review

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Diagnosis and treatment of microvascular invasion in hepatocellular carcinoma

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Summary
Background Microvascular invasion (MVI) is currently only confirmed by histopathological studies of surgical specimens. Preoperative diagnosis of MVI combined with clinical treatment is still a research problem and direction in hepatocellular carcinoma (HCC). How to assess the presence of MVI early and give appropriate treatment has become a research hotspot.
Methods This review focuses on recent advances in MVI-related research, including the use of serum markers, tumor tissue markers, and new imaging techniques to predict MVI, as well as the molecular biology mechanisms and therapeutic advances in MVI.
Results The emergence of MVI may be caused by the interaction of many complex biological processes and various pathogenic factors. We need to try to select several risk factors and establish a systematic evaluation method to solve their respective deficiencies, so as to provide more practical applications for the preoperative prediction of MVI program. Simultaneously, the preoperative, intraoperative, and postoperative comprehensive treatment strategies for MVI are particularly important.
Conclusion The presence of MVI is thought to reflect increased capacity for local infiltration and distant metastases and affects the prognosis of HCC patients. To accurately assess MVI early based on some biomarkers prior to surgery, we need to work hard to explore and integrate various treatments to create a personalized treatment plan for MVI.

Keywords Hepatocellular carcinoma · Microvascular invasion · Diagnosis · Treatment · Biomarkers

Introduction

Hepatocellular carcinoma (HCC) ranks among the most common malignancies worldwide [1]. Hepatectomy and liver transplantation (LT) are the most important HCC treatments [2]. The 5-year recurrence rate were as high as 70% and 35%, respectively [3]. MVI significantly increased the risk of recurrence and extrahepatic metastasis after hepatectomy or LT in patients with HCC [4, 5]. But it can only be diagnosed by postoperative histopathology [6] with significant hysteresis. It is very important to diagnose MVI before surgery [7]. The possible mechanism of MVI is that hepatoma cells destroy vascular endothelial cells through receptor-mediated necroptosis [8], leading to cancer cells invading blood vessels and distant metastasis [9]. MVI can be found in tumor stroma, tumor cyst and paracancerous tissues [10]. Small vein branches are connected with the small branches of the peripheral portal vein of HCC, which can become the main metastatic pathway of HCC. If the diagnosis of MVI is difficult, immunohistochemical staining is feasible, such as CD34, CD31, SMA, D2-40, etc. [11]. The incidence of MVI in HCC was high (15–57.1%) [12]. There have been many studies in the world,

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including predicting MVI with serum markers, tumor tissue markers, and new imaging technologies, and trying to carry out a variety of treatment studies on MVI.

Preoperative diagnosis of MVI

Many researchers have devoted themselves to searching for a method for preoperative detection of MVI, so that we can better assess the patient's tumor invasion. Table 1 shows some of the current studies on preoperative prediction of the risk of MVI in HCC.

Correlation between clinical factors and MVI

MVI was one of the independent risk factors for tumor recurrence after hepatectomy in HCC patients who meet the Milan criteria [13]. Some studies have pointed out that MVI was closely related to the size, number, morphology, and degree of differentiation of hepatic neoplasms [14–16]. In patients with small HCC, long-term survival was not affected by MVI ($p = 0.8$), whereas in patients with larger HCC, significantly worse survival was observed in patients with MVI ($p < 0.001$) [17]. According to a study by Eguchi et al. [18], the average diameter of tumors in the MVI group was 5.2 cm and 3 cm in the non-MVI group. Yamashita et al. [19] reported that 28.9% of patients with tumor diameter <2 cm developed MVI. Gouw et al. [20] reported that when the tumor diameter is >4 cm, the probability of developing MVI is twice that of a tumor with <4 cm. Total tumor diameter >8 cm and tumor number >3 were also preoperative predictors of MVI in patients with multinodular HCC [21]. Different MVI types also affected post-hepatectomy survival [22]. Esnaola et al. [23] reported that 12% of patients with well-differentiated HCC developed MVI, and the incidence of MVI in moderately differentiated cases was 29%, while the incidence of MVI in low differentiation cases was up to 50%. Fujita et al. [24] classify the following risks for MVI: M0 level: no MVI was found; M1 (low-risk group): ≤5 MVI and occurred in the near-cancer area (≤1 cm); M2 (high-risk group): >5 MVI or MVI occurred in the distant cancer area (>1 cm). The higher the MVI group, the worse the prognosis. In addition, local nodal metastasis, body mass index, and other tumor characteristics have been reported to be significant predictors of MVI [25].

Predicting MVI with serum markers

Detection of the expression of certain HCC-specific antigens in serum can predict the occurrence of MVI. Studies have shown that MVI was correlated with the levels of aspartate aminotransferase (AST); gamma glutamyl transpeptidase (GGT); and lactate dehydrogenase (LDH) [26]; Li-cadherin [27]; alkaline phosphatase (ALP) [28]; preoperative neutrophil-to-lymphocyte ratio (NLR) [29] and DES-γ-carboxyprothrombin (DCP) [30] can predict the presence of MVI at a definite level. Patients with non-AFP-producing tumors had fewer MVI ($P < 0.001$) [31]. Studies suggested that elevated AFP was an independent risk factor for MVI [15, 32]. Zhang et al. found that a lower level of albumin, a higher level of AFP, and a larger tumor on preoperative imaging were independently associated with MVI [33]. However, some studies have found no significant correlation between AFP and MVI [7, 34]. Miyaaki et al. believed that AFP mainly reflects the differentiation of tumors and is not specific to HCC vascular invasion [35]. Some studies suggest that preoperative serum DCP levels are associated with the development of MVI [18, 36], but similar high levels of DCP and AFP are also present in the serum of patients with chronic hepatitis and cirrhosis, indicating that DCP expression is not specific [37]. miR-125b is the post-transcriptional regulation factor of HOTTIP [38] and can be used to predict MVI of HCC patients before hepatectomy [39]. The multivariate analysis showed that serum HSP70 and Eno-1 were potential biomarkers for preoperative prediction of MVI [40]. Paraoxonase 1 (PON1) is a hepatic-induced glycoprotein [41] and Huang et al. data indicated that serum PON1 was a novel diagnostic biomarker for MVI [42]. The second-generation sequencing technology has made great progress, and the application of blood as a material to detect tumor mutations has become more and more widespread. This has provided a more in-depth understanding of the occurrence and development of HCC from a genetic perspective, and provides an effective means for the diagnosis, prediction, and prevention of MVI.

Correlation between imaging techniques and MVI

In the preoperative imaging diagnosis, some breakthroughs have also been made in recent years. A non-smooth tumor margin on imaging was independently associated with the presence of MVI [43–45]. Chou et al. [46] performed a comparative analysis of preoperative CT images and postoperative disease specimens in 102 patients with HCC. The borders of non-smooth tumors revealed by CT were significantly associated with MVI ($P < 0.001$), sensitivity was 81.7%, and specificity was 88.1%. Cheung et al. reported that 18F-FDG-labeled PET can better predict MVI [47], and pointed out that the imaging agent 11C-acetate (11C-AC) can increase the sensitivity of the prediction effect. Tumor FDG avidity measured by tumor-to-normal liver standardized uptake value ratio (TLR) on FDG PET/CT was a preoperative imaging biomarker for the prediction of MVI in patients with HCC [48]. Xu et al. used diffusion-weighted MRI and found the sensitivity and specificity of low diffusion coefficient plus irregular peripheral enhancement for prediction of the presence of MVI to be 66.7 and 78.6%, respectively [49]. A recent magnetic imaging study showed that disproportionately weighted imaging of HCC and

Table 1 Predictive biomarkers or prediction clinical model potentially associated with MVI in reported studies

