Comparison of International Guidelines for Noninvasive Diagnosis of Hepatocellular Carcinoma

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Abstract
The aim of this review is to present the similarities and differences between the latest guidelines for noninvasive diagnosis of hepatocellular carcinoma (HCC) of American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and Japanese Society of Hepatology. All the four guidelines defined a typical HCC vascular pattern as the homogeneous hyperenhancement (wash-in) in the arterial phase followed by wash-out in the venous or late phase. The AASLD and EASL guidelines accept only four-phase computed tomography and dynamic contrast magnetic resonance imaging (MRI) for HCC diagnosis, whereas the APASL and Japanese guidelines also accept contrast-enhanced ultrasound (CEUS). Regarding CEUS, the APASL guidelines accept the use of Levovist or Sonazoid as contrast agents, whereas the Japanese guidelines accept only the use of Sonazoid. The AASLD and EASL guidelines recommend using only extracellular contrast agents such as gadolinium for MRI, whereas the APASL guidelines also included the use of super paramagnetic iron oxid-MRI, and the Japanese guidelines recommended the use of gadolinium-ethoxybenzyl-diethylentriamine pentaacetic acid-MRI. The AASLD and EASL guidelines propose a diagnostic algorithm starting from the tumor size, whereas the APASL and Japanese guidelines recommend an algorithm starting from arterial tumor vascularity (hyper- or hypovascular in the arterial phase). In conclusion, important differences exist among the Western and Eastern guidelines for noninvasive HCC diagnosis.
Introduction

Liver cirrhosis is a major risk factor in the development of hepatocellular carcinoma (HCC), which is currently the 5th most common cancer and the 3rd leading cause of cancer-related deaths worldwide [1, 2]. The risk of progression to HCC depends on the etiology of cirrhosis; 2%–8% per year in hepatitis C-related liver cirrhosis, 2.5% per year in chronic hepatitis B-related cirrhosis, and <2% in primary biliary and autoimmune cirrhosis [3, 4]. HCC can develop in patients with chronic hepatitis B infections in the absence of the cirrhosis criteria. The risk of HCC increases if more than one virus is present or if there is an association of alcohol consumption in conjunction with hepatitis infection. Cirrhotic patients should undergo HCC surveillance by ultrasound (US) examination every 6 months [5, 6], and when a focal liver lesion is detected by standard US examination in a cirrhotic patient, HCC should be suspected immediately [7].

Until 2000, HCC diagnosis was based on biopsy results. In 2001, the European Association for the Study of the Liver (EASL) gathered a panel of HCC experts who, for the first time, accepted noninvasive criteria for HCC on the basis of a combination of imaging and laboratory findings [8]. Today, HCC is the only tumor for which noninvasive diagnosis is accepted.

Updated guidelines were recently published for HCC diagnosis by the following three important organizations for the study of the liver: the American Association for the Study of Liver Diseases (AASLD) [9], the Asian Pacific Association for the Study of the Liver (APASL) [10], and the EASL [6].

Approximately 30% of HCCs are diagnosed in Japanese patients when the tumor diameter is <2cm [6] thanks to strict and widespread surveillance and great expertise in ultrasonography. This figure is different from those in Europe and USA, where only around 5-15% of HCC are found in the early stage. Therefore, we also decided to include the updated guidelines of the Japanese Society of Hepatology (JSH) in the present review [11].

The aim of this review is to present the similarities and differences between the latest AASLD, EASL, APASL, and JSH guidelines [6,9–11] for noninvasive HCC diagnosis.

Surveillance

The AASLD guidelines [9] recommend HCC surveillance in cirrhotic patients and in those with active chronic hepatitis B infection, either from certain Asian areas or at least 40–50 years of age, whereas the EASL guidelines [6] include noncirrhotic patients with chronic hepatitis C infection and advanced liver fibrosis (stage F3).

The AASLD [9] and EASL [6] guidelines recommend abdominal ultrasonography every 6 months for surveillance; however, these guidelines do not recommend the use of alpha fetoprotein (AFP) in addition to ultrasonography during surveillance because the aim is to detect early HCC, which usually does not overproduce AFP.

The latest APASL guidelines [10] recommend surveillance in patients with liver cirrhosis due to hepatitis B or C. As a screening tool, they recommend a combination of ultrasonography and AFP surveillance every 6 months.

