularity is the highest among the existing imaging modalities (75%).

(6) In order to differentiate HCC from a dysplastic nodule, biopsy is mandatory for a small hypovascular nodule (≤1–1.5 cm) that is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS (90%).

(7) Intensive follow-up by dynamic EOB-MRI (60%) or alternating dynamic EOB-MRI and dynamic CT (25%)

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**Fig. 15. Surveillance and Diagnostic Algorithm for HCC, proposed by the LCSGJ in 2014.**

1 = Cavernous hemangioma may show hypointensity in the equilibrium (transitional) phase of dynamic EOB-MRI (pseudo-washout). It should be excluded by other sequences of MRI and/or other imaging modalities.

2 = Cavernous hemangioma usually shows hypointensity in the hepatobiliary phase of EOB-MRI. It should be excluded by other sequences of MRI and/or other imaging modalities.

3 = Biopsy may be considered for confirmation.
should be performed for a hypovascular nodule that is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS or malignancy on biopsy (85%).

(8) The recommended interval of intensive follow-up by dynamic EOB-MRI for the nodule described in (7) is 3–6 months (3–4 months interval: 56%, 6 months interval: 43%; total: 99%).

(9) The recommended interval of intensive follow-up by alternating dynamic EOB-MRI and dynamic CT for the nodule described in (7) is recommended to be 3–6 months (99%).

Informative Statements (≈50% Agreement)
(1) Dynamic CT is more frequently performed as a first-line screening tool (58%; percentages indicate the agreement ratio among 350 participants) than dynamic EOB-MRI (40%).

(2) Dynamic CT is more frequently performed as a second-line diagnostic tool (60%) than dynamic EOB-MRI (32%) for confirming the diagnosis of a nodule detected by US.

(3) Diagnosis of HCC can be made without biopsy for a hypovascular nodule that is hypointense in the hepatobiliary phase of EOB-MRI and shows decreased uptake in the Kupffer phase of Sonazoid CEUS (58%). In such cases, biopsy is optional and determined on a case-by-case basis.

(4) The recommended interval of intensive follow-up by dynamic EOB-MRI of a hypovascular nodule that is hypointense in the hepatobiliary phase of EOB-MRI and shows no defect in the Kupffer phase of Sonazoid CEUS or malignancy on biopsy is 3–4 months (56%).

(5) The recommended interval of intensive follow-up by dynamic CT for the nodule described in (4) is 6 months (54%).

(6) The recommend interval of intensive follow-up by Sonazoid CEUS for the nodule described in (4) is 6 months (50%).

Conclusion
The 2014 updated version of the surveillance and diagnostic algorithm proposed by the LCSGJ was developed at a consensus meeting involving 350 experts in the diagnosis and treatment of liver cancer. This algorithm will be adopted shortly as part of the JSH Consensus-Based Clinical Practice Guideline.

Disclosure Statement
The authors declare that no financial or other conflicts of interest exist in relation to the content of this paper.


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