Author	Year	Treatment	*N*	Predictive factors or model of MVI (diagnostic value and sensitivity/specificity)
Zhu et al. [28]	2018	Hepatectomy	165	ALP was a simple, accurate, and inexpensive alternative to predict MVI and an independent risk factor of prognosis for HCC patients
Imura et al. [32]	2017	Hepatectomy	159	Multiple tumors (OR = 3.49, $P < 0.05$) and high AFP-L3 value (OR = 2.69, $P < 0.05$) were independent predictive factors for MVI
McHugh et al. [15]	2010	LT	100	Tumor size ≤3 cm, >3 cm, OR: 4.1 [1.2–13.5][a], $P = 0.013$. AFP ≤100 ng/mL, >100 ng/mL, OR: 5.0 [1.4–18.1], $P = 0.006$
Kim et al. [16]	2008	PH	190	Tumor size <2 cm, >5 cm, RR: 2.929 [2.138–9.491], $P = 0.043$
Wu et al. [44]	2016	PH	79	Smooth tumor margin on imaging, non-smooth, OR: 18.3 [3.27–102.6], $P = 0.0009$
Kaibori et al. [34]	2010	PH	434	Age <65 years, ≥65 years, OR: 2.03 [1.11–4.03], $P = 0.039$. PIVKA-II <200 mAU/ml, ≥200 mAU/ml, OR: 2.13 [1.10–4.11], $P = 0.025$. Tumor size <5 cm, ≥5 cm, OR: 7.12 [2.57–19.76], $P = 0.0002$
Siegel et al. [25]	2010	PH	138	AFP <28 ng/ml, ≥28 ng/ml, OR: 3.33 [1.15–9.62], $P = 0.03$. Tumor size <3 cm, ≥3 cm, OR: 0.43 [0.16–1.24], $P = 0.12$. BMI <25 kg/m^2, >30 kg/m^2, OR: 1.67 [0.37–7.52], $P = 0.5$
Chou et al. [45]	2014	PH/LT	102	Smooth tumor margin on CT, non-smooth, OR: 28.828 [7.718–107.68], $P < 0.001$
Ding et al. [27]	2009	PH	255	Negative LI-cadherin expression, positive, $P = 0.01$
Poté et al. [7]	2015	PH/LT	85	PIVKA-II level >90 mAU/ml: predictor of MVI (HR 3.5; 95% CI 1.08–11.8; $p = 0.043$). 77% sensitivity/82% specificity. Well-differentiated tumor, moderately/poorly, HR: 3.4 [1.04–11.05], $P = 0.037$
Yu et al. [40]	2016	Curative resection	61	High titer of anti-HSP 70 antibodies: predictor of MVI (HR 0.608; 95% CI 0.425–0.870; $p = 0.006$). The cut-off value: 5.856, 82.86% sensitivity/53.85% specificity
Yu et al. [40]	2016	Curative resection	61	Low titer of anti-Eno-1 antibodies: predictor of MVI (HR 1.915; 95% CI 1.228–2.987; $p = 0.004$). The cut-off value: 4.301, 88.57% sensitivity/50% specificity
Xu et al. [49]	2014	PH	92	ADC <1.227 × 10–3 mm^2/s on DWI of MRI, ADC ≥1.227 × 10–3 mm^2/s, OR: 7.63 [1.63–35.71], $P = 0.009$
Cheung et al. [47]	2011	PH/LT	58	18F-FDG-negative on PET, 18F-FDG-avid, $P = 0.06$
Li et al. [53]	2018	Hepatectomy	41	Histogram analysis of IVIM based on whole tumor volume can be useful for predicting MVI and the 5th percentile of D was most useful value to predict MVI of HCC
Mínguez et al. [64]	2011	PH	214	A 35-gene signature of vascular invasion, OR: 3.38 [1.48–7.71], $P = 0.003$. Tumor size ≤3 cm, >3 cm, OR: 2.66 [1.17–6.05], $P = 0.02$
Liu et al. [39]	2016	Hepatectomy	108	miR-125b: predictive of MVI (HR 0.371; 95% CI 0.211–0.654; $P = 0.001$). The predictive accuracy of miR-125b was 76.95% (51.32% specificity/87.50% sensitivity); the combination of tumor size, AFP, and miR-125b yielded an ROC curve area of 86.68% (72.37% specificity/84.38% sensitivity)
Huang et al. [42]	2013	Hepatectomy	387	PON1: predictive of MVI (HR 0.847; 95% CI 0.804–0.889; $P < 0.001$)
Xu et al. [61]	2017	Hepatectomy	108	ciRS-7/miR-7: the risk factors of MVI: (HR: 4.08, 95% CI: 1.06–15.74; $P = 0.041$), the cutoff value: 0.135, AUC: 0.68 (95% CI 0.58, 0.79, $p = 0.001$)
Banerjee et al. [3]	2015	Hepatectomy	156	The accuracy, sensitivity, and specificity of RVI in predicting MVI were 89, 76, and 94%, respectively
Yu et al. [29]	2017	Hepatectomy	157	NLR (HR, 1.705; 95% CI, 0.467–6.232; $P = 0.022$), PLR (HR, 1.048; 95% CI, 1.006–1.092; $P = 0.025$), AFP (HR, 1.012; 95% CI, 1.003–1.021; $P = 0.007$)
Grat et al. [95]	2017	LT	200	Prediction model: 0.293 × (tumor number) + 0.283 × (tumor size in cm) + 0.164 × $\log_e$(alpha-fetoprotein in ng/ml; c statistic = 0.743). Sensitivity/specificity of 72%
Zhao et al. [87]	2017	Hepatectomy	233	Prediction scoring system for MVI was built up by the three independent predictors (tumor size >3.5 cm, AFP >200 ng/mL, and GGT >53 U/L)
Yan et al. [26]	2016	Hepatectomy	47	MVI was shown correlated with the levels of aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), and lactate dehydrogenase (LDH; $P < 0.05$)
Imura et al. [13]	2018	Hepatectomy	159	Multiple tumors and AFP-L3 >10% were significant independent risk factors for MVI
Poté et al. [30]	2017	Hepatectomy	106	In virtual biopsies, PIVKA-II/H4K16ac: 30% sensitivity, 97% specificity, 91% PPV, and 56% PNV $P = 0.037$. In CNB, PIVKA-II/H4K20me2: 43% sensitivity, 95% specificity, 90% PPV, and 62% NPV $P = 0.026$
Imai et al. [130]	2018	RFA	149	AFP ≥15 ng/ml (relative risk [RR] 3.05, $p = 0.02$), DCP ≥100 mAU/ml (RR 4.19, $p = 0.003$), and tumor size ≥2 cm (RR 3.37, $p = 0.03$) were independent risk factors of MVI
Shirabe et al. [14]	2014	Hepatectomy	63	The tumor size was 3.6 cm, SUV max was 4.2, and the serum DCP level was 101 mAU/ml
Cucchetti et al. [88]	2010	PH/LT	250	ANN model, ROC: 0.92 [0.86–0.96]

Table 1 (Continued)