The JSH guidelines [11] divided the risk population into two categories—a super-high-risk population (hepatitis B- and C-related liver cirrhosis) and a high-risk population (patients with active chronic hepatitis B or C and those with nonviral etiology of liver cirrhosis). For super-high-risk patients, the JCH guidelines recommend a combination of ultrasonography with serological markers every 3–4 months and dynamic computed tomography (CT) or magnetic resonance imaging (MRI) every 6–12 months. Although the EASL [6] and AASLD guidelines [9] do not recommend the use of serological markers, the JSH guidelines [11] recommend monitoring of three serological markers—AFP, AFP lectin fraction (AFP-L3), and protein induced by vitamin K absence or antagonist-II (PIVKA-II). US examination combined
with monitoring of the three serological markers every 6 months is recommended for high-risk patients.

**Underlying liver disease**

The EASL [6] and AASLD [9] guidelines for noninvasive HCC diagnosis are applicable only in patients considered at risk and in whom surveillance is recommended. The JSH guidelines [11] include cirrhotic patients and those with chronic hepatopathies B and C. The APASL guidelines [10] do not clearly state whether noninvasive HCC diagnosis is applicable only in cirrhotic patients, but it seems logical that they would be valid for patients in whom surveillance is recommended.

**Serological markers**

AFP is considered a useful marker for HCC diagnosis for many years. However, elevated AFP levels are also observed in some patients with intrahepatic cholangiocarcinoma (ICC), metastases from the colon [12], testicular cancers [13], and most of all, during flare-ups of chronic viral hepatitis in the absence of HCC.

Currently, AASLD and EASL guidelines [6,9] do not recommend the use of AFP or other serological markers for HCC non-invasive diagnosis in addition to imaging techniques.

The APASL guidelines [10] are unclear regarding the use of AFP as a diagnostic marker. In fact, they state that AFP alone, in the absence of typical focal liver lesions, is not recommended for HCC diagnosis because of the risk of false positive results. However, they also state that AFP values >200 ng/ml can be utilized for HCC diagnosis because this relatively high threshold reduces the risk of false positive cases, but they do not specify whether the diagnosis can be accepted in the presence of a focal lesion even without acquisition of the typical contrast pattern. In addition, they specified that simultaneous measurement of AFP and des-carboxyprothrombin provides higher sensitivity without decreasing specificity. However, if a typical contrast pattern would be nonetheless required at AFP >200 ng/ml, the utility of this serum oncomarker would then be nullified (but this issue remains unclear in the text).

The JSH guidelines [11] recommend the use of AFP (≥200 ng/ml with a temporal increase), PIVKA-II (≥40 mAU/ml with a temporal increase), and AFP-L3 (>15%) in addition to the imaging techniques. They state that elevation (with a rising trend) of AFP, AFP-L3, or PIVKA-II, even in combination with chronic liver disease, cannot be used for HCC diagnosis in the absence of a typical imaging pattern, but it is only highly suspicious.

In brief, all of the aforementioned guidelines suggested that AFP cannot be considered diagnostic in the absence of a typical contrast pattern; thus, the ideal role would be to confirm lesions diagnosed by imaging or to suggest (not diagnose) HCC when a typical pattern is absent to provide prognostic information.

**HCC vascular pattern on imaging techniques**

All four guidelines [6,9–11] define a typical HCC vascular pattern as the presence of homogeneous hyperenhancement (wash-in) in the arterial phase followed by wash-out in the venous or late phase.

