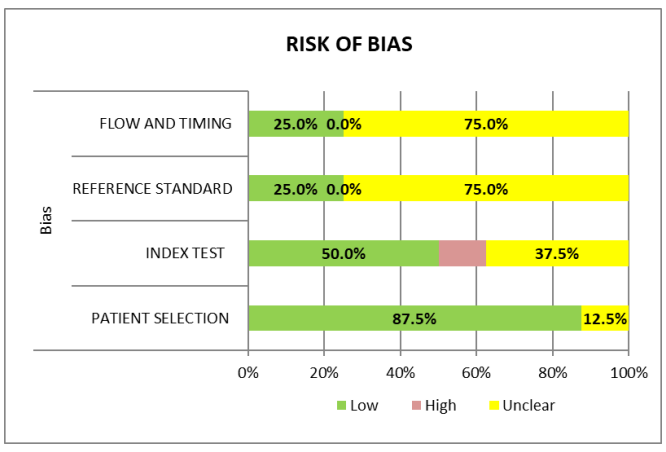
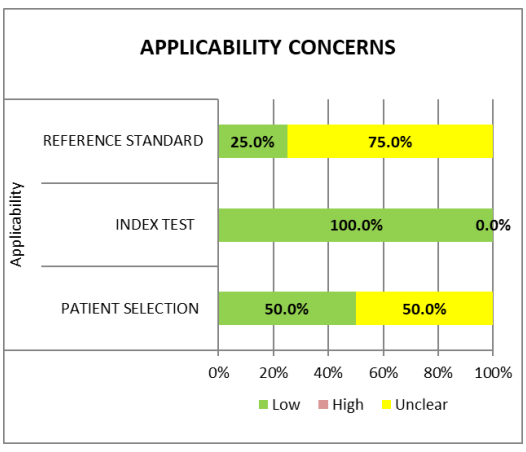
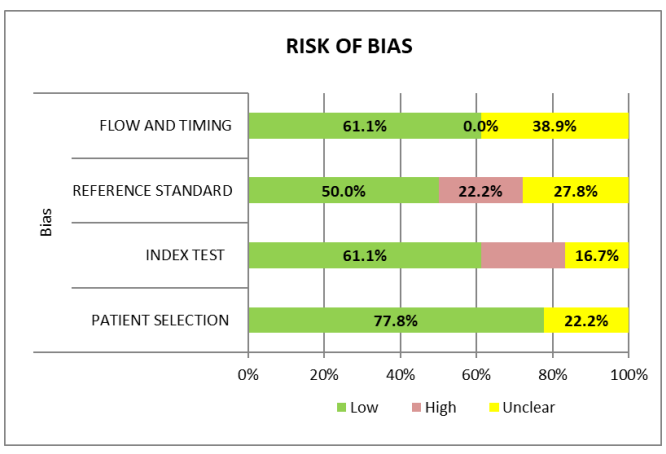
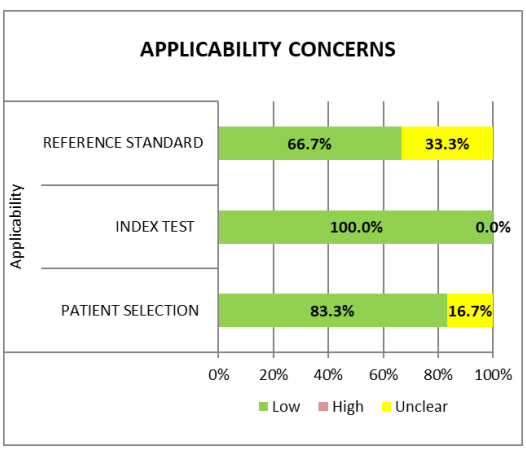
**KQ1-1. Is it appropriate that 'nonrim APHE' and 'late (≥ 60 sec) and mild washout' are major imaging features of HCC in Sonazoid CEUS?**
**KQ1-2. Can 'Kupffer phase washout' be used a major feature of HCC diagnosis using Sonazoid CEUS?**



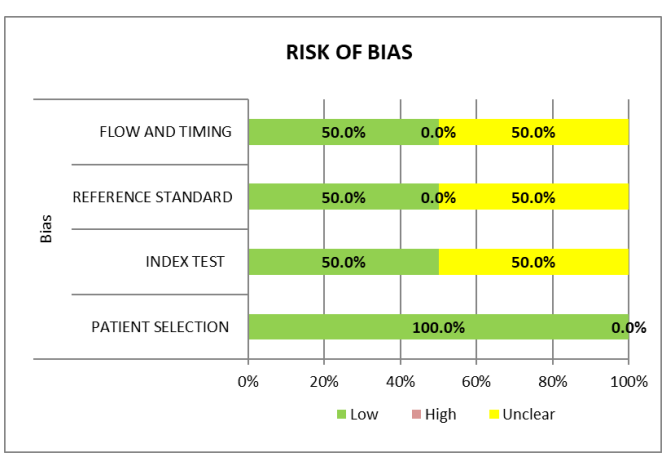



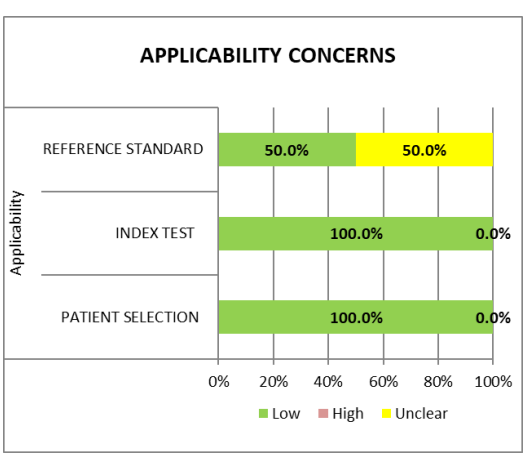

**KQ2. What is the appropriate diagnostic criteria for diagnosis of HCC using Sonazoid CEUS in at-risk patients?**



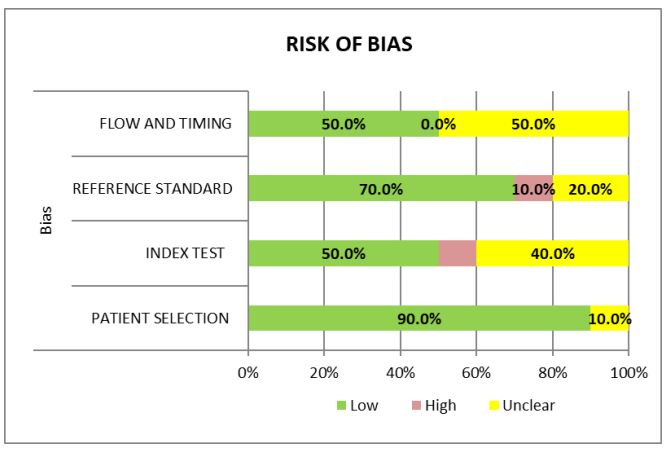



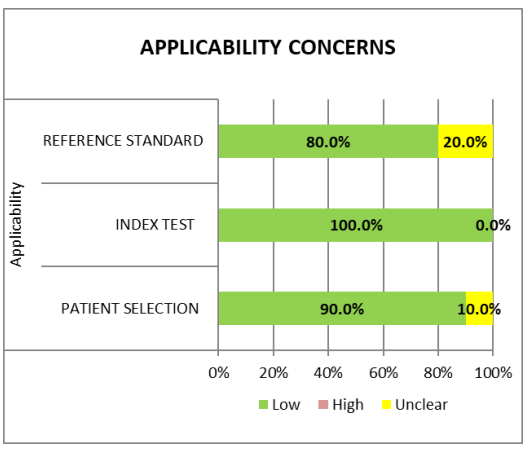

**KQ3. Can Sonazoid-CEUS be used to characterize inconclusive nodules detected at CT or MRI in patients with high risk for HCC?**