Author	Year	Treatment	*N*	Predictive factors or model of MVI (diagnostic value and sensitivity/specificity)
Lei et al. [89]	2016	PH	1004	Nomogram, C-index: 0.81 [0.78–0.85]
Lai et al. [90]	2016	LT	289	The proposed TRAIN score was the best predictor of MVI. A TRAIN score ≥1.0 excellently stratified both the investigated populations in terms of ITT and recurrence survivals
Zhao et al. [21]	2013	PH	266	Serum AFP level >400 μg/L, serum GGT level >130 U/L, total tumor diameter >8 cm, and tumor number >3 were preoperative predictors of MVI in patients with multinodular HCC. Scoring system, AUC: 0.832 [0.744–0.920]
Hirokawa et al. [113]	2014	Hepatectomy	167	PIVKA-II ≥150 mAU/mL (OR, 5.19; 95% CI, 1.44–24.87; $P = 0.0109$) and positive L3-AFP (OR, 3.47; 95% CI, 1.19–10.75; $P = 0.0229$)
Lee et al. [43]	2017	Hepatectomy	197	Arterial peritumoral enhancement ([OR] = 5.184; 95% [CI]: 2.228, 12.063; $p < 0.001$), non-smooth tumor margin (OR = 3.555; 95% CI: 1.627, 7.769; $p = 0.001$), and peritumoral hypointensity on hepatobiliary phase (HBP; OR = 4.705; 95% CI: 1.671, 13.246; $p = 0.003$), specificity >90%
Zhang et al. [33]	2017	Hepatectomy	370	The lower level of albumin, the higher level of AFP, and larger tumor

MVI microvascular invasion, *HCC* hepatocellular cancer, *PH* partial hepatectomy, *LT* liver transplantation, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *AFP* a-fetoprotein, *HR* hazard ratio, *95%CI* 95% confidence interval, *PPV* predictive positive value, *PNV* predictive negative value, *DCP* serum des-gamma-carboxy prothrombin, *SUVmax* maximum standardized uptake value, *RFA* radiofrequency ablation, *OR* odds ratio, *BMI* body mass index, *HSP* heat shock protein, *Eno-1* alpha-enolase, *CT* computed tomography, *RVI* radiogenomic venous invasion, *ADC* apparent diffusion coefficient, *DWI* diffusion-weighted imaging, *MRI* magnetic resonance imaging, *18F-FDG* 18F-fludeoxyglucose, *PET* positron emission tomography, *ANN* artificial neural network, *ROC* receiver operating characteristics curve, *AUC* area under curve, *HR* hazard ratio
[a]95% confidence interval (CI)

T2-weighted imaging mismatch were independent predictors of MVI with a high specificity (95.65%) [50]. Higher mean kurtosis values in combination with irregular circumferential enhancement were also potential predictive biomarkers for MVI [51]. RVI is a noninvasive radiogenomic biomarker that accurately predicts histological MVI in HCC surgical candidates. This accurately predicts preoperative tissue MVI in patients undergoing HCC surgery and helps identify whether patients can benefit from surgical treatment [3]. The radiomics nomogram, as a noninvasive preoperative prediction method, can show a favorable predictive accuracy for MVI status in patients with HBV-related HCC [52]. A recent study found histogram analysis of intravoxel incoherent motion (IVIM) based on whole tumor volume can be useful for predicting MVI [53]. Preoperative IVIM DW imaging and Gd-EOB-DTPA-enhanced MRI (DCE-MRI) of 51 patients who were analyzed, Zhao et al. found that an irregular shape and D value $\leq 1.16 \times 10{-}3\,mm2/s$ may suggest the presence of MVI in HCC [54]. Unfortunately, these imaging features depend primarily on the personal experience of the imaging physician. At the same time, there is a lack of prospective studies and it is currently not available for preoperative screening of MVI [50].

Predict MVI with HCC signaling pathway protein or mRNA

The emergence of MVI may be caused by the interaction of many complex biological processes and various pathogenic factors, which may involve many signaling pathways [55]. Tumor cells in the microenvironment can produce a variety of cytokines that affect the tumor progression [56]. HBV infection and active HBV replication were associated with vascular invasion [57]. HBV infection in the liver microenvironment increased the activity of TGF-β signaling and induced Treg cell recruitment and promoted venous metastasis of HCC [58]. Treg cells can help cancer cells escape immune surveillance, while tumor blood vessels provided the necessary nutrient supply and immune microenvironment for tumor growth to accelerate the malignant progression of the tumor [12]. Table 2 shows some MVI-related biomarkers and their biological functions in HCC studies.

By detecting pathological samples, genes or proteins closely related to MVI were found. Yuan et al. found that lncRNA MVIH was overexpressed in MVI-related HCC patients by microarray analysis [59]. MVIH activates tumor-induced angiogenesis by inhibiting the secretion of phosphoglycerate kinase 1 (PGK1) to promote tumor growth and intrahepatic metastasis. At the same time, MVIH expression was positively correlated with microvessel density [59]. Poté et al. [60] used mass spectrometry to find that histone H4 modifications (H4K16ac and H4K20me2) were highly expressed in the MVI-positive group. The expression of ciRS-7 in HCC tissues with concurrent MVI was inversely correlated with that of miR-7 and positively related to that of two miR-7-targeted genes (PIK3CD and p70S6K) [61]. Xu et al. [62] identified the epithelial–mesenchymal transition (EMT) as an important part of MVI. By inhibiting the transcription factor FOXC1, which plays an important role in EMT, EMT can be reversed and the probability of metastasis can be reduced. Fransvea et al. [63] found that B1 integrin was indispensable in the MVI course of HCC patients. Inhibition of TGF-β1 receptors can inhibit the phosphorylation of B1 integrin, thereby cutting off the vascular invasion path of cancer cells.

Table 2 Biomarkers associated with MVI in HCC studies, their biological functions and affected pathways

Author	Year	Tumor markers	Biological function	Genes/proteins/ pathways affected	Diagnostic/ prognostic of HCC	MVI presence (%)	Correlation between expression and MVI (*p*-value)
Xu et al. [62]	2012	FOXC1	EMT (+), proliferation (–), invasion and metastasis (+)	Down-regulate MMPs and VEGF-A	NA	27/50 (54%)	0.041
Yuan et al. [59]	2012	MVIH	Metastasis (+), cell proliferation (+), apoptosis (–)	Inhibiting PGK1	RFS	62/153 (41.4%)	0.016
Potéet al. [60]	2013	Histone H4	NA	Down-regulation of KAT8	NA	30/56 (53.7%)	Not significant
Xu et al. [61]	2017	ciRS-7/miR-7	Tumorigenesis (–) and metastasis (–), cell proliferation and invasion (+)	Suppress CCNE1 and PIK3CD expression	RFS	46/108 (42.6%)	0.03
Huang et al. [65]	2017	miRNA-135a	Migration and invasion (+)	Suppressed Atg14/ inhibited autophagic	RFS	66/103 (64.7%)	0.007
Lin et al. [66]	2017	Kindlin-2	Cell adhesion, migration, and invasion (+)	Wnt/β-catenin signaling	OS	61/127 (48%, cohort 1), 29/50 (58%, cohort 2)	0.041/0.019
Govaereet al. [67]	2017	PDGFRα	Invadopodia formation and cell invasion (+)	PDGFRα-La/SSB-LAMB1 pathway	OS	80/136 (58.8%)	<0.001
Fu et al. [68]	2017	Circ-0005986	Cell proliferation (+)	Decreased miR-129-5p/Notch1 expression, promoting the G0/G1 to S phase transition	NA	25/81 (31.2%)	0.026
Xiao et al. [82]	2017	LINC RP1130-1	NA	NA	RFS	19/51 (37.3)	0.047
Zhu et al. [69]	2016	GPC3-AS1	Cell proliferation and migration (+)	Activating GPC3	OS/RFS	31/90 (34.4%)	0.015
Jeon et al. [70]	2016	GPC3	NA	NA	OS/RFS	81/153 (43.8%)	0.01
Calderaro et al. [71]	2016	PD-L1	Immune checkpoint, tumor aggressiveness	Wnt/β-catenin signaling	RFS	111/217 (51%)	<0.001
Liu et al. [72]	2015	TLR4	Invasion and metastasis (+), EMT (+)	NA	OS/RFS	41/88 (46.6%)	0.002
Cai et al. [73]	2014	Gal-4	Migration and invasion (+)	Binding cancer-associated TF disaccharides on MUC1	OS/RFS	55/201 (27.4%)	0.004
Govaere et al. [74]	2014	K19	Migration and invasion (+), drug resistance (+)	Invasion related-/ metastasis-related markers (e.g., VASP, TACSTD2, LAMB1, LAMC2, PDGFRA) (+)	OS/RFS	119/242 (49.2%)	<0.001
Park et al. [75]	2013	MT-1/-2	Cell proliferation (+), apoptosis (–), DNA repair and cell adhesion (–)	PI3K/Akt signaling pathway	OS/RFS	135/370 (36.5%)	0.033
Shim et al. [76]	2013	HNF1β	EMT (+), migration and invasion (+)	NA	RFS	13/159 (8.2)	<0.05
Chung et al. [77]	2011	BOP1	EMT (+), migration and invasion (+)	RhoA-GTPase activity	OS/RFS	52/65 (80%)	0.006
Liu et al. [79]	2017	lncRNA NEAT1	Cell proliferation (+), cell apoptosis (+), cell cycle (+)	NA	OS/RFS	55/86 (64%)	0.023
Ding et al. [27]	2009	LI-cadherin; CDH-17	Cell migration, adhesion, and invasion (+)	NA	OS/RFS	33/255 (13%)	0.018
Yang et al. [78]	2017	FLNC	Cell migration (–), cell proliferation, and promoted apoptosis (–)	Inhibited MEK1/2 and ERK1/2 activation	OS	33/53 (62.2%)	0.002

Table 2 (Continued)

Author	Year	Tumor markers	Biological function	Genes/proteins/ pathways affected	Diagnostic/ prognostic of HCC	MVI presence (%)	Correlation between expression and MVI (*p*-value)
Zhou et al. [80]	2013	CD44v6	Cell invasion (+)	Regulated by hnRNPA1	OS/RFS	148/323 (45.8%)	0.029
Zhuang et al. [81]	2016	miR-92b	Cell proliferation and metastasis (+)	XIST/miR-92b/Smad7 signaling axis	NA	24/48 (50%)	0.026

HCC hepatocellular cancer, *EMT* epithelial–mesenchymal transition, *PI3K* phosphatidylinositol 3-kinase, *Akt* protein kinase B, *TF* Thomsen-Friedenreich, *ERK* adenosine monophosphate-activated protein kinase, *MAPK* mitogen-activated protein kinase, *PGK1* phosphoglycerate kinase 1, *MMPs* matrix metalloproteinases, *VEGFA* vascular endothelial growth factor A, *ITT* intention-to-treat, *Kat8* histone acetyltransferase, *CCNE1* cyclin E1, *PIK3CD* phosphatidylinositol 3-kinase, *RFS* recurrence-free survival, *DFS* disease-free survival, *OS* overall survival, *MVI* microvascular invasion, *NA* not adopted

Mínguez et al. [64] found that 35 gene markers were associated with vascular invasion and the accuracy of MVI prediction was 69%.

In addition to the above studies, there are many studies on MVI biomarkers [65–82]. However, despite the success of these approaches in preclinical translational studies, the clinical application of gene expression profiling is still immature [83]. The sensitivity and specificity of these biological markers are not very satisfactory [84, 85], making it difficult to translate basic research into clinical applications.

Integrating multiple factors to predict MVI

A single tumor feature cannot accurately predict whether MVI has occurred. The researchers proposed to predict MVI by integrating multiple biomarkers. Small HCC (≤3 cm) were generally considered to have low malignant potential; however, matching at least one factor among three (tumor diameter ≥2 cm, AFP ≥200 ng/mL, or DCP ≥40 mAU/mL) can predict pathological MVI in small HCC [86]. A prediction scoring system for MVI was built up according to three independent predictors (tumor size >3.5 cm, AFP >200 ng/mL, and GGT >53 U/L). The prevalence of MVI in HCC patients with predictive score ≥2 was 58.3%, which was obviously higher than in patients with predictive score <2 (20.8%) [87]. Serum AFP level >400 μg/L, serum GGT level >130 U/L, total tumor diameter >8 cm, and tumor number >3 were also preoperative predictors of MVI in patients with multinodular HCC [21]. Cucchetti et al. established an artificial neural network (ANN) model using noninvasive parameters, which included preoperative AFP level, tumor number, and size to predict the occurrence of MVI [88]. Lei et al. developed a nomogram score that patients who had a nomogram score of less than 200 or 200 or greater were considered to have low or high risks of MVI presence, respectively [89]. Lai et al. [90] proposed that "Time-Radiological-response-Alpha-fetoprotein-Inflammation" (TRAIN) score was the best predictor of MVI. A TRAIN score ≥1.0 excellently stratified both the investigated populations in terms of intention-to-treat (ITT) and recurrence survivals. Poté et al. developed an original virtual biopsy to evaluate the immunohistochemical performance of three MVI biomarkers (H4K16ac, H4K20me2, DCP) for predicting MVI in HCC core needle biopsy (CNB). Studies have shown that DCP/H4K16ac performed best in predicting MVI and paved the way for future development of prognostic biomarkers of HCC that can guide treatment strategies [91].

Many of the factors in the above studies were closely related to the occurrence and appearance of MVI, but all factors have different deficiencies. We need to try to select several risk factors and establish a systematic evaluation method to solve their respective deficiencies, so as to provide more practical applications for the preoperative prediction of MVI program.

Comprehensive treatment strategy for MVI of HCC

MVI is currently considered to be closely related to the recurrence of HCC after surgery [92]. Similar results were obtained in patients with metastatic HCC [93], and the rate of extrahepatic recurrence in patients with MVI was higher than in patients without MVI [94]. The preoperative, intraoperative, and postoperative comprehensive treatment strategies for MVI are particularly important. Table 3 shows MVI treatment-related research in the reported studies.

Preoperative treatment strategy of MVI

Preoperative early prediction of MVI can help guide surgery and adjuvant therapy. A systematic retrospective analysis indicated that the correlation coefficient between MVI and the 3-year disease-free survival (DFS) reduction after LT and hepatectomy was 3.4 and 1.8, respectively. This showed that the prognosis of HCC patients with LT was more closely related to MVI [12]. Pre-transplant prediction of high-risk MVI using both morphological and biological tumor characteristics prior to LT is also a prerequisite to ensure proper allocation of liver sources [95]. Mazzaferro et al. [96] established an MVI-related LT prognostic assessment system—the Up7 criteria—and the 5-year survival rates of MVI-negative patients meeting this criterion were close to the Milan standard of 71.2%. The results of this study showed that MVI can be used as a new LT selection criterion. Vitale et al. found that patients with a model-based end-stage liver disease

Table 3 MVI treatment-related research in the reported studies

Author	Year	Treatment	Patient information	MVI presence (%)	*N*	Potential significance[a]
Eguchi et al. [18]	2010	Hepatectomy	HCC with microscopic portal venous invasion	22.7	229	The average diameter of tumors in the MVI group was 5.2 cm, and 3 cm in the non-MVI group
Lim et al. [92]	2010	Hepatectomy	(Milan +, MVI −), (Milan +, MVI +), (Milan −, MVI −), (Milan −, MVI +)	31	454	All pairwise comparisons between groups relative to OS were significant except (Milan +, MVI −; OS, 90%, 73%, and 60% at 1, 3, and 5 years, respectively) with (Milan −, MVI −; OS, 86%, 71%, and 61% at 1, 3, 5 years, respectively) and (Milan +, MVI +) with (Milan −, MVI +)
Cucchetti et al. [109]	2014	PH	Cirrhotic patients in Child–Pugh class A for early HCC	57.10	543	In cirrhotic patients with early HCC, AR decreased recurrence in patients with poorly differentiated tumors or with MVI presence; while NAR had similar results in patients with well-differentiated tumors or without MVI presence
Liu et al. [39]	2016	PH	HCC patients	29.60	108	A wide surgical margin (>10 mm) was associated with a better RFS only in patients with HCC with MVI presence
Mazzaferro et al. [96]	2009	LT	Patients with tumors that exceed the Milan criteria	33.80	1556	MVI positivity was associated with a worse outcome after liver transplantation for patients with HCC meeting either the Milan or up-to-seven criteria
Vitale et al. [99]	2014	PH/LT	HCC cirrhotic patients	58.10	1023	Patients with resectable HCC with MVI presence might not benefit from liver transplantation
Chen et al. [129]	2013	PH	Postoperative recurrence of HCC	45.60	68	^{125}I brachytherapy at surgical margin significantly prolonged DFS after liver resection for HCC, possibly through eliminating residual MVI
Nishikawa et al. [102]	2013	PH	Surgical resection with curative intent	34.00	235	The presence of MVI decreased OS after hepatectomy. The response to preoperative TACE might be associated with a better surgical outcome
Ho et al. [94]	2014	Hepatectomy	T2 (the solitary tumor with MVI or multiple tumors, none >5 cm)	81.40	312	The OS rates of patients with MVI were inferior to the rates in patients without MVI ($P = 0.037$). Within the with-MVI group, the survival rate of patients with tumor sizes ≥5 cm was inferior to that of patients with tumors <5 cm ($P < 0.01$)
Zhao et al. [110]	2017	Hepatectomy	Positive HBsAg and liver cirrhosis	39.10	295	The OS and RFS rates of the high-MVI group were significantly poorer than those of low-MVI and no-MVI groups ($P < 0.001$ and $P = 0.003$). In the high-MVI group, AR showed better OS and RFS rates compared with NAR ($P = 0.012$ and $P = 0.002$)
Marubashi et al. [111]	2015	AR/NAR	Propensity score matching	43.3 (227/524), 29.0 (142/490)	1102	The early RFS rate in patients with and without MVI revealed no significant differences between the groups ($P = 0.312$ and $P = 0.479$, respectively). The resection method had no impact on the risk of HCC recurrence or survival
Hou et al. [13]	2015	Second hepatectomy	Milan criteria, recurrent HCC	31.00	329	OS was significantly improved by a second hepatectomy in the MVI-positive group compared with the original MVI-positive group meeting the Milan criteria, 60 (26–82) versus 49 (11–82) months. The biology of MVI may change following the second hepatectomy
Hou et al. [13]	2015	Second hepatectomy	Milan criteria, recurrent HCC	31.00	329	OS was significantly improved by a second hepatectomy in the MVI-positive group compared with the original MVI-positive group meeting the Milan criteria, 60 (26–82) versus 49 (11–82) months. The biology of MVI may change following the second hepatectomy
Hou et al. [22]	2016	First/second hepatectomies	Second hepatectomy/original hepatectomy	38.6, 50.9	933	For survival after the second hepatectomy, MVI patterns that were positive-positive or negative-positive and a total recurrent tumor diameter >5 cm were significant risk factors for survival. Different MVI patterns affect survival after the second hepatectomy
Goh et al. [101]	2014	Hepatectomy	Multifocal HCC	42.70	110	The number of nodules (>3), margin positivity, Child–Pugh status, and presence of MVI were independent prognostic factors of OS
Shindoh et al. [21]	2013	Hepatectomy	Solitary HCC	59.60	1109	In patients with small HCC, long-term survival was not affected by MVI ($p = 0.8$), whereas in patients with larger HCC, significantly worse survival was observed in patients with MVI ($p < 0.0001$). Small HCC is not affected by the presence of MVI

Table 3 (Continued)

Author	Year	Treatment	Patient information	MVI presence (%)	*N*	Potential significance[a]
Shindoh et al. [17]	2013	Hepatectomy	Solitary HCC	59.60	1109	In patients with small HCC, long-term survival was not affected by MVI ($p = 0.8$), whereas in patients with larger HCC, significantly worse survival was observed in patients with MVI ($p < 0.0001$). Small HCC is not affected by the presence of MVI
Vitale et al. [97]	2015	LT	Stage I (within Milan), stage II (within up-to-7), stage III (beyond Milan and up-to-7)	52	1106	LT reached a survival benefit, versus hepatectomy only in HCC patients with a MELD score of ≥10 and without MVI (3.08 months, 95% CI 2.78 to 3.39), whatever the tumor stage
El-Fattah et al. [98]	2017	LT	Solitary primary HCC lesion ≤5 cm	16	570	Multivariate models revealed that age ≥60 years (HR 2.08), MVI (HR 2.26), and poor tumor differentiation (HR 2.42) were significant risk factors of a dismal CSS with HCC size >2 cm. Primary HCC tumor size ≤2 cm had an excellent prognosis after LT and was not affected by the presence of MVI or poor tumor differentiation
Grat et al. [95]	2017	LT	MVI-positive/negative group	28.50	200	MVI was not an independent risk factor for recurrence ($p = 0.307$). Recurrence-free survival at 5 years for patients without MVI was 85.9% as compared to 83.3% ($p = 0.546$) and 55.3% ($p = 0.001$) for patients with false-negative and true-positive prediction of MVI
Mazzaferro et al. [96]	2009	LT	Exceeding Milan criteria	41	1112	The presence of MVI doubled HRs in all scenarios. MVI: New Selection Criteria for Liver Transplantation (up-to-seven criteria)
Mehta et al. [115]	2017	LT	Milan criteria, development/validation	14	1061	Three variables were independently associated with HCC recurrence: MVI, AFP at time of LT, and the sum of the largest viable tumor diameter and number of viable tumors on explant. MVI can be used as one variable of the RETREAT scores that may improve post-LT HCC surveillance strategies
Iguchi et al. [36]	2015	LT	LDLT, high MVI group/low MVI group	36.70	142	High MVI group had significantly higher AFP levels, DCP levels, number of tumors, a larger tumor size, and a higher percentage of poorly differentiated HCC than no-MVI group. In LDLT for HCC, high MVI is a novel pathologic marker for predicting prognosis
Suh et al. [116]	2014	LT	LDLT, the degree of congestion ≤10% for group A and >10% for group B	12.40	153	MVI (HR = 5.43, 95% CI = 2.04–14.44, $P < 0.01$) and an AFP level >200 IU/L (HR = 2.98, 95% CI = 1.10–8.03, $P = 0.03$) were significantly related to tumor recurrence. Liver congestion may promote the recurrence of HCC after LDLT
Sun et al. [117]	2016	PA-TACE	Well-tolerated liver function underwent PA-TACE after R0 hepatectomy (RH)/RH alone	100	370	PA-TACE may be beneficial for HCC patients with MVI ($p < 0.05$)
Jin et al. [118]	2014	TACE and surgery/RFA	BCLC stage 0 or A after curative resection	49	68	TACE showed significantly higher OS and RFS rates than surgery/RFA in MVI-positive patients ($P < 0.05$) but not in MVI-negative patients ($P > 0.05$). In early-recurred MVI-positive patients, TACE had a significantly higher OS rate than surgery/RFA ($P = 0.01$)
Gao et al. [119]	2017	Postoperative adjuvant TACE	HCC after radical resection, TACE/no TACE	8	320	Compared to those who received no TACE, patients who underwent 2 ($P = 0.003$) or 3 ($P = 0.04$) TACE showed delayed recurrence. Adjuvant TACE (twice or thrice) after radical resection is beneficial for HCC patients with poor differentiation and MVI, especially for those with a tumor diameter of >5 cm
Wang et al. [120]	2017	Postoperative adjuvant CT, TACE, and RT	Postoperative, MVI classification (M1/M2)	100	136	The RT group has significantly improved RFS (RT vs. TACE: $p = 0.011$; RT vs. CT: $p < 0.001$) and OS (RT vs. TACE: $p = 0.034$; RT vs. CT: $P < 0.001$) compared to TACE and CT groups. Adjuvant radiotherapy following hepatectomy could result in better survival outcomes for HCC patients with MVI than TACE or CT
Meniconi et al. [131]	2015	RR/RFA, SLT, TACE or CT	Recurrent HCC, (RR/RFA, SLT, TACE, other)	50.70	150	Satellitosis and MVI at initial resection as negative prognostic factors of survival after recurrence ($P < 0.05$). RR/RFA led to better survival outcomes than TACE for early stage intrahepatic recurrences in the absence of satellitosis or MVI on the primary resected tumor

Table 3 (Continued)

Author	Year	Treatment	Patient information	MVI presence (%)	*N*	Potential significance[a]
Imai et al. [130]	2018	RFA	Solitary small-sized HCC (≤3 cm)	18.10	149	AFP ≥15 ng/ml (relative risk [RR] 3.05, $p = 0.02$), DCP ≥100 mAU/ml (RR 4.19, $p = 0.003$), and tumor size ≥2 cm (RR 3.37, $p = 0.03$) were independent risk factors of MVI. The survival in patients with risk factors 2–3 was significantly worse
Li et al. [104]	2018	Preoperative AVT/ hepatectomy	R0 resection for HBV-related HCC	38.7–48.6	2362	A high preoperative HBV DNA level was an independent risk factor of MVI. Antiviral treatment administered more than 90 days before surgery was associated with reduced incidences of MVI and early tumor recurrence after partial hepatectomy for HBV-related HCC
Wang et al. [123]	2014	Sorafenib	Take sorafenib/not take sorafenib	41.90	31	Patients with MVI or satellite lesions who received sorafenib orally for 4 months postoperatively had significantly better DFS than those who did not take sorafenib
Renzulli et al. [103]	2017	DAA therapy	HCV-related cirrhosis	69	92	Imaging features of MVI were present in 29/41 nodules (70.7%, CI: 54–84), HCC occurs rapidly after DAA therapy, and aggressive features of MVI characterize most neoplastic nodules

MVI microvascular invasion, *HCC* hepatocellular cancer, *PH* partial hepatectomy, *LT* liver transplantation, *BCLC* Barcelona Clinic Liver Cancer, *LDLT* living-donor liver transplantation, *STR* spontaneous tumor rupture, *RR* repeat resection, *RFA* radiofrequency ablation, *SLT* salvage liver transplantation, *TACE* transarterial chemoembolization, *RT* radiotherapy, *CT* conservative therapy, *RFS* recurrence-free survival, *DFS* disease-free survival, *OS* overall survival, *MVI* microvascular invasion, *HR* hazard ratio, *CSS* cancer-specific survival, *RETREAT* Risk Estimation of Tumor Recurrence After Transplant, *DCP* des-γ-carboxy prothrombin, *TRAIN* Time-Radiological-response-Alpha-fetoprotein-INflammation
[a]All the presented data were based on the presence/absence of pathologically identified MVI

(MELD) score greater than 10 and MVI-negativity had a better survival rate when selected for LT, while with a score <10 points or in MVI-positive patients, surgical resection may be the better choice [97]. Primary HCC tumor size <2 cm had a good prognosis after LT and was not affected by MVI or tumor differentiation [98]. However, the medical resources and costs required for LT far exceed liver resection, so it cannot be used as the preferred treatment for HCC. Hepatectomy was more preferred for patients with MVI because of similar 5-year survival rates in these two procedures [99].

Currently, neoadjuvant therapy with systemic chemotherapy or TACE for resectable HCC is not recommended [100]. Due to its poor therapeutic effect, the optimal timing of surgical treatment may be delayed, resulting in the resectable HCC becoming unresectable. The therapeutic effect of preoperative TACE can only be obtained after treatment. TACE-treated patients were divided into TACE responders and non-responders. TACE responders had better survival outcomes and MVI positivity was a poor prognostic factor for these patients [101, 102]. Whether or not neoadjuvant TACE provides a good prognosis deserves further investigation in patients at a high risk of MVI [37]. In HCV cirrhosis, patients HCC developed soon after DAA therapy [103]. A high preoperative HBV DNA level was an independent risk factor of MVI. Antiviral treatment administered more than 90 days before surgery was associated with reduced incidences of MVI and early tumor recurrence after partial hepatectomy for HBV-related HCC [104].

Intraoperative treatment strategy of MVI

Liver surgery has become the standard of care for HCC [105]. The choice of surgical approach and margins was of great importance to MVI-positive patients. An adequate incisal margin can be used to completely remove the micrometastatic lesion, prevent recurrence, and prolong long-term survival. If the surgical margin reaches a distance of more than 5 cm from the tumor margin, the 5-year DFS rate of patients after surgery can increase from 21 to 33%. Nevertheless, most of the HCC patients were accompanied by basic diseases such as hepatocirrhosis and hepatocirrhosis. Extended resection may easily cause liver dysfunction and other complications [106]. In patients with a high risk of MVI and well-preserved liver function, anatomic resection (AR) may be worth considering [21].

It remains controversial as to whether AR really confers a survival advantage over non-anatomical resection (NAR) for HCC [107, 108]. A recent study showed that AR reduced early recurrence in patients with poorly differentiated tumor or with MVI [109]. In the high MVI group, the prognosis of patients undergoing AR was significantly better than for NAR [110], and the incidence of MVI was higher in the AR group ($P = 0.048$). This suggested that AR can more completely remove the MVI [111]. However, using the propensity score matching analysis found no significant difference in the early recurrence of the tumor after AR and NAR in both MVI-positive and MVI-negative patients [111]. In view of the higher frequency of MVI in the portal vein system, Hasegawa et al. rec-

ommend AR to slow recurrence and prolong survival [112]. When the surgical margin of MVI-positive patients is >1 cm, the patient's DFS rate is significantly better than that of MVI-positive patients with surgical margin <1 cm [113]. In MVI-positive patients relapsed after hepatectomy for the first time, a second repeat operation can significantly prolong the overall survival. This study suggested that the biology of MVI may change after secondary liver resection [114]. LT replaced the entire diseased liver, i.e., not only removed the tumor but also replaced the soil upon which the tumor relies. It was a more thorough surgical method for patients with MVI [115]. A study on 1024 patients with early stage HCC who underwent hepatectomy or LT, the emergence of MVI had a more significant impact on LT patients [99]. MVI was a relevant factor for the recurrence of HCC patients after LT, MVI patients did not benefit from LT [37]. Liver congestion may promote the recurrence of HCC after living-donor LT [116]. Liver congestion should be reduced during surgery. In addition, preoperative puncture for HCC was difficult to reflect the overall condition of the tumor because of the small number of specimens, and the operation itself has been proved to significantly increase the risk of metastasis. However, intraoperative liver puncture may help the choice of cutting margins of HCC.

Postoperative treatment strategy of MVI

Although postoperative pathological diagnosis of MVI is lagging, it can help predict the risk of recurrence and metastasis and guide postoperative anti-relapse therapy [117].

Sun et al. retrospectively analyzed data from 322 patients with MVI, suggesting that postoperative adjuvant TACE (PA-TACE) can improve the long-term prognosis of these patients [117]. MVI-positive patients with well-tolerated liver function who underwent PA-TACE after R0 hepatectomy (RH) or RH alone were studied retrospectively. This study showed that PA-TACE may be beneficial for HCC patients with MVI [117]. TACE may be the more effective treatment option for recurrent HCC of BCLC stage 0 or A than surgery/RFA in MVI-positive patients, especially in those who recur early after curative resection [118], while in the MVI-negative group there was no significant difference. Adjuvant TACE (twice or thrice) after radical resection was beneficial for HCC patients with poor differentiation and MVI, especially for those with a tumor diameter of >5 cm [119]. Adjuvant radiotherapy after hepatectomy had a better survival prognosis for HCC patients with MVI than TACE or conservative treatment [120]. However, it is also reported in the literature that PA-TACE can not only reduce the tumor recurrence rate of HCC patients but may also cause more extrahepatic metastases. It has been confirmed that the microvessel density (MVD) of HCC patients after TACE was significantly increased, and vascular endothelial growth factor was also significantly increased. These unfavorable factors increased the invasiveness of tumor cells within the microvessel and accelerated the recurrence and metastasis of HCC [121]. Therefore, the effect of PA-TACE still requires a clear multicenter meta-analysis.

Current international guidelines for the treatment of HCC recommend sorafenib as a molecularly targeted drug for MVI treatment [122]. A pilot study, patients with MVI can effectively improve DFS after receiving sorafenib for 4 months [123]. The above-mentioned clinical trials suggested that certain targeted drugs may inhibit the recurrence and metastasis of HCC patients with MVI. Postoperative adjuvant therapy with sorafenib in patients with MVI can reduce HCC recurrence and improve patient survival [123]. However, Jordi Bruix et al. believed that hepatectomy of HCC patients with adjuvant treatment with sorafenib does not prolong survival [124]. It has also been reported that doxycycline non-selectively inhibits the synthesis of matrix metalloproteinase-9 (MMP-9). MMP-9 can increase the permeability of hepatoma cells. Therefore, doxycycline was considered to inhibit vascular metastasis of HCC [125]. In addition, some new anti-neoplastic vasculogenic drugs such as TNP-470, Flk-1, endostatin, and IFN-α were considered to be able to resist the invasion of HCC and reduce the recurrence and metastasis of tumors [126–128].

Fewer studies on other treatments for MVI, such as the efficacy of direct-acting antiviral (DAA) therapy [103], implantation of [125] I particles in the hepatic cut surface [129], and radiofrequency ablation (RFA) [130, 131] are in dispute and need further evaluation.

Conclusion

In summary, MVI is an important marker of tumor invasion behavior and affects the prognosis of HCC patients. How to detect MVI early by some biomarkers before surgery is still a problem worth exploring. At the same time, there is still controversy about the preoperative TACE and drug treatment of HCC with MVI. It is necessary to conduct a multicenter large randomized controlled trial (RCT) study of these controversial treatments. For postoperative adjuvant therapy, TACE or targeted therapy still requires further research. Today, with the rapid development of precision medicine, MVI's diagnosis and treatment strategies still have no strong evidence-based medicine foundation. Based on an accurate assessment, we need to work hard to explore and integrate various treatments to create a personalized treatment plan.

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Compliance with ethical guidelines

Conflict of interest R.-S. Ke, Q.-c. Cai, Y.-t. Chen, L.-Z. Lv, and Y. Jiang declare that they have no competing interests.

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References

1. Ringelhan M, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. Nat Immunol. 2018; https://doi.org/10.1038/s41590-018-0044-z.
2. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012;379(9822):1245–55.
3. Banerjee S, Wang DS, Kim HJ, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology. 2015;62(3):792–800.
4. Zheng J, Chakraborty J, Chapman WC, et al. Preoperative prediction of microvascular invasion in hepatocellular carcinoma using quantitative image analysis. J Am Coll Surg. 2017; https://doi.org/10.1016/j.jamcollsurg.2017.09.003.
5. Jang SY, Park SY, Lee HW, et al. The combination of periostin overexpression and microvascular invasion is related to a poor prognosis for hepatocellular carcinoma. Gut Liver. 2016;10(6):948–54.
6. Zhang X, Li J, Shen F. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. 2017.
7. Pote N, Cauchy F, Albuquerque M, et al. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. J Hepatol. 2015;62(4):848–54.
8. Strilic B, Yang L, Albarran-Juarez J, et al. Tumour-cell-induced endothelial cell necroptosis via death receptor 6 promotes metastasis. Nature. 2016;536(7615):215–8.
9. Ding T, Xu J, Zhang Y, et al. Endothelium-coated tumor clusters are associated with poor prognosis and micrometastasis of hepatocellular carcinoma after resection. Cancer. 2011;117(21):4878–89.
10. Roayaie S, Blume IN, Thung SN, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology. 2009;137(3):850–5.
11. Sumie S, Nakashima O, Okuda K, et al. The significance of classifying microvascular invasion in patients with hepatocellular carcinoma. Ann Surg Oncol. 2014;21(3):1002–9.
12. Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol. 2013;20(1):325–39.
13. Imura S, Teraoku H, Yoshikawa M, et al. Potential predictive factors for microvascular invasion in hepatocellular carcinoma classified within the Milan criteria. Int J Clin Oncol. 2018;23(1):98–103.
14. Shirabe K, Toshima T, Kimura K, et al. New scoring system for prediction of microvascular invasion in patients with hepatocellular carcinoma. Liver Int. 2014;34(6):937–41.
15. McHugh PP, Gilbert J, Vera S, Koch A, Ranjan D, Gedaly R. Alpha-fetoprotein and tumour size are associated with microvascular invasion in explanted livers of patients undergoing transplantation with hepatocellular carcinoma. HPB (Oxford). 2010;12(1):56–61.
16. Kim BK, Han KH, Park YN, et al. Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol. 2008;97(3):246–52.
17. Shindoh J, Andreou A, Aloia TA, et al. Microvascular invasion does not predict long-term survival in hepatocellular carcinoma up to 2 cm: reappraisal of the staging system for solitary tumors. Ann Surg Oncol. 2013;20(4):1223–9.
18. Eguchi S, Takatsuki M, Hidaka M, et al. Predictor for histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. World J Surg. 2010;34(5):1034–8.
19. Yamashita Y, Tsuijita E, Takeishi K, et al. Predictors for microinvasion of small hepatocellular carcinoma ⟨/= 2 cm. Ann Surg Oncol. 2012;19(6):2027–34.
20. Gouw AS, Balabaud C, Kusano H, Todo S, Ichida T, Kojiro M. Markers for microvascular invasion in hepatocellular carcinoma: where do we stand? Liver Transplant. 2011;17(Suppl 2):S72–S80.
21. Zhao WC, Fan LF, Yang N, Zhang HB, Chen BD, Yang GS. Preoperative predictors of microvascular invasion in multinodular hepatocellular carcinoma. Eur J Surg Oncol. 2013;39(8):858–64.
22. Hou YF, Wei YG, Yang JY, et al. Microvascular invasion patterns affect survival in hepatocellular carcinoma patients after second hepatectomy. J Surg Res. 2016;200(1):82–90.
23. Esnaola NF, Lauwers GY, Mirza NQ, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. J Gastrointest Surg. 2002;6(2):224–32. discussion 232.
24. Fujita N, Aishima S, Iguchi T, et al. Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma. Hum Pathol. 2011;42(10):1531–8.
25. Siegel AB, Wang S, Jacobson JS, et al. Obesity and microvascular invasion in hepatocellular carcinoma. Cancer Invest. 2010;28(10):1063–9.
26. Yan X, Fu X, Deng M, et al. Infiltrative hepatocellular carcinoma: assessment of factors associated with outcomes in patients undergoing hepatectomy. Medicine. 2016;95(19):e3589.
27. Ding ZB, Shi YH, Zhou J, et al. Liver-intestine cadherin predicts microvascular invasion and poor prognosis of hepatitis B virus-positive hepatocellular carcinoma. Cancer. 2009;115(20):4753–65.
28. Zhu Y, Xu D, Zhang Z, et al. A new laboratory-based algorithm to predict microvascular invasion and survival in patients with hepatocellular carcinoma. Int J Surg. 2018. https://doi.org/10.1016/j.ijsu.2018.07.011
29. Yu Y, Song J, Zhang R, et al. Preoperative neutrophil-to-lymphocyte ratio and tumor-related factors to predict microvascular invasion in patients with hepatocellular carcinoma. Oncotarget. 2017;8(45):79722–30.
30. Pote N, Cauchy F, Albuquerque M, et al. Contribution of virtual biopsy to the screening of microvascular invasion in hepatocellular carcinoma: a pilot study. Liver Int. 2018;38(4):687–94.

31. Agopian VG, Harlander-Locke MP, Markovic D, et al. Evaluation of patients with hepatocellular carcinomas that do not produce alpha-fetoprotein. JAMA Surg. 2017;152(1):55–64.
32. Imura S, Teraoku H, Yoshikawa M, et al. Potential predictive factors for microvascular invasion in hepatocellular carcinoma classified within the Milan criteria. Int J Clin Oncol. 2017. https://doi.org/10.1007/s10147-017-1189-8
33. Zheng J, Seier K, Gonen M, et al. Utility of serum inflammatory markers for predicting microvascular invasion and survival for patients with hepatocellular carcinoma. Ann Surg Oncol. 2017;24(12):3706–14.
34. Kaibori M, Ishizaki M, Matsui K, Kwon AH. Predictors of microvascular invasion before hepatectomy for hepatocellular carcinoma. J Surg Oncol. 2010;102(5):462–8.
35. Miyaaki H, Nakashima O, Kurogi M, Eguchi K, Kojiro M. Lens culinaris agglutinin-reactive alpha-fetoprotein and protein induced by vitamin K absence II are potential indicators of a poor prognosis: a histopathological study of surgically resected hepatocellular carcinoma. J Gastroenterol. 2007;42(12):962–8.
36. Iguchi T, Shirabe K, Aishima S, et al. New pathologic stratification of microvascular invasion in Hepatocellular carcinoma: predicting prognosis after living-donor liver transplantation. Transplantation. 2015;99(6):1236–42.
37. Zhang X, Li J, Shen F, Lau WY. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. J Gastroenterol Hepatol. 2018;33(2):347–54.
38. Tsang F, Au S, Wei L, et al. Long non-coding RNA HOTTIP is frequently up-regulated in hepatocellular carcinoma and is targeted by tumour suppressive miR-125b. Liver Int. 2015;35(5):1597–606.
39. Liu M, Wang L, Zhu H, et al. A preoperative measurement of serum microRNA-125b May predict the presence of Microvascular invasion in hepatocellular carcinomas patients. Transl Oncol. 2016;9(3):167–72.
40. Yu YQ, Wang L, Jin Y, et al. Identification of serologic biomarkers for predicting microvascular invasion in hepatocellular carcinoma. Oncotarget. 2016;7(13):16362–71.
41. Lao X, Wang X, Liu Y, et al. Association of paraoxonase 1 gene polymorphisms with the risk of hepatitis B virus-related liver diseases in a Guangxi population: a case-control study. Medicine. 2015;94(48):e2179.
42. Huang C, Wang Y, Liu S, et al. Quantitative proteomic analysis identified paraoxonase 1 as a novel serum biomarker for microvascular invasion in hepatocellular carcinoma. J Proteome Res. 2013;12(4):1838–46.
43. Lee S, Kim SH, Lee JE, Sinn DH, Park CK. Preoperative gadoxetic acid-enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. J Hepatol. 2017;67(3):526–34.
44. Wu TH, Hatano E, Yamanaka K, et al. A non-smooth tumor margin on preoperative imaging predicts microvascular invasion of hepatocellular carcinoma. Surg Today. 2016;46(11):1275–81.
45. Chou CT, Chen RC, Lin WC, Ko CJ, Chen CB, Chen YL. Prediction of microvascular invasion of hepatocellular carcinoma: preoperative CT and histopathologic correlation. AJR Am J Roentgenol. 2014;203(3):W253–W9.
46. Chou CT, Chen RC, Lee CW, Ko CJ, Wu HK, Chen YL. Prediction of microvascular invasion of hepatocellular carcinoma by pre-operative CT imaging. Br J Radiol. 2012;85(1014):778–83.
47. Cheung TT, Chan SC, Ho CL, et al. Can positron emission tomography with the dual tracers [11 C]acetate and [18 F]fludeoxyglucose predict microvascular invasion in hepatocellular carcinoma? Liver Transplant. 2011;17(10):1218–25.
48. Hyun SH, Eo JS, Song BI, et al. Preoperative prediction of microvascular invasion of hepatocellular carcinoma using (18)F-FDG PET/CT: a multicenter retrospective cohort study. Eur J Nucl Med Mol Imaging. 2018;45(5):720–6.
49. Xu P, Zeng M, Liu K, Shan Y, Xu C, Lin J. Microvascular invasion in small hepatocellular carcinoma: is it predictable with preoperative diffusion-weighted imaging? J Gastroenterol Hepatol. 2014;29(2):330–6.
50. Yang C, Wang H, Sheng R, Ji Y, Rao S, Zeng M. Microvascular invasion in hepatocellular carcinoma: is it predictable with a new, preoperative application of diffusion-weighted imaging? Clin Imaging. 2017;41:101–5.
51. Wang WT, Yang L, Yang ZX, et al. Assessment of microvascular invasion of hepatocellular carcinoma with diffusion Kurtosis imaging. Radiology. 2018;286(2):571–80.
52. Peng J, Zhang J, Zhang Q, Xu Y, Zhou J, Liu L. A radiomics nomogram for preoperative prediction of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma. Diagnostic Interv Radiol. 2018;24(3):121–7.
53. Li H, Zhang J, Zheng Z, et al. Preoperative histogram analysis of intravoxel incoherent motion (IVIM) for predicting microvascular invasion in patients with single hepatocellular carcinoma. Eur J Radiol. 2018;105:65–71.
54. Zhao W, Liu W, Liu H, et al. Preoperative prediction of microvascular invasion of hepatocellular carcinoma with IVIM diffusion-weighted MR imaging and Gd-EOB-DTPA-enhanced MR imaging. PLoS ONE. 2018;13(5):e197488.
55. Marquardt JU, Galle PR, Teufel A. Molecular diagnosis and therapy of hepatocellular carcinoma (HCC): an emerging field for advanced technologies. J Hepatol. 2012;56(1):267–75.
56. Ye J, Wu D, Wu P, Chen Z, Huang J. The cancer stem cell niche: cross talk between cancer stem cells and their microenvironment. Tumour Biol. 2014;35(5):3945–51.
57. Wei X, Li N, Li S, et al. Hepatitis B virus infection and active replication promote the formation of vascular invasion in hepatocellular carcinoma. BMC Cancer. 2017;17(1):304.
58. Yang P, Li QJ, Feng Y, et al. TGF-beta-miR-34a-CCL22 signaling-induced Treg cell recruitment promotes venous metastases of HBV-positive hepatocellular carcinoma. