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The prediction of microvascular invasion of hepatocellular carcinoma using multiple imaging modalities

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Abstract

To implement an adequate treatment strategy for solitary hepatocellular carcinoma (HCC), the prediction of microvascular invasion (MVI) is crucial. Metastatic recurrences after curative treatments can result from occult metastasis derived from invisible MVI. For predicting MVI, poorly differentiated or non-singular nodular HCC with a high risk of MVI should be evaluated by common imaging modalities such as ultrasound, contrast enhanced computed tomography (CECT), or magnetic resonance imaging (MRI). Summarizing these predictabilities in previous reports, the accuracies for predicting MVI were 78% in contrast enhanced ultrasonography (CEUS), 76%-89% in CECT, and 62%-77% in MRI. Those for predicting poor differentiation were 69%-92% in CEUS, 52%-90% in CECT, and 71%-75% in MRI. Those for predicting non-singular nodular type were 92%-95% in CEUS, 81%-89% in MRI, and 91%-93% in the combination of MRI and CECT. Among common imaging modalities, MRI can provide tissue characterization of the HCC using signal intensity. Gadolinium-ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced MRI including diffusion imaging is the most informative imaging modality to predict MVI. Combination of MRI with other imaging modalities or tumor markers may provide a more accurate predicting for MVI. HCC with a high risk of MVI should be treated as advanced HCC even after curative treatment.

Keywords: Hepatocellular carcinoma, microvascular invasion, histologic differentiation, ultrasound, computed tomography, magnetic resonance imaging

INTRODUCTION

There have been rapid advances in the development of imaging modalities as diagnostic tools in recent years. In hepatocellular carcinoma (HCC), imaging plays a greater part than biopsy in its diagnosis. In addition,



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imaging is used not just for its diagnosis, but also for disease surveillance, determination of tumor stage, evaluation of treatment efficacy, and navigation of local treatments. Importantly, imaging has the ability to predict histologic differentiations that reflect the malignant potential of HCC.

As the HCC tumor grows larger, it has a stronger tendency to invade the adjacent portal vein or hepatic vein. HCC with intrahepatic or extrahepatic metastasis derived from vascular invasion is an advanced cancer that is difficult to treat radically^[1]. However, even if the tumor is solitary on imaging, metastatic recurrences after curative treatments such as surgical resection or local ablation is not uncommon. These metastatic recurrences may result from occult metastasis derived from invisible microvascular invasion (MVI) at the time of diagnostic imaging before treatment was initiated. Therefore, HCC with MVI can be considered as an advanced cancer with occult metastasis. However, there is a limitation in the diagnostic imaging of MVI or occult metastasis. To make an adequate treatment strategy for solitary HCC, the prediction of MVI is crucial. In this review, the present status of the prediction of MVI of HCC using common imaging modalities such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) is presented.

FACTORS RELATED TO MVI IN HCC

HCC develops in a multistep fashion^[2]. Therefore, most HCCs consist of heterogeneously differentiated components. For example, nodule in nodule or mosaic pattern on US imaging represents multistep carcinogenesis^[2]. As histologic differentiation advances from well differentiated to poorly differentiated, the prevalence of MVI becomes higher^[3]. Poor histologic differentiation is a strong predictor of MVI^[4]. A large proportion of poorly differentiated HCCs has MVI and intrahepatic metastasis even when the tumor is small^[3]. As the tumor size increases, a fibrous capsule forms such that a typical HCC is visualized as a nodule within a fibrous capsule. Cancer cell infiltration into the fibrous capsule demonstrates a morphologically invasive feature, and HCCs with infiltrations to the fibrous capsule tend to be poorly differentiated and to have MVI^[5]. Small nodular HCCs can be macroscopically classified into three types such as single nodular (SN), single nodular with extra-nodular growth (SNEG), and contiguous multinodular (CMN)^[6]. Both SNEG and CMN types have a stronger invasive potential, and tend to be more poorly differentiated than the SN type. The prevalence of MVI or microscopic intrahepatic metastasis is also higher in the SNEG and CMN types than in the SN type^[7-9]. Since MVI is strongly associated with histologic differentiation and the macroscopic type of HCC, the accurate prediction of MVI by imaging will require accurate evaluation of these two parameters.