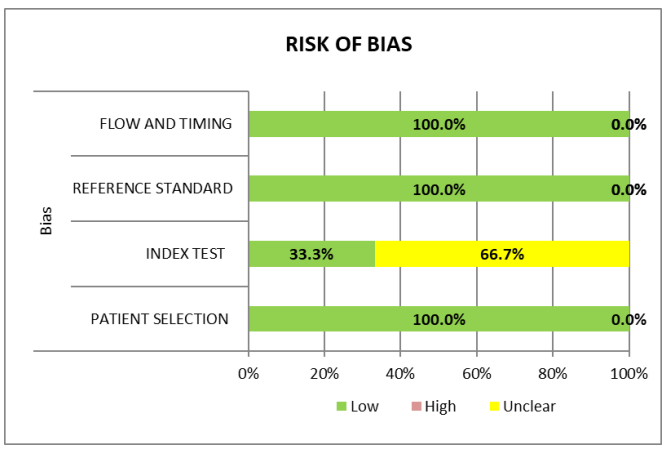



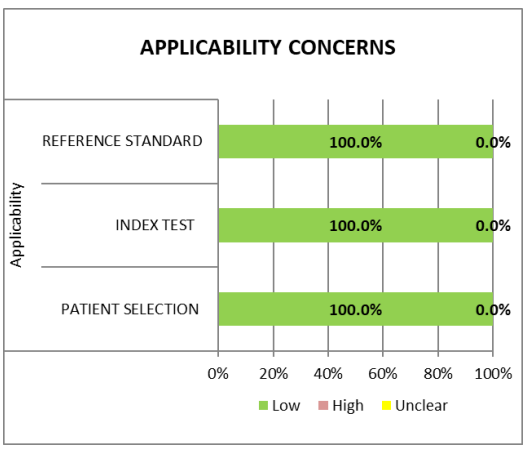

**KQ4. Can Sonazoid contrast-enhanced ultrasound (CEUS) differentiate hepatocellular carcinoma (HCC) from non-HCC malignancies?**



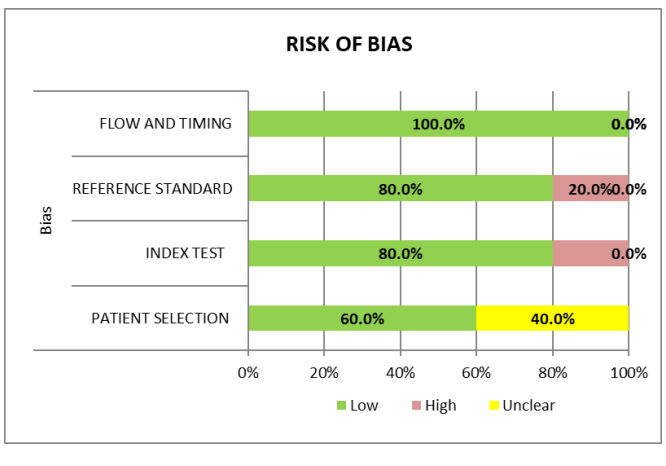



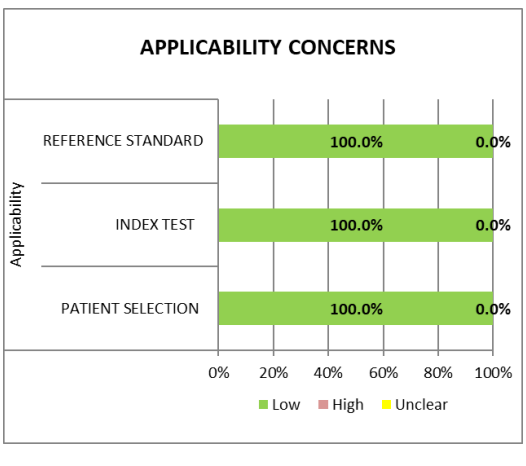

**KQ5. Can Sonazoid-enhanced US be used as a surveillance tool for HCC in high-risk patients?**



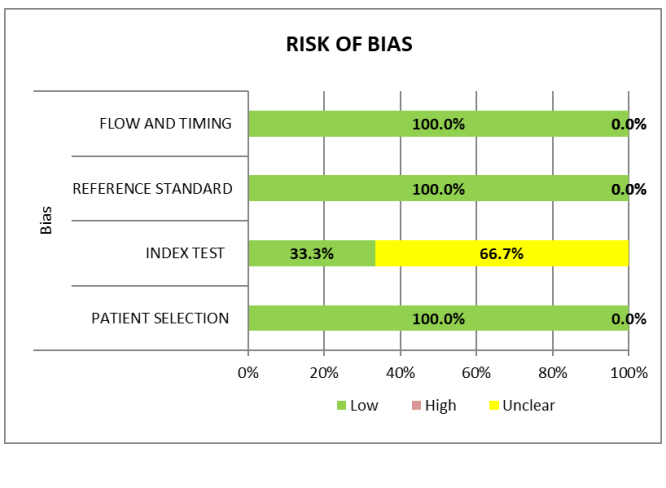



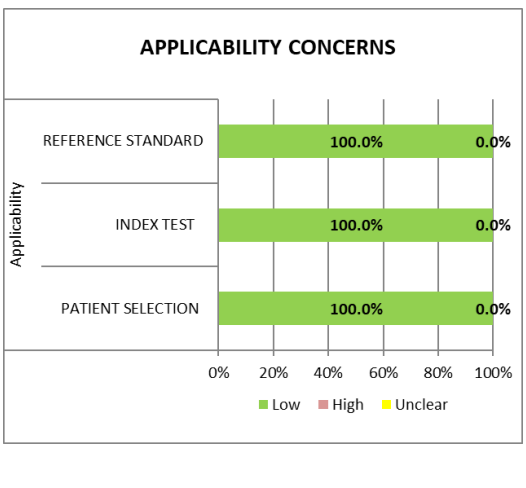

**KQ6. Is Sonazoid CEUS helpful for the guidance of local ablation therapy for HCC?**




**KQ7. Is it appropriate that treatment response for HCC is assessed with Sonazoid CEUS in the patients who underwent TACE or RFA?**



**Supplementary table 1A.** Evidence table of KQ1

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Hwang (2021) [13] | retrospective cohort | 203 | 203 | | On CEUS of 203 nodules, 89.6% of CT/MRI LR-5 and 85.9% of LR-4 nodules showed hyperenhancement in the arterial phase, while 57.6% of LR-3 nodules showed hyperenhancement. Among the CT/MRI LR-5 nodules that showed arterial phase hyperenhancement or isoenhancement, 59.7% showed hypoenhancing changes from the portal venous phase, 23.9% from the late phase, and 13.4% additionally in the Kupffer phase. The modified CEUS LI-RADS showed higher sensitivity than CEUS LI-RADS (83.2% vs. 74.2%, P=0.008) without compromising specificity (63.6% vs. 69.7%, P=0.500). | The Kupffer phase best shows hypoenhancing changes in LR-5 lesions and is expected to improve the sensitivity for HCC in high-risk patients. |

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| Saito (2020) [21] | cohort | 146 | 146 | | Starting in 2007, we performed Sonazoid CEUS in 146 pathologically confirmed hepatic nodules; 118 HCC (8 poorly [Pd], 73 moderately [Md] and 37 well-differentiated [Wd]) and 28 benign nodules. We focused on the pure arterial and early portal phases up to 45 seconds after Sonazoid injection, and then the subsequent phase up to 30 minutes. We calculated covariance-adjusted sensitivities for nodule enhancement combinations of these three phases. Nodule enhancements were divided into hypo, iso and hyper. A positive predictive value of 100% was obtained for the following patterns: iso-iso-hypo, hypo-iso-iso, and hypo-hypo-hypo for Wd, hyper-iso-hypo and hyper-hypo-hypo for Md, hypo-hyper-hypo for Pd, and hyper-hyper-hyper for benign nodules. In Wd HCC (early HCC), there were seven enhancement patterns, thought to be characterized by various hemodynamic changes from early to advanced HCC. Two patterns allowing a diagnosis of Wd HCC were hypo in the pure arterial phase. Subsequent iso-enhancement in the early portal phase indicated a portal blood supply. Decreased enhancement in the early portal phase allows a diagnosis of Md HCC. However, gradual enhancement observed from the pure arterial to the early portal phase allows a diagnosis of Pd HCC. Therefore, even in the early portal phase, hemodynamic changes were visible not only in Wd but also in Md and Pd HCC. | with division of the early phase hemodynamics into pure arterial and early portal phases, CEUS can provide information useful for determining the likely degree of HCC differentiation and for distinguishing early stage HCC from benign nodules. |