**Imaging techniques used for HCC diagnosis**

Contrast agents used by different techniques can be classified as either extracellular vascular contrast agents or postvascular phase agents. Iodine contrast agents are most commonly used for vascular contrast via CT, whereas gadolinium chelates are used for MRI, and the second-generation contrast agent SonoVue (Bracco SpA, Milan, Italy) is used for contrast-enhanced US (CEUS). The most utilized postvascular agents are divided into two main categories—(1) agents taken-up by Kupffer and/or reticuloendothelial cells and (2) agents taken-
up by hepatocytes and usually excreted in the bile (hepatocyte-specific contrast agents). In the former group, the agents utilized are Sonazoid (GE Healthcare, Chalfont St. Giles, UK) and Levovist (Bayer Schering, Berlin, Germany) for CEUS (production of the latter agent has nearly ceased) and super paramagnetic iron oxide agents for MRI (SPIO-MRI). When Sonazoid is used, a postvascular Kupffer cell-specific enhancement phase is observed starting from 10 min postinjection. The Kupffer phase is very stable in contrast to that with Levovist, whereas the postvascular phase with SonoVue has negligible enhancement and is not utilized. In the second group, there are two MRI agents that have a regular vascular phase immediately postinjection, but subsequently undergo uptake by hepatocytes, starting from 4–5 min postinjection. These agents are Gadofuchsian acid (Gd-EOB-DTPA; Primovist®, Bayer-Shering, Germany) or Gadobenate dimeglumine (Gd-BOPTA; Multihance®, Bracco, Milan, Italy), the postvascular phases of which are acquired 10–20 min and 120 min, respectively, postinjection. The AASLD and EASL guidelines [6, 9] accept only four-phase CT and dynamic contrast MRI for HCC diagnosis and have dropped the use of CEUS even for second/third-line diagnosis. The APASL and JSH guidelines [10, 11] also accept CEUS as a diagnostic tool. However, the APASL guidelines recommend the use of either CT or MRI as a first-line technique and resort to CEUS for second/third-line in the absence of typical diagnostic CT and/or MRI patterns, whereas the JSH guidelines accept CEUS even as a first-line option.

According to all of these guidelines, any first-line assessment is to be made according to vascular contrast phases, regardless of the imaging technique. As previously mentioned, however, some contrast agents also provide postvascular phases with either MRI or CEUS, and different guidelines accept these postvascular patterns at different degrees, which are better detailed in the following section. The AASLD and EASL guidelines [6, 9] accept only the findings provided by extracellular vascular contrast agents. Regarding the use of MRI, the APASL guidelines [10] also accept the use of SPIO-MRI for nodules not completely fulfilling typical vascular patterns. The JSH guidelines [11] recommend the use of Gd-EOB-DTPA-MRI. Regarding the CEUS postvascular phases, the APASL guidelines [10] accept Levovist or Sonazoid as contrast agents, whereas the JSH guidelines [11] accept only the use of Sonazoid. Sonazoid is an important US contrast agent that was available only in Japan until 2011 and is now available in Korea since 2012; SonoVue is available in many countries but is not licensed in USA for abdominal applications.

In the 2005 edition of the AASLD [5] guidelines for HCC, CEUS, CT, and MRI were included as acceptable techniques for noninvasive HCC diagnosis. However, in 2010, Vilana et al. [14] from the Barcelona Clinic Liver Cancer (BCLC) group published their CEUS findings from a cohort of 21 retrospectively identified cirrhotic patients with pathological ICC and found that the contrast patterns of ICC corresponded to those diagnostic of HCC in approximately half of the patients. On the basis of this study, CEUS was excluded from the 2011 edition of the AASLD guidelines [9] for HCC diagnosis and subsequently also from the 2012 EASL guidelines [6], mainly because of the theoretical risk of ICC misdiagnosis.

The JSH guidelines [11] include addition of CT during hepatic arteriography and arterial portography as a diagnostic tool. None of the guidelines included positron emission tomography-CT for HCC diagnosis.

Figure 1 shows a liver lesion in a cirrhotic patient with typical HCC vascular patterns using three different imaging techniques (CEUS, CT, and MRI), whereas Fig. 2 shows a liver lesion with atypical vascular HCC patterns using the same three imaging techniques. Following the lack of diagnostic criteria at imaging, nodule biopsy established an HCC diagnosis.

**HCC diagnostic algorithms**

The AASLD [9] and EASL [6] guidelines proposed a diagnostic algorithm starting from the tumor size, whereas the APASL [10] and JSH [11] guidelines recommended an algorithm
starting from tumor arterial enhancement. The AASLD guidelines [9] divided focal liver lesions into two categories—<1 cm or >1 cm. The EASL guidelines used three categories according to tumor size—<1 cm, 1–2 cm, and >2 cm. Both guidelines [6, 9] recommend only US follow-ups for tumors with diameters <1 cm. The time of follow-up is 3 months according to the AASLD guidelines [9] and 4 months according to the EASL guidelines [6]. If the tumor remains stable, strict US follow-up should continue for at least 2 years, while morphological changes must be evaluated according to the size.