PREDICTION OF MVI USING US

US has the highest spatial resolution among common imaging modalities, therefore it can potentially provide an accurate assessment of the macroscopic morphology of HCC. Moribata *et al.*^[10] reported the correlation between B mode ultrasonogram and histologic differentiation of small HCC. They revealed that most poorly differentiated small HCCs were visualized as hypoechoic tumor with an irregular or unclear margin on B mode US. However, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of diagnosis for poorly differentiated HCC on the basis of their data are 89%, 67%, 19%, 99%, and 69% respectively.

There have been several reports on the prediction of poorly differentiated HCC or MVI using CEUS, based on the evaluation of intra-tumoral angioarchitecture. Sugimoto *et al.*^[11] showed the correlation between the angioarchitecture and histologic differentiation using microflow imaging (MFI) by CEUS. The deadwood pattern of tumoral blood vessels was visualized clearly, but they gradually tapered off and were interrupted suddenly. When HCCs with deadwood pattern were assessed as poorly differentiated, the sensitivity, specificity, positive PPV, NPV, and accuracy of diagnosis for poorly differentiated HCC on the basis of their data are 80%, 96%, 86%, 94%, and 92%, respectively. Tanaka *et al.*^[12] implemented the malignant grading system based on the combined assessment of Kupffer imaging and the maximum intensity projection imaging

made by the accumulation for each MFI sequence using CEUS with perflubutane microbubbles (Sonazoid®; Daiichi-Sankyo, Tokyo, Japan). They classified HCCs into four grades: grade 1 (iso-fine/vascular), grade 2 (hypo-fine), grade 3 (hypovascular), and grade 4 (hypo-irregular). When HCC was assessed as grade 4, sensitivity, specificity, positive PPV, NPV, and accuracy of the diagnosis for poorly differentiated HCC are 100%, 91%, 50%, and 92% respectively, and those of the diagnosis for MVI are 40%, 92%, 67%, 80%, and 78% respectively.

The correlation between histologic grading and tumor enhancement washout time on CEUS has also been reported^[13-17]. For example, Xu *et al.*^[14] analyzed the enhancement pattern of HCC using time-intensity curve. They observed that the time to peak, contrast-enhanced time, and wash-out time of well differentiated HCCs were longer than those of the moderately to poorly differentiated HCCs, whereas the enhancement slope and clearance slope of the well differentiated lesions were lower than those of the moderately to poorly differentiated lesions. However, Pei *et al.*^[15] reported that washout time is the only significant factor (among all the time-intensity curve parameters) correlated to histologic grading. Washout time in the well-, moderately-, and poorly differentiated HCCs was 36.66 ± 9.61 , 19.37 ± 2.83 , and 11.61 ± 2.78 s, respectively. Feng *et al.*^[17] reported using the washout rate to predict HCC differentiation. They demonstrated that when the cutoff point was set at washout before 40 s from contrast injection, the ability to distinguish poorly differentiated from moderately- and well differentiated HCCs could be performed with a sensitivity, specificity, and area under the curve (AUC) of 24%, 97%, and 0.68, respectively.