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| Inoue (2008) [25] | retrospective cohort | 77 | 77 | | The sensitivities of CE-US and SPIO-MRI in detecting tumors were 98 and 95%, respectively (nonsignificant, chi(2) test). The postvascular phase ratio correlated with the SPIO intensity index for HCCs (Pearson r = 0.803, $p < 0.05$). The image conformity of the result from the liver parenchymal phase CE-US and SPIO-MRI was 92%. Dedifferentiation spots of nodule-in-nodule HCCs were detected in 4 (80%) of 5 on postvascular phase images of CE-US, and in 2 (40%) of 5 on SPIO-MRI (nonsignificant, chi(2) test). | Postvascular phase images of CE-US with Sonazoid appear promising as an alternative to SPIO-enhanced MRI. Further study cases are needed to confirm the usefulness of postvascular phase images of CE-US compared to SPIO-MRI for the detection of dedifferentiation foci in hepatic tumors. |
| Yang (2017) [26] | retrospective cohort | 154 | 154 | | On Kupffer-phase CEUS, 31 (20.1%) lesions were invisible, 17 (11.1%) were vaguely visible, and 106 (68.9%) were clearly visible. On the hepatobiliary-phase MRI, 9 (5.9%) lesions were invisible, 45 (29.2%) were vaguely visible, and 100 (64.9%) were clearly visible. Overall, lesion visibility scores were not significantly different between the two modalities ($p = 0.121$), but the visibility was significantly better on MRI in smaller lesions. Twenty-eight lesions (18.2%) showed discrepancy in the visibility on CEUS and MRI, and most of the cases (89.7%) were lesions that were invisible on CEUS but visible on MRI. | The overall visibility of FLLs was comparable between the Kupffer phase of Sonazoid-CEUS and the hepatobiliary-phase images of gadoxetic acid-enhanced MRI, with a discrepancy between the two modalities in 18% of the cases. |

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| Alaboudy (2011) [29] | retrospective cohort | 32 | 32 | | A total of 50 histologically proven HCCs were obtained from 32 patients; their mean (± SD) age was 68.3 years ± 8.1. The mean (± SD) nodule size was 2.6 cm ± 1.9. Twenty percent were well-differentiated HCC, 64% were moderately differentiated HCC, 10% were poorly differentiated HCC, 4% were combined HCC and CCC, and 2% were HCC with severe necrosis. The overall diagnostic sensitivity of CEUS, CECT, and Gd-EOB-DTPA MRI was 72, 74, and 86%, respectively; however, there was no significant difference between the three imaging modalities in diagnosing typical HCC ($p = 0.092$). When combining the diagnostic ability of the different imaging modalities, the diagnostic sensitivity of Sonazoid-enhanced US and Gd-EOB-DTPA MRI was 90%, while addition of Sonazoid-enhanced US to CECT and CECT to Gd-EOB-DTPA MRI had a sensitivity of 82 and 88%, respectively. There was no significant difference between the three imaging combinations ($p = 0.970$). | Sonazoid-enhanced US and Gd-EOB-DTPA MRI can be confidently used in daily clinical practice for the management of HCC. |
| Hatanaka (2008) [31] | cohort | 74 | 74 | | 108 nodules were diagnosed as malignant tumors (hepatocellular carcinoma: n = 90; metastasis: n = 16; intrahepatic cholangiocarcinoma: n = 2) and the remaining five tumors were diagnosed as benign tumors (dysplastic nodules: n = 5). Sonazoid-enhanced US correctly depicted the presence or absence of tumors in 74 patients, with a sensitivity of 95.4%, an accuracy of 94.7%, and a positive predictive rate of 99%. Contrast-enhanced CT depicted the malignancies with a sensitivity of 85.2%, an accuracy of 82.3%, and a positive predictive rate of 95.8%. There were significant differences between Sonazoid-enhanced US and contrast-enhanced CT for sensitivity and accuracy (both $p < 0.05$). | Sonazoid-enhanced US has a higher sensitivity and accuracy for the diagnosis of hepatic malignancies than contrast-enhanced CT. |

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| Hatanaka (2008) [32] | retrospective cohort | 249 | 249 | | In metastases, the presence of rim-like enhancement with peripheral tumor vessels (sensitivity, 88.1%; specificity, 100%) was the typical pattern. | Contrast-enhanced harmonic US with Sonazoid allowed intimate vascular and Kupffer imaging and, therefore, is useful for the differential diagnosis of hepatic tumors. |
| Lv (2021) [38] | prospective cohort | 424 | 424 | | Sonazoid-enhanced and SonoVue-enhanced ultrasound provided a statistically significant improvement in specificity for all 3 readers comparing to unenhanced ultrasound (for Sonazoid: p = 0.0093, < 0.0001, 0.0011; for SonoVue: p = 0.002, 0.03, 0.12, respectively). Difference in accuracy improvement between the 2 groups was within the pre-specified non-inferiority margin of 20% for all 3 readers (6.1%, 95% CI: - 5.0 to 17.2; - 7.5%, 95% CI: - 18.4 to 3.5; - 0.3%, 95% CI: - 11.3 to 10.7). The diagnostic confidence level for all 3 readers increased with post-contrast images relative to pre-contrast images. Both contrast agents were well tolerated. | Results showed a similar efficacy for Sonazoid™ and SonoVue® in diagnosing FLLs as benign or malignant, and underlined the benefit of CEUS imaging over unenhanced ultrasound imaging in reaching a confident diagnosis without having to refer patients for additional imaging exams. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript.

**Supplemntary table 1B.** Evidence table of KQ2

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Hwang (2021) [13] | retrospective cohort | 203 | 203 | | On CEUS of 203 nodules, 89.6% of CT/MRI LR-5 and 85.9% of LR-4 nodules showed hyperenhancement in the arterial phase, while 57.6% of LR-3 nodules showed hyperenhancement. Among the CT/MRI LR-5 nodules that showed arterial phase hyperenhancement or isoenhancement, 59.7% showed hypoenhancing changes from the portal venous phase, 23.9% from the late phase, and 13.4% additionally in the Kupffer phase. The modified CEUS LI-RADS showed higher sensitivity than CEUS LI-RADS (83.2% vs. 74.2%, P=0.008) without compromising specificity (63.6% vs. 69.7%, P=0.500). | The Kupffer phase best shows hypoenhancing changes in LR-5 lesions and is expected to improve the sensitivity for HCC in high-risk patients. |
| Kang (2020) [14] | prospective cohort | 59 | 59 | | Fifty percent (five of 10) of non-HCC malignancies manifested with rim APHE. Most malignancies (92% [49 of 53]) had hypoenhancement in the Kupffer phase, except for three HCCs (7.0% [three of 43]) and one angiosarcoma (100% [one of one]) | Noninvasive US diagnosis of hepatocellular carcinoma by using perfluorobutane-enhanced US had higher diagnostic performance than sulfur hexafluoride–enhanced US. |
| Sugimoto (2020) [27] | retrospective cohort | 104 | 104 | | The 22 (21.2%) LR-M lesions included 16 non-HCC malignancies and 6 HCCs. The PPV of LR-M for non-HCC malignancies, including six intrahepatic cholangiocarcinomas, was 100% (95% CI: 69.8–100%). | The modified CEUS LI-RADS for Sonazoid, LR-5 and LR-M are good predictors of HCC and non-HCC malignancies, respectively. |

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| Alaboudy (2011) [29] | retrospective cohort | 32 | 32 | | A total of 50 histologically proven HCCs were obtained from 32 patients; their mean (± SD) age was 68.3 years ± 8.1. The mean (± SD) nodule size was 2.6 cm ± 1.9. Twenty percent were well-differentiated HCC, 64% were moderately differentiated HCC, 10% were poorly differentiated HCC, 4% were combined HCC and CCC, and 2% were HCC with severe necrosis. The overall diagnostic sensitivity of CEUS, CECT, and Gd-EOB-DTPA MRI was 72, 74, and 86%, respectively; however, there was no significant difference between the three imaging modalities in diagnosing typical HCC ($p = 0.092$). When combining the diagnostic ability of the different imaging modalities, the diagnostic sensitivity of Sonazoid-enhanced US and Gd-EOB-DTPA MRI was 90%, while addition of Sonazoid-enhanced US to CECT and CECT to Gd-EOB-DTPA MRI had a sensitivity of 82 and 88%, respectively. There was no significant difference between the three imaging combinations ($p = 0.970$). | Sonazoid-enhanced US and Gd-EOB-DTPA MRI can be confidently used in daily clinical practice for the management of HCC. |
| Goto (2012) [30] | retrospective cohort | 100 | 100 | | A total of 138 HCC nodules (mean diameter 20.3 mm) were detected in 123 of 400 segments. Detection sensitivity of B-mode US was 0.837 for reader A and 0.846 for reader B, and that of CEUS was 0.732 for reader A and 0.831 for reader B. Specificity of B-mode US was 0.902 for reader A and 0.949 for reader B, and that of CEUS was 0.986 for reader A and 0.978 for reader B. CEUS false positives were mainly due to misidentification of hepatic cysts. A significant proportion of false-negative nodules are hyperechoic in B-mode US, likely because echogenicity hampers visualization of the defect in Kupffer imaging. | Kupffer imaging by CEUS with Sonazoid showed very high specificity but rather mediocre sensitivity for HCC detection. CEUS is highly suitable for confirmatory diagnosis of HCC; however, caution should be exercised in reaching a diagnosis based only on CEUS. |

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| Hatanaka (2008) [31] | cohort | 74 | 74 | | 108 nodules were diagnosed as malignant tumors (hepatocellular carcinoma: n = 90; metastasis: n = 16; intrahepatic cholangiocarcinoma: n = 2) and the remaining five tumors were diagnosed as benign tumors (dysplastic nodules: n = 5). Sonazoid-enhanced US correctly depicted the presence or absence of tumors in 74 patients, with a sensitivity of 95.4%, an accuracy of 94.7%, and a positive predictive rate of 99%. Contrast-enhanced CT depicted the malignancies with a sensitivity of 85.2%, an accuracy of 82.3%, and a positive predictive rate of 95.8%. There were significant differences between Sonazoid-enhanced US and contrast-enhanced CT for sensitivity and accuracy (both $p < 0.05$). | Sonazoid-enhanced US has a higher sensitivity and accuracy for the diagnosis of hepatic malignancies than contrast-enhanced CT. |
| Hatanaka (2008) [32] | retrospective cohort | 249 | 249 | | In metastases, the presence of rim-like enhancement with peripheral tumor vessels (sensitivity, 88.1%; specificity, 100%) was the typical pattern. | Contrast-enhanced harmonic US with Sonazoid allowed intimate vascular and Kupffer imaging and, therefore, is useful for the differential diagnosis of hepatic tumors. |
| Hsiao (2019) [33] | prospective cohort | 66 | 66 | | diagnostic odds ratio (DOR, 95% CI) for metastasis: CEUS (200, 19.1–2095), MRI (24, 5.05–114), and CT (32, 6.56–156); and all liver malignancy: CEUS (260, 12.7–5310), MRI (2.57, 0.55–12.1), and CT (5.22, 1.25–21.8).<br>Sensitivity, specificity, PPV, and NPV for metastasis: 92.9%, 100%, 92.3%, and 94.5% | CEUS outperformed dynamic CT and MRI in terms of diagnostic performance when dealing with small liver tumors (<3 cm). |

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| Kan (2010) [34] | cohort | 70 | 70 | | Seventy-nine nodules in 69 patients with chronic liver disease, suspected as HCCs were studied. The nodules were selected based on the results of B-mode ultrasonography and/or Dy-CT conducted between January and August 2007. The nodules were divided into two groups: the S-group with tumors ≤2 cm (49 nodules), and the L-group with tumors >2 cm (30 nodules). Typical HCCs were defined, and the nodules were enhanced and shown as defects in the arterial and late phase of Dy-CT, respectively. Target lesions were scanned using CEUS, and the results were compared with those of Dy-CT. The L-group nodules diagnosed as HCCs using Dy-CT were also diagnosed as HCCs using CEUS. In the S-group, the diagnostic sensitivity of CEUS was 94.7% and the specificity was 81.8%. We diagnosed two liver tumors that were detected by CEUS but not by Dy-CT; biopsies revealed one tumor to be a well-differentiated HCC and the other to be an atypical adenomatous hyperplasia. The sensitivity and specificity of CEUS against HCC were high even in the small-size HCCs. | Sonazoid is useful in the screening for small HCCs. |
| Kawada (2010) [35] | retrospective cohort | 13 | 13 | | By multidetector computed tomography (MDCT), six of 15 (40%) nodules were diagnosed as HCC. Gd-EOB-DTPA-enhanced MRI diagnosed HCC in nine of the 15 (60%) nodules. Of the nine nodules that were not diagnosed by MDCT, four could be diagnosed by Gd-EOB-DTPA-enhanced MRI. In Sonazoid CEUS, 10 of 15 nodules (67%) were diagnosed as HCC. Four of nine nodules that could not be diagnosed as HCC by MDCT, were diagnosed by Sonazoid CEUS. A total of 11 of the 15 (73%) nodules were diagnosed as HCC by Gd-EOB-DTPA-enhanced MRI and Sonazoid CEUS in addition to MDCT. | Gd-EOB-DTPA-enhanced MRI and Sonazoid CEUS had greater diagnostic value for small, well-differentiated HCC than did conventional MDCT. |

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| Luo (2009) [36] | retrospective cohort | 139 | 139 | | sensitivity, specificity, PPV, and Az for metastasis: 88%, 97%, 91%, and 0.94 for reader 1; 85%, 95%, 85%, and 0.89 for reader 2 | Contrast-enhanced 3D US potentially can be used to characterize focal liver tumors. |
| Luo (2010) [37] | prospective & retrospective cohort | 163 | 163 | | At CEUS, the prospective differentiation of lesions showed sensitivity 84% (mean for two readers), specificity 97% and Az value 0.95 for metastasis. | CE 3D US provides a spatial perspective for liver tumor enhancement, and could help in differentiating focal liver lesions. |
| Lv (2021) [38] | prospective cohort | 424 | 424 | | Sonazoid-enhanced and SonoVue-enhanced ultrasound provided a statistically significant improvement in specificity for all 3 readers comparing to unenhanced ultrasound (for Sonazoid: p = 0.0093, < 0.0001, 0.0011; for SonoVue: p = 0.002, 0.03, 0.12, respectively). Difference in accuracy improvement between the 2 groups was within the pre-specified non-inferiority margin of 20% for all 3 readers (6.1%, 95% CI: - 5.0 to 17.2; - 7.5%, 95% CI: - 18.4 to 3.5; - 0.3%, 95% CI: - 11.3 to 10.7). The diagnostic confidence level for all 3 readers increased with post-contrast images relative to pre-contrast images. Both contrast agents were well tolerated. | Results showed a similar efficacy for Sonazoid™ and SonoVue® in diagnosing FLLs as benign or malignant, and underlined the benefit of CEUS imaging over unenhanced ultrasound imaging in reaching a confident diagnosis without having to refer patients for additional imaging exams. |
| Masuzaki (2011) [39] | cohort | 316 | 316 | | Detectability of tumor nodule was 83.5% in conventional ultrasonography and 93.2% in CEUS (P=0.04). Sixty-nine nodules in 52 patients were additionally detected with CEUS. The number of additionally detected tumor nodules was positively correlated with serum albumin level (P=0.016). The number of RFA sessions was 1.33±0.45 with CEUS as compared to 1.49±0.76 in the historical controls (P=0.0019). | CEUS with Sonazoid is useful for HCC detection in patients with a well-conserved liver function reservoir. The decrease in RFA session numbers indicated the utility of Sonazoid in RFA treatment of HCC. |

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| Mita (2010) [40] | cohort | 29 | 29 | | Overall, the sensitivity of diagnosing HCC smaller than 2 cm was 52.9% (18/34) (95% CI: 35.1-70.2) by CECT; 67.6% (23/34) (95% CI: 49.5-82.6) by Sonazoid CEUS; 76.5% (26/34) (95% CI: 58.8-89.3) by Gd-EOB-DTPA MRI; and 88.2% (30/34) (95% CI: 72.5-96.7) by CT arterioportal angiography. The diagnostic sensitivity of detecting moderately-differentiated HCC by CECT, Sonazoid CEUS, Gd-EOB-DTPA MRI and CT arterioportal angiography was 62.5% (15/24) (95% CI: 40.6-81.2), 79.2% (19/24) (95% CI: 57.8-92.9), 75.0% (18/24) (95% CI: 53.3-90.2) and 95.8% (23/24) (95% CI: 78.9-99.9), respectively. A significant difference ($P < 0.05$) was observed between CECT and CT arterioportal angiography in all nodules. There was no difference between Sonazoid CEUS, Gd-EOB-DTPA MRI, and CT arterioportal angiography. The combined sensitivity of Sonazoid CEUS and Gd-EOB-DTPA MRI was 94.1% (32/34). | Changing the main diagnostic modality for HCC smaller than 2 cm from CT arterioportal angiography to Sonazoid CEUS and Gd-EOB-DTPA MRI is recommended. |
| Moriyasu (2009) [41] | retrospective cohort | 190 | 190 | | rate of correct Dx using CEUS for metastasis, 78.9 (30/38); other malignant lesion, 80.0 (4/5) | Compared with unenhanced ultrasound and dynamic CT, contrastenhanced ultrasound with perflubutane microbubbles improved diagnostic efficacy in both characterization and detection of focal liver lesions with no serious adverse drug reactions. |

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| Sugimoto (2016) [42] | prospective cohort | 13 | 13 | | For all lesions, the contrast ratio was not significantly different between the two injection rates. For HCCs, the contrast ratio was higher at 0.5 mL/s (7.41 ± 6.56) than at 2.0 mL/s (4.28 ± 4.66, p = 0.025). For all lesions, the mean area under the ROC curve (AUC) was not significantly different between the two injection rates. For HCCs, the AUC was greater at 0.5 mL/s than at 2.0 mL/s (AUC: 0.86, p = 0.013). | In contrast-enhanced US, an injection rate of 0.5 mL/s is superior to an injection rate of 2.0 mL/s for the quantitative and qualitative analysis of HCCs in the cirrhotic liver. |
| Sugimoto (2015) [43] | retrospective cohort | 27 | 27 | | No difference was observed in tumor size and tumor markers between the 2 types; however, the sensitivity of contrast-enhanced CT, contrast-enhanced ultrasonography and arterioportal angiography was significantly different between the 2 types, whereas that by Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging (Gd-EOB-DTPA MRI) demonstrated no difference. | Hypovascular HCC could be diagnosed by Gd-EOB-DTPA MRI in the hepatobiliary phase. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript. A total number of included articles for making this guideline is 45. Some articles (*) are used redundantly as the evidences for multiple key questions.

**Supplementary table 1C.** Evidence table of KQ3

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Mandai (2011) [48] | prospective cohort | 88 | 88 | | Detection of vascularity at the early vascular phase was 88% in nodules that were found to be hypervascular on dynamic CT and 28% in hypo-/isovascular nodules; the detection of local recurrence nodules was 92%. The detection of vascularity was significantly lower in nodules >9 cm deep than in those ≤9 cm deep, but was not affected by tumour size. The detection of tumours at the post-vascular phase on CEUS was 83% in nodules with low density in the portal phase on dynamic CT and 82% in nodules with isodensity. The rate did not depend on the severity of underlying liver disease; rates decreased in nodules deeper than 9 cm, those smaller than 2 cm in diameter and in iso-enhancing nodules at the early vascular phase of CEUS. | CEUS with Sonazoid is a useful tool for assessing the vascularity of HCC and is equal to that of dynamic CT; however, the detectability of HCC vascularity is affected by location. |

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| Wang (2021) [49] | retrospective cohort | 128 | 128 | | When precontrast images were used to adjust the AP enhancement ratio, the proportion of inconsistent interpretations of AP vascularity declined from 26.2% (43/164; 29 non-hypervascularity instances using EOB-MRI and 14 using SCEUS) to 16.5% (27/164; 7 using EOB-MRI and 20 using SCEUS). Greater lesion depth (P = 0.017), ill-defined tumoral margin (P = 0.028), absence of halo sign (P = 0.034), and histologically early HCC (P = 0.007) on SCEUS, and small size (P = 0.012) and heterogeneity (P = 0.013) of lesions and slight enhancement (low AP enhancement ratio) (P = 0.018 and 0.009 before and after adjustment) on EOB-MRI, may relate to undetectable hypervascularity. | SCEUS and EOB-MRI may show discrepancies in evaluating AP vascularity in the case of deep, ill-defined, heterogeneous, slightly enhanced lesions, and histologically early HCCs. We recommend adjusting AP with precontrast images in EOB-MRI, and combining both modalities to detect hypervascularity. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript.

**Supplementary table 1D.** Evidence table of KQ4

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Kang (2020) [14] | prospective cohort | 59 | 59 | | Fifty percent (five of 10) of non-HCC malignancies manifested with rim APHE. Most malignancies (92% [49 of 53]) had hypoenhancement in the Kupffer phase, except for three HCCs (7.0% [three of 43]) and one angiosarcoma (100% [one of one]) | Noninvasive US diagnosis of hepatocellular carcinoma by using perfluorobutane-enhanced US had higher diagnostic performance than sulfur hexafluoride–enhanced US. |
| Sugimoto (2020) [27] | retrospective cohort | 104 | 104 | | The 22 (21.2%) LR-M lesions included 16 non-HCC malignancies and 6 HCCs. The PPV of LR-M for non-HCC malignancies, including six intrahepatic cholangiocarcinomas, was 100% (95% CI: 69.8–100%). | The modified CEUS LI-RADS for Sonazoid, LR-5 and LR-M are good predictors of HCC and non-HCC malignancies, respectively. |
| Hatanaka (2008) [32] | retrospective cohort | 249 | 249 | | In metastases, the presence of rim-like enhancement with peripheral tumor vessels (sensitivity, 88.1%; specificity, 100%) was the typical pattern. | Contrast-enhanced harmonic US with Sonazoid allowed intimate vascular and Kupffer imaging and, therefore, is useful for the differential diagnosis of hepatic tumors. |

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| Hsiao (2019) [33] | prospective cohort | 66 | 66 | | diagnostic odds ratio (DOR, 95% CI) for metastasis: CEUS (200, 19.1–2095), MRI (24, 5.05–114), and CT (32, 6.56–156); and all liver malignancy: CEUS (260, 12.7–5310), MRI (2.57, 0.55–12.1), and CT (5.22, 1.25–21.8).<br>Sensitivity, specificity, PPV, and NPV for metastasis: 92.9%, 100%, 92.3%, and 94.5% | CEUS outperformed dynamic CT and MRI in terms of diagnostic performance when dealing with small liver tumors (<3 cm). |
| Luo (2009) [36] | retrospective cohort | 139 | 139 | | sensitivity, specificity, PPV, and Az for metastasis: 88%, 97%, 91%, and 0.94 for reader 1; 85%, 95%, 85%, and 0.89 for reader 2 | Contrast-enhanced 3D US potentially can be used to characterize focal liver tumors. |
| Luo (2010) [37] | prospective & retrospective cohort | 163 | 163 | | At CEUS, the prospective differentiation of lesions showed sensitivity 84% (mean for two readers), specificity 97% and Az value 0.95 for metastasis. | CE 3D US provides a spatial perspective for liver tumor enhancement, and could help in differentiating focal liver lesions. |
| Moriyasu (2009) [41] | retrospective cohort | 190 | 190 | | rate of correct Dx using CEUS for metastasis, 78.9 (30/38); other malignant lesion, 80.0 (4/5) | Compared with unenhanced ultrasound and dynamic CT, contrastenhanced ultrasound with perflubutane microbubbles improved diagnostic efficacy in both characterization and detection of focal liver lesions with no serious adverse drug reactions. |
| Zhai (2019) [44] | prospective cohort | 65 | 65 | | The improvement of diagnostic accuracy was 0.30 in the Sonazoid group and 0.16 in the SonoVue group (95% confidence interval, –0.828–0.168; P = .24).<br>Sensitivity and specificity for metastasis; 85.5%, 96.1% | The diagnosis value of Sonazoid is noninferior to SonoVue, and this new contrast agent can improves the whole-liver image quality. |

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| Patel (2010) [61] | retrospective cohort | 61 | 61 | | Of the 42 malignant lesions, 38 lesions (90.5%) showed washout on both SEUS and CECT. The remaining four malignant lesions, of which three lesions contained fibrosis (two CC, and one scirrhous HCC), showed washout on SEUS but not on CECT. | The overall concordance rate between SEUS and CECT was good, but some differences were seen in the washout patterns of malignant lesions. |
| Luo (2009) [66] | prospective cohort | 142 | 142 | | For metastasis, a combination of peripheral ringlike enhancement with peritumoral vessels and peripheral ringlike enhancement with intratumoral vessels yielded sensitivity of 79%, specificity of 95%, and a PPV of 85%. | Sonazoid-enhanced ultrasonography using intermittent imaging with a high MI can potentially be used for evaluating the enhancement patterns of focal liver tumors in the late phase |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript. A total number of included articles for making this guideline is 45. Some articles (*) are used redundantly as the evidences for multiple key questions.

**Supplementary table 1E.** Evidence table of KQ5

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Kudo (2010) [68] | cohort | 262 | 262 | | A total of 7 small HCCs were depicted and confirmed as HCCs by Kupffer phase surveillance and defect reperfusion US imaging. | defect reperfusion US imaging is extremely useful in the depiction and confirmation of US undetectable HCCs as well as in the surveillance of HCC in cirrhotic patients. |
| Kudo (2019) [69] | RCT | 622 | 309 | 313 | The mean HCC size at the first detection was significantly smaller in the CEUS (13.0 ± 4.1 mm; n = 28) than in the B-mode US group (16.7 ± 4.1 mm; n = 26) (p = 0.011). Of the 38 patients with HCV cirrhosis diagnosed with HCC by US alone, mean tumor size at the first detection was significantly smaller in the 20 patients diagnosed by CEUS alone than in the 18 diagnosed by B-mode US alone (12.7 ± 3.1 vs. 17.6 ± 7.0 mm, p = 0.012). In contrast, among the 16 patients with HBV cirrhosis diagnosed by US alone, mean tumor size at the first detection was similar in the 8 patients diagnosed by CEUS alone and the 8 diagnosed by B-mode US (13.6 ± 6.0 vs. 14.5 ± 2.7 mm, p = 0.715). | Kupffer phase CEUS surveillance with Sonazoid is extremely useful for the early detection and confirmation of HCC using a reinjection technique. Kupffer phase CEUS with Sonazoid contrast combined with the reinjection technique is, therefore, recommended as first-line screening tool for HCC in patients with liver cirrhosis, especially those with very coarse liver parenchyma. |

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| Park (2019) [70] | prospective cohort | 524 | 524 | | A total of 524 participants (mean age, 54 years ± 9 [standard deviation]) were included. Of these, 493 (94.1%) had liver cirrhosis related to the hepatitis B virus. Ten HCCs were confirmed in eight participants. The detection rate of early-stage HCC was not significantly improved by adding perfluorobutane-enhanced US to conventional B-mode US (difference, 0.4% [95% confidence interval: -0.3%, 1.1%]; P = .16). The false referral rate was significantly reduced (difference, -3.2% [95% confidence interval: -5.0%, -1.4%]; P < .001). | The addition of perfluorobutane-enhanced US to conventional B-mode US reduced the false referral rate without a significant improvement in the detection rate of early-stage hepatocellular carcinoma for surveillance in a population in which the hepatitis B virus predominated. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript.

**Supplementary table 1F.** Evidence table of KQ6

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Masuzaki (2011) [39] | cohort | 316 | 316 | | Detectability of tumor nodule was 83.5% in conventional ultrasonography and 93.2% in CEUS (P=0.04). Sixty-nine nodules in 52 patients were additionally detected with CEUS. The number of additionally detected tumor nodules was positively correlated with serum albumin level (P=0.016). The number of RFA sessions was 1.33±0.45 with CEUS as compared to 1.49±0.76 in the historical controls (P=0.0019). | CEUS with Sonazoid is useful for HCC detection in patients with a well-conserved liver function reservoir. The decrease in RFA session numbers indicated the utility of Sonazoid in RFA treatment of HCC. |
| Dohmen (2012) [75] | Case-control | 102 | 71 | 31 | The clinical characteristics (sex, virus marker, Child-Pugh grade, with or without transcatheter arterial infusion chemotherapy with lipiodol, and T factor) did not differ significantly between group A and group B. Mean age was significantly older and tumor size was significantly larger in group B. Group B had significantly better radicality compared with group A. The non-local recurrence rate was significantly higher in group B as compared with group A. | CE-US with Sonazoid(®) greatly helps to improve RFA efficacy in HCC treatment. We suggest that the ability of CE-US with Sonazoid(®) to detect an accurate area of HCC before RFA and to immediately detect a residual tumor during RFA might contribute to an increase of the radicality and reduction of local recurrence after RFA. |

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| Lee (2017) [76] | prospective cohort | 38 | 38 | | A total of 38 patients with 43 HCCs (mean size, 1.6 cm; range, 0.5-2.9 cm) were enrolled. The vascular phase of Sonazoid-enhanced ultrasonography showed good tumor enhancement in 30/43 HCCs (70%). The Kupffer phase increased lesion conspicuity and operator's diagnostic confidence in 29 patients with 31 HCCs (31/43, 72%) compared with conventional US. | CEUS with Sonazoid is useful for detection and targeting of small HCC prior to RFA. |
| Minami (2010) [77] | retrospective cohort | 66 | 66 | | The maximal diameters of all tumours ranged from 0.7 to 3.5 cm (mean +/- SD, 1.7 cm +/- 0.9) on sonography. Complete tumour necrosis was achieved by a single session of RF ablation in 62 (94%) of the 66 patients, while two sessions were required for the remaining four (6%) patients. The average number of treatment sessions was 1.1 +/- 0.3. In the post-vascular phase, 105 (97%) of a total of 108 malignant hepatic tumours were depicted as a defect with a margin. Clinical courses have been satisfactory without any signs of local tumour progression during 1-12 months of follow-up (mean, 4.3 months). | Using perfluorocarbon microbubbles, contrast harmonic sonographic-guided RF ablation is an efficient approach for guiding further ablation of hepatic malignancies that are not clearly demarcated by B-mode sonography. |
| Lee (2018) [78] | Case-control | 90 | 21 | 69 | After adding CEUS, 90.5% (19/21) of all tumors initially inconspicuous on FI became conspicuous, thus enabling direct targeting for RFA. Technical success and primary technique efficacy rates were 94.7% (18/19) and 100% (19/19), respectively. No major complications were observed after RFA. Cumulative local tumor progression rates after RFA were estimated to be 5.3%, 10.8%, and 10.8% at 1, 2, and 3 years, respectively. | Adding CEUS to FI is useful for improving the conspicuity of HCCs inconspicuous on FI alone, thus enabling successful percutaneous RFA with excellent therapeutic outcomes. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript. A total number of included articles for making this guideline is 45. Some articles (*) are used redundantly as the evidences for multiple key questions.

**Supplementary table 1G.** Evidence table of KQ7.

| Author (year) | Type | subject (N) | intervention (N) | comparator/control (N) | results | conclusion |
|---|---|---|---|---|---|---|
| Inoue (2013) [80] | retrospective cohort | 70 | 70 | intraindividual comparison | CEUS judged 33 cases as CRSM+, while dynamic CT identified 49 cases. None of these 33 cases from the CEUS group had local recurrences, while dynamic CT had 1 case. CEUS judged 49 cases as CRSM-, compared to 34 cases with dynamic CT. Of these, 9 cases of CEUS and 8 cases of dynamic CT showed local recurrences. Two cases diagnosed as 'incomplete' by CEUS and dynamic CT had recurrences within 1 year. | CEUS can be used to assess the efficacy of RFA for HCC, with the potential to reduce the number of CT scans required for confirmation. |
| Nishigaki (2015) [81] | retrospective cohort | 87 | 87 | N/A | In 78 patients (89.7%), the outline of the coagulated tumors could be recognized by ultrasonography, and CEUS assessment of the ablative margin was successful. The remaining nine patients were assessed by computed tomography. The 5-year cumulative survival rate after the assessment of the treatment response with CEUS was 58.4%, and the 4-year cumulative total recurrence rate was 72.3%. The 5-year cumulative local tumor recurrence rate was very low (2.3%). | The assessment with CEUS at 3 h after the PRFA procedure was successful in the majority of the patients, and it yielded a very low rate of local recurrence. |

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| Takahashi (2012) [82] | prospective cohort | 179 | 33 | 146 | Seventeen of them were followed up with no treatment (remaining 16; dropout in eight, additional RFA in six and ineffective treatment in two) and three lesions (3/17, 17.6%) showed local tumor progression corresponding to linear enhancement at 7, 14, 19 months after RFA. Although there was no significant difference in local recurrence rate between the lesions with (3/17) and without linear enhancement (10/35), local tumor progression inside the ablation zone occurred only in the lesions with linear enhancement. | linear enhancement inside the RFA-treated area should be followed up within 7 months because it has a risk of local tumor progression. Histology of linear enhancement and its influence on distant recurrence remain to be solved. |
| Shiozawa (2010) [83] | retrospective cohort | 71 | 71 (HCC=87; RFA=55, TACE=22, combination=10) | intraindividual comparison | The Az value for dynamic CT (presence of recurrence) was significantly lower in observer 1 than 2 ($p < 0.05$). The sensitivity of CEUS was 79% in observer 1 and 83.9% in observer 2, and that of dynamic CT was 83.9% and 90.3%, respectively. The specificity of CEUS was 96%, and that of dynamic CT was 92%, in both observers. | This study suggests that CEUS using Sonazoid is less affected by the observer's experience and is more accurate in the diagnosis of local recurrence after treatment for HCC than dynamic CT. |
| Shiozawa (2021) [84] | retrospective cohort | 32 | 32 (HCC=39) | N/A | The enhancement patterns on CEUS performed within 3 days after DEB-TACE were defined as Pattern A in 17 cases, B in 7, C in 13, and D in 2. The complete response rates at one month after treatment were 94.1% (16/17 lesions) for Pattern A, 85.7% (6/7) for B, 15.4% (2/13) for C, and 50% (1/2) for D. The response rates were significantly higher for lesions with Pattern A compared to those with Pattern C at one month ($p = 0.009$) and 12 months ($p < 0.001$) after treatment, and significantly higher for lesions with Pattern B compared to those with Pattern C at 12 months after treatment ($p = 0.031$). | Comparisons between other patterns showed no significant differences. CEUS immediately after DEB-TACE may allow early assessment of therapeutic efficacy, with findings of no enhancement or peripheral ring enhancement suggesting a positive outcome. |

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| Takizawa (2013) [85] | prospective cohort | 32 | 32 (HCC=59) | intraindividual comparison | Forty-seven (79.7%) of the 59 HCC lesions were diagnosed as having residual viability based on DSA and contrast-enhanced CT findings obtained 2-6 months after TACE. Eight (17.0%) of the 47 HCC lesions that were diagnosed as having residual viability using one-day contrast-enhanced US were not detected using one-month contrast-enhanced CT because of artifacts produced by the high attenuation of the iodized oil. The detection rate for residual HCC lesions using one-day contrast-enhanced US (95.7%, 45/47) was significantly higher than that using one-month contrast-enhanced CT (78.7%, 37/47) ($P<0.05$). | Contrast-enhanced US performed one day after TACE is more sensitive than contrast-enhanced CT performed one month after TACE for detecting residual viable HCC. |
| Xia (2008) [86] | prospective cohort | 28 | 28 (HCC=43) | intraindividual comparison | The detection rates of positive enhancement with Sonazoid-enhanced harmonic US and dynamic CT 1 week after TACE were 25 (58.1%) of 43 lesions and 17 (39.5%) of 43 lesions, respectively. Sonazoid-enhanced harmonic US was significantly more sensitive than dynamic CT in depicting the residual tumor blood supply to HCCs 1 week after TACE ($p < 0.01$; chi(2) test). The Sonazoid-enhanced harmonic US results of the 16 lesions 1 week after chemoembolization were consistent with the follow-up results of dynamic CT 2 months after chemoembolization. | Sonazoid-enhanced harmonic US appears to be a highly sensitive and accurate modality for evaluating responses of HCCs shortly after TACE. |

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| Funaoka (2021) [87] | retrospective cohort | 59 | 59 | N/A | Tumor size and tumor vascularity were evaluated using SCEUS before and 1, 3, 7, 10, and 13 months after radiotherapy. The median follow-up period was 44.5 months (range: 16-82 months). Of the HCCs, 95% (56/59) had no local recurrence, while 5% (3/59) did. At 13 months after radiotherapy, in cases with no local recurrence, SCEUS showed a reduction in tumor vascularity in all cases, while tumor size reduction (>30% reduction, compared with pre-radiotherapy) was observed in 82.1% (46/56). In all three cases of local recurrence, vascularity and tumor size reduction were not observed during the follow-up period and residual HCCs were demonstrated pathologically. Compared with cases with local recurrence, tumor size reduction and reduction in tumor vascularity ($p < 0.001$) were significantly greater in cases with no local recurrence at 13 months after radiotherapy. | SCEUS may be useful in evaluating radiotherapy efficacy for HCC. |

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| Kamachi (2021) [88] | prospective cohort | 19 | 19 | N/A | Mean ± standard deviation (SD) values of the brightness of blood flow in the background liver before and 1 and 4 weeks after LEN administration were 2.84 × 10-4 ± 2.94 × 10-4 , 3.07 × 10-4 ± 3.79 × 10-4 , and 10.0 × 10-4 ± 20.8 × 10-4 dB, respectively. Blood flow in the background liver did not significantly decrease at 1 and 4 weeks compared with that before treatment. Mean ± SD values of the brightness of blood flow in HCC before and 1 and 4 weeks after administration were 3.49 × 10-3 ± 4.58 × 10-3 , 1.16 × 10-3 ± 1.57 × 10-3 , and 6.39 × 10-3 ± 22.8 × 10-3 dB, respectively. Blood flow in HCC after 1 week was significantly lower than that before administration (p = .0192). The therapeutic effects were significantly higher in the group with ≥50% blood flow reduction in HCC at 1 week after administration (p = .0038) and the group with reduced blood flow in HCC at 4 weeks after administration (p = .0051) than those before administration. | Early blood flow evaluation by CEUS may be useful in predicting the therapeutic effect of LEN for unresectable advanced HCC. |
| Shiozawa (2017) [89] | retrospective cohort | 21 | 21 | N/A | In the MT (mean arrival time of Sonazoid) (+) (11 patients) and MT (-) (10 patients) groups, the median survival time was 792 and 403 days, respectively, which was statistically significant. | The results suggested that AtPI was useful for evaluating early response to sorafenib for advanced HCC with low AFP level. |

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| Siozawa (2016) [90] | retrospective cohort | 26 | 26 | N/A | The number of patients in the intratumoral necrosis (+) and (-) groups was 8 and 18 patients, respectively, and the median survival time (MST) was 7.2 months [95% confidence interval (CI), 2.2-12.2] and 9.5 months (95% CI, 5.1-13.8), respectively (P=0.44). The MFI findings were observed in 11 patients in the Vd group, 10 patients in the Vnc group and 5 patients in the Vi group. The MSTs in the Vd, Vnc and Vi groups were 15.6 months (95% CI, 5.0-23.3), 11.0 months (95% CI, 3.5-17.6) and 3.6 months (95% CI: 1.2-6.0), respectively. The P-value for the differences between the Vd and Vnc groups, Vd and Vi groups, and Vnc and Vi groups were 0.78, 0.016 and 0.047, respectively, which indicated that the survival time decreased significantly in the Vi group. | Evaluation of intratumoral vascular architecture using MFI demonstrates promise for assessing the therapeutic response to sorafenib in patients with HCC. |
| Sugimoto (2013) [91] | prospective cohort | 37 | 37 | N/A | Tumour perfusion parameters based on the area under the time-intensity curve (AUC) were statistically significant, with AUC during washin on day 14, the most relevant for tumour response (P = 0.0016) and AUC during washin on day 7, the most relevant for both PFS (P = 0.009) and OS (P = 0.037). A decrease in total AUC between days 0 and 7 in the liver parenchyma was strongly correlated with major AEs (P = 0.0002). | DCE-US may be useful for the early prediction of tumour response and major AEs in patients with HCC. |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript. A total number of included articles for making this guideline is 45. Some articles (*) are used redundantly as the evidences for multiple key questions.

**Supplementary table 2.** Sonazoid CEUS protocols and QUADAS II evaluation of the evidences (n=45)

| Author (year) | Sonazoid CEUS protocol | | | QUADAS II | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | risk of bias | | | | applicability concern | | |
| | vascular phase | Kupffer phase | Kupffer phase first and re-injection | patient selection | index test | reference standard | flow and timing | patient selection | index test | reference standard |
| Hwang (2021) [13] | Yes | 10 minutes | x | Low | Low | Unclear | Unclear | Low | Low | Unclear |
| Kang (2020) [14] | Yes | 10 minutes | x | Low | Low | Low | Unclear | Low | Low | Unclear |
| Saito (2020) [21] | Yes | 10, 20, 30 minutes | x | Low | Low | Low | Low | Unclear | Low | Low |
| Inoue (2008) [25] | Unclear | 10 minutes | x | Unclear | Low | Unclear | Unclear | Low | Low | Unclear |
| Yang (2017) [26] | Yes | 5-10 minutes | x | Low | Unclear | Unclear | Unclear | Unclear | Low | Unclear |
| Sugimoto (2020) [27] | Yes, early vascular only | 10 minutes | x | Low | Low | Low | Unclear | Unclear | Low | Unclear |
| Alaboudy (2011) [29] | Yes | 15 minutes | Yes | Low | High | Low | Low | Low | Low | Low |
| Goto (2012) [30] | x | 15 minutes | x | Low | Low | High | Low | Low | Low | Unclear |
| Hatanaka (2008) [31] | Yes, early vascular only (<60 s) | 10 minutes | x | Low | Low | Unclear | Unclear | Unclear | Low | Unclear |
| Hatanaka (2008) [32] | Yes, early vascular only (<60 s) | 10 minutes | x | Low | Unclear | Unclear | Unclear | Unclear | Low | Unclear |
| Hsiao (2019) [33] | Yes, early vascular only | 10 minutes | x | Low | Low | Low | Low | Unclear | Low | Low |
| Kan (2010) [34] | Yes, early vascular only | 10 minutes | x | Unclear | High | High | Low | Unclear | Low | Unclear |
| Kawada (2010) [35] | Yes | 15-20 minutes | x | Unclear | Low | Low | Low | Low | Low | Low |

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|---|---|---|---|---|---|---|---|---|---|---|
| Luo (2009) [36] | Yes | longer than 5 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Luo (2010) [37] | Yes | longer than 5 minutes | x | Low | Unclear | Low | Unclear | Unclear | Low | Low |
| Lv (2021) [38] | Yes | 10 minutes | x | Low | Unclear | Unclear | Unclear | Unclear | Low | Unclear |
| Masuzaki (2011) [39] | Unlcear | 10 minutes | x | Low | High | High | Low | Low | Low | Unclear |
| Mita (2010) [40] | Yes, early vascular only | 10 minutes | x | Unclear | Low | Low | Low | Low | Low | Low |
| Moriyasu (2009) [41] | Yes, early vascular only | 10 minutes | x | Low | High | High | Low | Unclear | Low | Unclear |
| Sugimoto (2015) [42] | Yes, early vascular only | 10 minutes | Yes | Unclear | Low | Low | Low | Low | Low | Low |
| Sugimoto (2016) [43] | unclear | unclear (double injection after destrcution of remaining circulating microbubbleafter at least 20 mintues) | x | Low | Low | Unclear | Low | Low | Low | Low |
| Zhai (2019) [44] | Yes | 6-8 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Mandai (2011) [48] | Yes, early vascular only (<60 s) | 10 minutes | x | Low | Unclear | Unclear | Unclear | Low | Low | Unclear |
| Wang (2021) [49] | Yes | 10 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Patel (2010) [61] | Yes | 10, 20, 30 minutes | x | Unclear | Unclear | Low | Low | Unclear | Low | Low |
| Luo (2009) [66] | x | x (high MI imaging after 5 minutes) | x | Low | Unclear | Unclear | Unclear | Low | Low | Unclear |
| Kudo (2010) [68] | Yes, early vascular only | 10-60 minutes | Yes | High | Low | Low | Low | Unclear | Low | Unclear |
| Kudo (2019) [69] | x | 10-60 minutes | Yes | Low | Unclear | Unclear | Unclear | Low | Low | Unclear |
| Park (2019) [70] | Yes | 10 minutes | x | Low | Unclear | Unclear | Low | Low | Low | Unclear |
| Dohmen (2012) [75] | Unclear | 10 minutes | Yes | Unclear | Low | Low | Low | Low | Low | Low |
| Lee (2017) [76] | Yes | 10 minutes | x | Low | Low | Low | Low | Low | Low | Low |

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|---|---|---|---|---|---|---|---|---|---|---|
| Minami (2010) [77] | Yes | 10 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Lee (2018) [78] | Yes | 10 minutes | x | Unclear | Low | Low | Low | Low | Low | Low |
| Inoue (2013) [80] | Unclear | Yes, but unclear timing | x | Low | Low | Low | Low | Low | Low | Low |
| Nishigaki (2015) [81] | Yes | x | x | Low | Unclear | Low | Low | Low | Low | Low |
| Takahashi (2012) [82] | Yes | 10 minutes | x | Low | Unclear | Low | Low | Low | Low | Low |
| Shiozawa (2010) [83] | Yes, early vascular only | 15 minutes | x | Low | Unclear | Low | Low | Low | Low | Low |
| Shiozawa (2021) [84] | Yes, early vascular only | 10 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Takizawa (2013) [85] | Yes | 5 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Xia (2008) [86] | Yes (but, unclear timing) | 5-7 minutes | x | Low | Low | Low | Low | Low | Low | Low |
| Funaoka (2021) [87] | Yes | 10 minutes | x | Low | Unclear | Low | Low | Low | Low | Low |
| Kamachi (2021) [88] | Yes (but, unclear timing) | x | x | Low | Unclear | Low | Low | Low | Low | Low |
| Shiozawa (2017) [89] | Yes, early vascular only | x | x | Low | Unclear | Low | Low | Low | Low | Low |
| Siozawa (2016) [90] | x | 10-15 minutes | Yes | Low | Unclear | Low | Low | Low | Low | Low |
| Sugimoto (2013) [91] | Yes | x | x | Low | Unclear | Low | Low | Low | Low | Low |

Note. The references in the supplementary table refer to the reference number in the main guideline manuscript.