The AASLD guidelines [9] recommend the use of CT or MRI with contrast agents for tumors >1 cm. If a typical HCC contrast pattern is present in one of these techniques, an HCC diagnosis is confirmed, and subsequently, the treatment strategy can be directly applied. If a typical HCC contrast pattern is not present in either of these two imaging techniques, biopsy is recommended.

For tumors of 1–2 cm, the EASL guidelines [6] require either one or two imaging techniques with typical findings to reach an HCC diagnosis (only one technique is sufficient in centers with high-end radiological equipment, whereas two techniques in agreement are required in centers without). For tumors >2 cm, one technique with a typical HCC contrast pattern is sufficient for diagnosis regardless of the expertise of the center to establish non-invasive HCC diagnosis. For cases not exhibiting typical HCC vascular patterns, biopsy is recommended. The current EASL diagnostic algorithm in nonexpert centers is similar to that proposed by the 2005 AASLD guidelines [5], apart from CEUS exclusion.

The APASL and JSH guidelines use an algorithm starting from the hyper- or hypoenhancement of the tumor in the arterial phase. As previously mentioned, hypervascularity is demonstrated via CT or MRI as a first-line technique according to the APASL guidelines and via CEUS if the previous techniques fail via CT, MRI, or CEUS. Thus, before a nodule can be classified as hypovascular, more than one technique, always including CEUS, must be performed. Any cirrhotic nodule lacking arterial hyperenhancement is categorized as an arterial hypovascular nodule if it appears to be truly hypoenhanced in comparison to the surrounding parenchyma or isoenhanced, regardless of whether it is in the arterial phase. In the JSH guidelines, the portal and delayed vascular phases with Sonazoid (which corresponds to approximately 0.5–
Hypervascular lesions in the arterial phase with subsequent wash-out in the venous phase (or hypoenhancement in the postvascular phase of CEUS with Sonazoid in the JSH guidelines) are diagnosed as HCC.

Hypervascular lesions in the arterial phase that do not present wash-out in the portal or late phase should be biopsied according to the AASLD and EASL guidelines. These lesions can be further evaluated with SPIO-MRI [10] or hepatocyte-specific contrast agents in the postvascular phase either via MRI [11] or CEUS using Levovist [10] or Sonazoid [10, 11] according to the APASL guidelines. If these lesions are hypoenhanced in the postvascular phases of hepatocyte specific agents or are devoid of reticuloendothelial cells via SPIO-MRI, HCC diagnosis can still be established according to the APASL guidelines. The issue of ICC is not mentioned in these guidelines.

Once a pseudolesion corresponding to an arterioportal shunt has been ruled out, the APASL guidelines [10] recommend only close follow-ups for lesions with an excess of contrast uptake of hepatocyte-specific agents in the Kupffer phase, whereas the JSH guidelines [11] recommend biopsy. The probability of HCC in these lesions is in fact extremely low, but not completely null.

Hypovascular lesions in the arterial phase via CT and MRI can be evaluated by SPIO-MRI [10], Gd-EOB-DTPA-MRI [11], and CEUS with Levovist [10] or Sonazoid [10, 11] according to the APASL guidelines [10], which define HCC as hyperenhanced lesions at SPIO-MRI (indicating a lack of contrast uptake corresponding to the lack of reticuloendothelial cells, suggesting malignancy) or hypoenhancement in the Kupffer phase with Sonazoid/Levovist, regardless of hyper- or hypoenhancement in the arterial phase. Conversely, according to the JSH guidelines [11], only hypoenhanced lesions in the postvascular phase using both Gd-EOB-DTPA-MRI and Sonazoid can be diagnosed as HCC (well-differentiated) in the absence of arterial enhancement. Biopsy is recommended for arterial hypovascular lesions that are hypoenhanced only by Gd-EOB-DTPA-MRI or Sonazoid during the postvascular phase. For arterial hypovascular lesions, which take up the latter two contrast agents in the postvascular phase, HCC can be diagnosed according to the JSH guidelines.
lar phase (thus not appearing hypoenhanced), the APASL guidelines [10] recommend a close follow-up, whereas the JSH guidelines [11] recommend biopsy.

Pathological and imaging differentiation between high-grade dysplastic nodules (HGDN) and early HCC

Early HCC has been defined by Japanese pathologists [15] as small lesions with poorly defined margins [16] that are known as vaguely nodular tumors. Histologically, there are few unpaired arteries, but cells show varying grades of dysplasia. Invasion of the portal space by tumor cells may be present, but vascular invasion and intrahepatic metastatic dissemination are extremely rare [17]. By contrast imaging techniques, the lesions usually appear hypovascular (hypo- or isoenhanced) because they are still supplied by both portal arteries and poorly developed arterial tumor vessels, but the portal and arterial blood flow may be decreased [11]. Differentiation from HGDN may be extremely difficult or nearly impossible to detect on small biopsy specimens.

The AASLD [9] and EASL guidelines [6] recommend the following markers for histological differentiation between HGDN and HCC: glypican 3, heat shock protein 70, glutamine synthetase, CD 34 (from vascular endothelium), and cytokeratin 7 and 19.

Most early HCC nodules appear well-differentiated, whereas small “nodule-in-nodule” HCC that are moderately to poorly differentiated and contained in well-differentiated tumor tissue are more aggressive than early HCC. The JSH guidelines [11] recommend the following two histological markers to differentiate between these two types of nodules: p53 overexpression and Ki–67 labeling.

The APASL guidelines [10] do not recommend any specific histological marker to differentiate between HGDN and early HCC.

Regarding imaging differentiation between HCC and dysplastic nodules, the JSH guidelines [11] especially recommend the use of Gd-EOB-DTPA-MRI. In the hepatobiliary specific phase, the vast majority of dysplastic nodules are iso- or hyperintense, whereas most early HCC nodules are hypointense. This difference occurs because of the cell-specific presence of organic anion transporter 1 (OATP1B3) in the two types of lesions. The Kupffer phase in Sonazoid is less effective for differentiating between HGDN and early HCC because the latter are often isoenhanced in the postvascular phase. When a lack of Sonazoid uptake is present, diagnosis of early HCC is established and nonmalignant nodules can be excluded.

The AASLD [9] and EASL [6] guidelines do not endorse any noninvasive algorithm for differentiation between HGDN and early HCC.

Discussion

Important differences exist between the present guidelines for noninvasive HCC diagnosis. A summary of the most important similarities and differences of these four guidelines is presented in table 1. All of the guidelines interestingly rely on the presence of hyperenhancement in the arterial phase and subsequent wash-out as a pivotal pattern for HCC diagnosis. However, the AASLD and EASL guidelines accept only this pattern and resort to biopsy in case of absence of typical enhancements, whereas the APASL guidelines tend to stretch the resources of diagnostic techniques to achieve as many noninvasive diagnoses as possible by accepting nonvascular contrast findings (uptake of contrast agents in the postvascular phase) and including CEUS in the diagnostic armamentarium.

One of the most important differences among the aforementioned guidelines is the use of various liver imaging techniques. The AASLD and EASL guidelines do not endorse the use
of CEUS, mainly because of the risk of misdiagnosing ICC. Notably, the US Food and Drug Administration has not yet approved the use of US contrast agents for abdominal applications [18], whereas in many European and Asian countries, they are widely used in clinical practice.

Regarding the risk of misdiagnosis of ICC and HCC in patients with liver cirrhosis, only two retrospective studies have been published to date regarding CEUS vascular patterns in histologically proven ICC in cirrhotic patients [14, 19]; however, the number of cases were small (21 [14] and 16 patients [19], respectively) and were identified over a period of several years from large centers with contradictory results. The BCLC group study [14] showed a typical HCC vascular pattern in CEUS for ICC lesions (homogeneously wash-in in the arterial phase followed by wash-out in the venous or late phase) in 47.6% of patients, whereas in a Chinese study [19], a pattern leading to potential misdiagnosis occurred in only 18.7% of patients. One explanation for this difference can be the tumor size, which was much greater in the latter study compared with that in the BCLC group (median nodule sizes, 53 and 32 mm, respectively). Further details of the enhancement pattern of ICC presented in these two studies [14, 19] suggested that the following CEUS enhancement features can be used to indicate ICC for nodules in cirrhosis: presence of rim-like enhancement or heterogeneous hyperenhancement in the arterial phase and the occurrence of wash-out very early in the portal phase (within 60 s postinjection). In fact, HCC reportedly had a late onset of wash-out in a prospective study [20]. Vilana et al. [14] described MRI vascular patterns of ICC using gadoxetate as the contrast agent. In the present review, none of the lesions was misdiagnosed as HCC via MRI, but MRI was unable to establish a definitive diagnosis of malignancy. None of the lesions presented wash-out; thus, even the diagnosis of malignancy was not established, indicating the necessity of biopsy. However, in daily practice, this is not always technically feasible.

In summary, the low incidence of ICC in cirrhosis (1%–2%) and the utility of CEUS to establish the malignant nature of tumors, which is not suitable for biopsy in cirrhotic patients because of coagulopathies, ascites, or the localization of liver nodules, make the drawback of the use of CEUS negligible in comparison to its potential benefits [21]. Furthermore, biopsy presents a consistent risk of false negative diagnosis in small nodules because of the difficulty in obtaining adequate tissue specimens [22]; therefore, repeated attempts are made in up to 40% of all cases that might otherwise present a false negative diagnosis of malignancy. These issues are probably the basis for the maintenance of CEUS use in the updated APASL and JSH guidelines.

In many countries, the use of Gd-EOB-DTPA-MRI has recently increased in daily clinical practice for characterization of focal liver lesions. Gd-EOB-MRI requires a delay of approximately 15–20 min after injection before scanning; therefore, it does not significantly hamper the routine flow of radiological services. Approximately 50% of the Gd-EOB-DTPA dose is taken up by hepatocytes and excreted in bile, whereas the other 50% is excreted by the kidney. Hepatocellular uptake may be related to passive diffusion mediated by organic anion transporter 1 (OATP1) in the hepatocellular membrane in rats [23]. The Gd-EOB-DTPA uptake in humans is dependent on OATP1B3 [24] among various kinds of human OATP families. Usually, the OATP1B3 transporter remains present in most dysplastic nodules and absent in most HCC cases and begins to disappear in early HCC. The uptake transporter is always absent in poorly differentiated HCC, thereby making these lesions hypointense in the hepatobiliary-specific phase. Consequently, the Gd-EOB-DTPA uptake helps to differentiate HCC and specifically early HCC from dysplastic nodules according to the JSH guidelines. However, the sensitivity and specificity of these patterns to this end is far from perfect, which is likely the reason behind the lack of endorsement by Western guidelines. Several studies have demonstrated that Gd-EOB-DTPA-MRI is superior to dynamic MRI or CT for HCC detection.
but not to such an extent as to make this technique acceptable in all guidelines. To date, only the JSH guidelines have included this technique [11], although it has been approved in Europe and USA.

More relevant differences between the Western [6, 9] and Eastern [10, 11] guidelines lie in the algorithm for noninvasive HCC diagnosis. The AASLD [9] and EASL [6] guidelines allow noninvasive diagnosis only for hypervascular HCC. The APASL [10] and JSH guidelines [11] also include an algorithm for hypovascular lesions in the arterial phase, which is nonetheless capable of noninvasive HCC diagnosis by including the use of postvascular phase-specific imaging such as Levovist CEUS, Sonazoid CEUS (available only in Japan), Gd-EOB-DTPA-MRI, and SPIO-MRI. Various studies have demonstrated an improvement in CEUS accuracy for HCC diagnosis in Japanese patients during the Kupffer phase with Sonazoid [28, 29]. However, validation of these findings in Western populations is still lacking. Similar to Gd-EOB-DTPA, SPIO-agents are approved in Europe and USA but are not included in their respective guidelines. Moreover, they require a completely separate and relatively expensive MRI examination, other than Gd-EOB-DTPA, which requires only minor extension of the examination time.
For this reason, a future perspective of larger utilization of SPIO-MRI for lesions in cirrhosis and inclusion in Western guidelines is highly unlikely. This also stands true for CT arterial portography, which is an invasive and expensive technique and has been challenged by improvement in the most recent CT and MRI techniques, leading to very limited use in Japan. Accordingly, an extension of its use in Western guidelines does not appear probable.

**Conflict of Interest**

Fabio Piscaglia acted as a consultant for Bracco, speaker and advisory board member for Bayer, and speaker for Siemens and Roche; Luigi Bolondi acted as a speaker for Bracco, speaker and advisory board member for Bayer, and received a research grant from BMS. The other authors declare no conflicts of interest.

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