Additionally, several reports have demonstrated the correlation between macroscopic HCC type and Kupffer imaging (post vascular phase) using Sonazoid CEUS. Hatanaka *et al.*^[18] reported that the sensitivity, specificity, PPV, NPV, and accuracy of CEUS for predicting for the non-SN type were 80%, 96%, 92%, 89% and 90%, respectively. Tada *et al.*^[19] also reported that those in small HCCs (3 cm or less) were 87%, 93%, 91%, 84% and 94%, respectively. Furthermore, Hatanaka *et al.*^[20] demonstrated that CEUS was more accurate at distinguishing macroscopic type than contrast CT. This could be explained by the difficulty in evaluating the shapes of nodules on contrast CT because of the partial volume effect. Nuta *et al.*^[21] also indicated that HCCs with an irregular defect visualized during Kupffer-phase of CEUS were characterized by more frequent MVI and intrahepatic metastasis. They demonstrated that Kupffer-phase images were more accurate at predicting the macroscopic pathologic type with high grade malignancy (SNEG or CMN type) than conventional B mode (CEUS AUC 0.89 vs. B-mode US AUC 0.78), and diagnostic accuracy was also significantly higher with Kupffer-phase imaging (92%) than with conventional B-mode imaging (74%). The sensitivity, specificity, PPV, NPV, and accuracy of US studies cited in this review were summarized in [Table 1](#) except for not available reports.

PREDICTION OF MVI USING CONTRAST CT

Contrast multi-detector low CT is commonly used for the definite diagnostic imaging of HCC. The diagnostic information obtained by contrast CT is tumor vascularity and morphology. There are some reports about the correlation between histologic differentiation and tumor vascularity. For example, Asayama *et al.*^[22] indicated that the arterial blood supply decreases significantly in poorly differentiated HCCs compared to moderately differentiated HCCs. Sanada *et al.*^[23] demonstrated that small HCCs intermingled with hypovascular areas and hypervascular areas in the arterial phase of contrast CT included poorly differentiated HCC components. Kawamura *et al.*^[24] also reported that heterogeneous enhancement with irregular ring-like structures in the arterial phase was a significant independent predictor of poorly differentiated HCC. On the other hand, fast tumor enhancement washout is also associated with poorly differentiated HCC. Nishie *et al.*^[25] indicated that poorly differentiated HCCs show faster tumor enhancement washout on contrast CT than non-poorly differentiated HCCs. However, Nakachi *et al.*^[26] demonstrated that the diagnostic accuracy for poorly differentiated HCC using tumor enhancement washout in the venous phase was low compared with heterogeneous tumor enhancement in the arterial phase. They showed that sensitivity, specificity, PPV, NPV, and accuracy for predicting poor differentiation in small HCCs (up to 3 cm in diameter) by heterogeneous

Table 1. Studies with ultrasound for predicting poorly differentiation, non-single nodular type, or microvascular invasion

Ref.	Modalities	Findings	Prediction	Sensitivity	Specificity	PPV	NPV	Accuracy
Moribata <i>et al.</i> ^[10]	B-mode US	Irregular or unclear margin	Poorly diff.	89%	67%	19%	99%	69%
Nuta <i>et al.</i> ^[21]	B-mode US	Irregular or unclear margin	Non-SN type	72%	85%	96%	39%	74%
Sugimoto <i>et al.</i> ^[11]	CEUS	Dead wood pattern	Poorly diff.	80%	96%	86%	94%	92%
Tanaka <i>et al.</i> ^[12]	CEUS	Grade 4 (hypo-irregular)	Poorly diff.	100%	91%	50%	100%	92%
Tanaka <i>et al.</i> ^[12]	CEUS	Grade 4 (hypo-irregular)	MVI	40%	92%	67%	80%	78%
Feng <i>et al.</i> ^[17]	CEUS	Washout time < 40 s	Poorly diff.	24%	97%	65%	61%	69%
Hatanaka <i>et al.</i> ^[18]	CEUS	Irregular defect on Kupffer phase	Non-SN type	80%	96%	92%	89%	90%
Tada <i>et al.</i> ^[19]	CEUS	Irregular defect on Kupffer phase	Non-SN type	87%	93%	91%	84%	95%
Nuta <i>et al.</i> ^[21]	CEUS	Irregular defect on Kupffer phase	Non-SN type	93%	85%	97%	73%	92%

PPV: positive predictive value; NPV: negative predictive value; US: ultrasound; SN: single nodular; CEUS: contrast enhanced ultrasonography; MVI: microvascular invasion

tumor enhancement were 75%, 90%, 48%, 97% and 88%, respectively^[26]. Accordingly, heterogenous tumor enhancement even in small HCC is an important observation for predicting HCC with poorly differentiated components.

Some reports show that irregular tumor margin in the venous phase of contrast CT is an important finding for predicting MVI or tumor differentiation. Lee *et al.*^[27] demonstrated that the presence of intra-tumoral vessels and aneurysms, tumor necrosis, attenuation of pre-contrast, the relative timing of washout, intra-tumoral attenuation heterogeneity, tumor margin, and tumor size were correlated with the pathological differentiation of HCC. In particular, the presence of intra-tumoral aneurysm was a highly specific finding for poorly differentiated HCC. Chou *et al.*^[28] showed that the sensitivity, specificity, PPV, NPV, and accuracy of the irregular tumor margin in predicting MVI in their retrospective study were 66%, 86.5%, 82.5%, 72.6% and 76.5%, respectively, and those in their prospective study were 81.7%, 88.1%, 90.7%, 77.1% and 84.3%, respectively^[29]. Reginelli *et al.*^[30] indicated that irregularity in tumor margins, as well as defects of peritumoral capsule are the most significant characteristics predicting MVI in HCC. Wu *et al.*^[31] reported that irregular tumor margin was alone independent predictive factor for MVI among previously proposed predicting factors such as fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) results and serum tumor markers. Hu *et al.*^[32] demonstrated in a meta-analysis that CT is superior to MRI in evaluating an irregular tumor margin for MVI assessment. Banerjee *et al.*^[33] showed new features of contrast CT that can also accurately predict histological MVI in HCC surgical candidates. These features include: the positivity of radiogenic venous invasion consisting of three separate imaging features; the persistence of discrete arterial tumor enhancement in the venous phase; partial or complete absence of hypodense halo; and absence of tumor-liver difference in the absence of a halo. Zhao *et al.*^[34] demonstrated that the predictive scoring model based on intra-tumoral arteries, non-nodular type of HCC, and absence of the radiological tumor capsule on preoperative CECT is of great value in the prediction of MVI regardless of tumor size. The sensitivity, specificity, PPV, NPV, and accuracy of CT studies cited in this review were summarized in Table 2 except for not available reports.

PREDICTION OF MVI USING MRI

The signal intensity of MRI can also be used to distinguish well differentiated HCC from moderately/poorly differentiated HCC^[35-37]. For example, typical moderately/poorly differentiated HCC show hypointensity on T1-weighted imaging and hyperintensity on T2-weighted imaging. Enomoto *et al.*^[38] reported that hypointensity of tumor on T1-weighted imaging and tumor stain washout during the portal phase of dynamic MRI reflected poorer histological differentiation of HCCs, and the sensitivity, specificity, and the accuracy for diagnosis of poorly differentiated HCC using combined findings of hypointensity on T1-weighted imaging and tumor enhancement washout during the portal phase were 88%, 67% and 71%, respectively. On the contrary, most of well-differentiated HCCs (83%) showed non-hypointensity on T1-weighted image^[38]. Min *et al.*^[39]

Table 2. Studies with contrast enhanced computed tomography for predicting poorly differentiation, non-single nodular type, or microvascular invasion

Ref.	Modalities	Findings	Prediction	Sensitivity	Specificity	PPV	NPV	Accuracy
Nishie <i>et al.</i> ^[25]	CECT	Washout on portal-venous phase	Poorly diff.	63%	72%	38%	88%	70%
Nakachi <i>et al.</i> ^[26]	CECT	Enhancement with non-enhanced area	Poorly diff.	75%	90%	48%	97%	88%
Nakachi <i>et al.</i> ^[26]	CECT	Washout on portal-venous phase	Poorly diff.	100%	55%	22%	100%	60%
Nakachi <i>et al.</i> ^[26]	CECT	Above combination	Poorly diff.	75%	92%	55%	97%	90%
Lee <i>et al.</i> ^[27]	CECT	Intra-tumoral aneurysm	Poorly diff.	18%	99%	93%	77%	78%
Lee <i>et al.</i> ^[27]	CECT	Irregular tumor margin	Poorly diff.	74%	44%	32%	82%	52%
Chou <i>et al.</i> ^[28]	CECT	Irregular tumor margin (retrospective)	MVI	66%	87%	83%	73%	77%
Chou <i>et al.</i> ^[28]	CECT	Irregular tumor margin (prospective)	MVI	82%	87%	91%	77%	84%
Wu <i>et al.</i> ^[31]	CECT	Irregular tumor margin	MVI	87%	73%	43%	96%	76%
Reginelli <i>et al.</i> ^[30]	CECT	Irregular tumor margin	MVI	66%	94%	84%	86%	85%
Reginelli <i>et al.</i> ^[30]	CECT	Incomplete peritumoral capsule	MVI	81%	90%	76%	91%	89%
Banerjee <i>et al.</i> ^[33]	CECT	Positivity of radiogenic venous invasion	MVI	76%	94%	83%	91%	89%
Zhao <i>et al.</i> ^[34]	CECT	Score model (validation cohort)	MVI	82%	83%	74%	88%	N/A

PPV: positive predictive value; NPV: negative predictive value; CECT: contrast enhanced computed tomography; MVI: microvascular invasion; N/A: not available

reported that intra-tumoral fat detected by chemical-shift of T1-weighted image indicates lower risk for MVI of HCC.

The recent advances in MRI instrumentation has allowed high quality diffusion weighted images (DWI) to be obtained. The correlation between the apparent diffusion coefficient (ADC) values on DWI and histologic differentiation have been reported^[40-44], suggesting that low ADC values can be a useful predictor of MVI^[45-47]. However, there was no notable threshold of ADC value for predicting poorly differentiated HCC on meta-analysis^[48]. Park *et al.*^[49] showed that hypervascular HCCs with low ADC value could be interpreted as poorly differentiated HCCs, while it was difficult to differentiate between well- and poorly differentiated HCCs that are hypovascular. Among all ADC parameters, Moriya *et al.*^[50] demonstrated that the minimum ADC value was the most useful in distinguishing poorly differentiated HCC in 3D analysis of ADC histograms. On the other hand, Ogihara *et al.*^[51] indicated that contrast-to-noise ratio (CNR) between the lesion and the liver parenchyma on DWI might be more useful than the ADC values for predicting poorly differentiated HCCs. Iwasa *et al.*^[52] also indicated that DWI CNR and the lesion-to-liver relative contrast ratio (RCR) on DWI are superior in predicting histologic differentiation than the ADC values, T2-weighted RCR, and ethoxybenzyl-hepatobiliary RCR. Mori *et al.*^[53] showed the usefulness of ADC mapping in predicting pre-operative malignant potential of HCC. On the basis of their data, the sensitivity, specificity, PPV, NPV, and accuracy for predicting poorly differentiated HCC is 93%, 68%, 54%, 96% and 75%, respectively, and those for predicting MVI is 89%, 58%, 31%, 96% and 63%, respectively. They suggested that hypointense HCC on ADC mapping are characterized by poor histological differentiation and more frequent microscopic portal invasion^[53]. Zhao *et al.*^[54] showed the usefulness of the combination of the true diffusion coefficient value and an irregular shape on hepatobiliary phase for predicting MVI, and the sensitivity and specificity were improved to 94.4% and 63.6% respectively. Wang *et al.*^[55] reported that other diffusion parameters, such as mean kurtosis value on diffusion kurtosis imaging, and irregular circumferential enhancement on dynamic MRI were independent risk factors for MVI of HCC. The combination of higher mean kurtosis values and irregular shape are potential predictive biomarkers for MVI^[55].

Gadolinium-ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging (EOB-MRI) is now commonly used for the diagnosis of HCC. With its use, there have been increasing reports of predicting MVI using dynamic MRI including hepatobiliary phase of EOB-MRI. Chang *et al.*^[56] indicated that relatively low arterial enhancement on arterial phase of EOB-MRI and low ADC value were predictive of worse histological grades of HCC. Kim *et al.*^[57] suggested focusing on the peritumoral hypointensity on hepatobiliary phase of EOB-MRI for predicting MVI. The sensitivity, specificity, PPV and NPV

Table 3. Studies with magnetic resonance imaging for predicting poorly differentiation, non-single nodular type, or microvascular invasion

Ref.	Modalities	Findings	Prediction	Sensitivity	Specificity	PPV	NPV	Accuracy
Enomoto <i>et al.</i> ^[38]	Plain + dynamic MRI	Hypointensity on T1-weighted imaging and washout on portal-venous phase	Poorly diff.	88%	67%	N/A	N/A	71%
Mori <i>et al.</i> ^[53]	Plain MRI	Hypointensity on ADC map	Poorly diff.	93%	68%	54%	96%	75%
Mori <i>et al.</i> ^[53]	Plain MRI	Hypointensity on ADC map	MVI	89%	58%	31%	96%	63%
Wang <i>et al.</i> ^[55]	Plain MRI	Mean kurtosis values > 0.917	MVI	70%	77%	70%	77%	74%
Kim <i>et al.</i> ^[57]	EOB-MRI	Peritumoral hypointensity on HBP	MVI	38%	93%	89%	53%	62%
Zhao <i>et al.</i> ^[54]	EOB-MRI	Irregular tumor margin	MVI	50%	88%	69%	76%	75%
Lee <i>et al.</i> ^[58]	EOB-MRI	Arterial peritumoral enhancement	MVI	54%	88%	68%	80%	77%
Lee <i>et al.</i> ^[58]	EOB-MRI	Irregular tumor margin	MVI	70%	69%	51%	83%	69%
Lee <i>et al.</i> ^[58]	EOB-MRI	Peritumoral hypointensity on HBP	MVI	32%	92%	65%	74%	73%
Tada <i>et al.</i> ^[60]	EOB-MRI	Irregular tumor margin	Non-SN type	97%	72%	74%	97%	83%
Chen <i>et al.</i> ^[61]	EOB-MRI	Irregular tumor margin	Non-SN type	96%	79%	87%	94%	89%
Kobayashi <i>et al.</i> ^[62]	EOB-MRI	Irregular tumor margin	Non-SN type	64%	96%	93%	77%	81%
Chen <i>et al.</i> ^[61]	EOB-MRI + CECT	Irregular tumor margin	Non-SN type	98%	84%	90%	94%	93%
Kobayashi <i>et al.</i> ^[62]	EOB-MRI + CEUS	Irregular tumor margin	Non-SN type	85%	95%	94%	88%	91%

PPV: positive predictive value; NPV: negative predictive value; MRI: magnetic resonance imaging; N/A: not available; ADC: apparent diffusion coefficient; MVI: microvascular invasion; EOB-MRI: Gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging; HBP: hepatobiliary phase; SN: single nodular; CECT: contrast enhanced computed tomography; CEUS: contrast enhanced ultrasonography

were 38.3%, 93.2%, 88.5%, 52.6% and 62% respectively. Lee *et al.*^[58] also demonstrated that a combination of two or more of the following; arterial peritumoral enhancement, irregular tumor margin, and peritumoral hypointensity on hepatobiliary phase, can be used as a preoperative imaging biomarker for predicting MVI, with specificity > 90%. Hu *et al.*^[59] also reported in a systemic review and meta-analysis that peritumoral enhancement and peritumoral hypointensity on hepatobiliary phase were highly specific (90%-94%) but low sensitive findings (29%-40%) for predicting MVI.

On distinguishing between the SN type and non-SN type using EOB-MRI, Tada *et al.*^[60] demonstrated that the sensitivity, specificity, and accuracy of EOB-MRI for identifying non-SN were equal to or higher than that using angiography-assisted CT. Chen *et al.*^[61] also compared the diagnostic ability of EOB-MRI and contrast CT. The sensitivities, specificities, and accuracies for the diagnosis of non-SN type were 71.4%, 81.6%, and 75.5% in contrast CT, 96.4%, 78.9%, and 89.3% in EOB-MRI, and 98.2%, 84.2%, and 92.5% in combination, respectively. They concluded that contrast CT combined with EOB-MRI offers a more accurate imaging evaluation for HCC macroscopic classification than either modality alone^[61]. Kobayashi *et al.*^[62] compared the ability of EOB-MRI and CEUS to predict macroscopic type, and found that the sensitivity, specificity, PPV, NPV, and accuracy for the diagnosis of non-SN type were 64.1%, 95.7%, 92.6%, 76.9% and 81.2% in EOB-MRI, 56.4%, 97.8%, 95.7%, 72.6% and 78.8% in CEUS, and 84.6%, 95.7%, 94.3%, 88% and 90.6% in combination, respectively. The combined diagnosis of EOB-MRI and CEUS provides highest diagnostic ability^[62]. Iwamoto *et al.*^[63] also showed that the diagnostic ability for macroscopic classification of nodular HCC of the post-vascular phase of CEUS with Sonazoid was comparable with that of hepatobiliary phase of EOB-MRI, and the combination of the two modalities provided a more accurate diagnostic performance. The sensitivity, specificity, PPV, NPV, and accuracy of MRI studies cited in this review were summarized in Table 3 except for not available reports.

DISCUSSION

This article reviews the current status of predicting MVI using common imaging modalities for the diagnosis of HCC. MVI is strongly associated with histologic differentiation and macroscopic type. Poorly differentiated HCCs are characterized by hypovascular components and faster tumor enhancement washout on dynamic imaging. Non-SN type HCCs are characterized by irregular shape image. The possible mechanism

which could interpret the correlation between imaging features and probability of MVI is that HCC has a strong tendency of invasive growth along with de-differentiation from well to poorly differentiated HCC. Therefore, the accurate diagnosis of histologic differentiation and macroscopic type is essential for accurate prediction of MVI.

US including CEUS is the most non-invasive among imaging modalities. Although most of the previous reports cited in “US” section were about the diagnosis of HCC with poor differentiation or non-SN type, which suggested that direct connection between US and diagnosis of MVI was a few, useful US parameters for predicting poorly differentiated HCC or MVI are irregular intra-tumoral artery, fast washout of tumor enhancement, and irregular tumor margin. MFI should be used to assess the intra-tumoral angioarchitecture, with the deadwood pattern being a highly specific finding for predicting MVI. Although the optimal cut off time is yet unknown, shorter washout time of tumor enhancement is also a specific finding. Based on previous reports on assessing tumor shape by imaging, post-vascular phase (Kupffer phase) of CEUS is considered more accurate than B-mode US or contrast CT, and the diagnostic ability of CEUS for predicting HCC macroscopic type would be equal to that of the hepatobiliary phase of EOB-MRI. However, US has several disadvantages, such as poor visualization due to dead space, artifacts, and deep lesion, and difficulty of whole scan in larger tumors. Therefore, when the whole tumor cannot be scanned by US, another imaging assessment using EOB-MRI or contrast CT is necessary.

Factors to consider in predicting poorly differentiated HCC or MVI on contrast CT are heterogenous enhancement including hypovascular components, fast washout of tumor enhancement, complete or partial absence of peritumoral capsule (halo), the presence of intra-tumoral vessels and aneurysms on venous phase, and irregular tumor margin. Although complete or partial absence of peritumoral capsule, the presence of intra-tumoral vessels and aneurysms, and irregular tumor margin can be easily evaluated in large HCC, these parameters are difficult to assess in small HCCs. The heterogenous enhancement and fast tumor enhancement washout are useful findings in predicting poor histologic differentiation of small HCCs.

Tumor tissue characterization such as water, fat, and metal content, or diffusion of water molecules can be easily obtained by plain MRI. As non-hypointense HCC on T1-weighted image reflects well differentiation of HCC, the MVI risk would be low. Since intra-tumoral fat is also often seen in well differentiated HCCs, HCCs containing fat components would be at low risk of MVI. Accordingly, T1-weighted image including chemical shift is important in predicting low risk of MVI. Previous reports also demonstrated that low ADC value reflects poor differentiation. However, there is no adequate cut-off value to distinguish poorly and non-poorly differentiated HCC on meta-analysis. This may be because the absolute ADC value depends on the MRI equipment coil systems, imagers, vendors, and field strengths^[64]. Since the contrast between tumor and adjacent liver tissue, measured by CNR, and the RCR on DWI, are superior in predicting poor differentiation compared to the ADC values, the assessment of tumor contrast to adjacent liver tissue on DWI or ADC map should be more appropriate and universal in clinical practice than quantification of ADC values. As such, care should be taken when evaluating a very high intense HCC on DWI or low intense HCC on ADC map. When directly predicting MVI using EOB-MRI, the important parameters include irregular margin, arterial peritumoral enhancement (relative hypovascularity), and peritumoral hypointensity on hepatobiliary phase. Although the specificities of these findings for predicting MVI were very high, the sensitivities were low. Therefore, attention should be paid for the false negativity of these findings. To improve the sensitivity for predicting MVI, the combined evaluation with plain MRI including DWI and EOB-MRI may be useful, because the evaluation of diffusion parameters is highly sensitive for predicting poor differentiation or MVI. Among common imaging modalities, the most information for predicting MVI can be obtained from MRI. Furthermore, there are some reports that the combination of EOB-MRI with CECT or CEUS improved the accuracy in predicting non-SN type. As mentioned above, combination of MRI with other imaging modalities may provide a more accurate assessment of malignant potential of HCC.

As other tumor factors related to MVI, tumor markers^[65,66] and FDG-PET uptake^[67] have been reported. As FDG-PET is not used as common imaging modality for the diagnosis of HCC, the papers about the predictability of FDG-PET for MVI were omitted from this review. Although tumor markers such as alpha-fetoprotein and des- γ -carboxy prothrombin (DCP) are closely related to the presence of MVI, they are also highly expressed in patients with benign diseases such as chronic hepatitis and liver cirrhosis^[68]. Furthermore, as several cut-off values according to studies were suggested, the best cut-off value has not been unknown. However, Shirabe *et al.*^[69] reported that a scoring system for predicting MVI using tumor size, serum DCP levels, and FDG-PET uptake can provide a precise prediction of MVI, and the sensitivity and specificity were 100% and 90.9%, respectively. Probably, tumor marker levels would be helpful for predicting MVI.

There are some limitations in this research field. Firstly, although some highly specific or sensitive imaging findings for predicting poorly differentiated HCC or MVI have been reported, there are no highly accurate diagnostic findings. This may be due to limited accuracy of identifying histologic differentiation or MVI from resected specimens. MVI would often be missed if thorough microscopic examination is not performed, and histologic differentiation would be judged as non-poorly differentiated HCC if poorly differentiated components are not dominant. It is difficult to search for MVI throughout the whole tumor using a microscope, and MVI detection depends on the serial slice width of the tumor specimen. The thinner the specimen, the more accurate the MVI detection. Secondly, since most of previous reports are small-cohort, single-center, and retrospective, and diagnostic ability also depends on the performance of imaging equipment, their conclusions might be unreliable and biased. To validate their results, large scale prospective studies are needed. Lastly, adequate treatment strategy based on MVI prediction or histologic differentiation has not been established. At this time, if a HCC patient is predicted to have high risk of MVI as assessed by imaging, it should be treated as advanced HCC even after resection or local ablation.

In conclusion, HCCs with high grade malignant potential can be diagnosed with commonly used imaging modalities. For accurate prediction of MVI in HCC, the diagnosis of poor histologic differentiation or non-SN type is needed, and the combination of MRI with other imaging modalities should be used.

DECLARATIONS

Authors' contributions

The author contributed solely to the article.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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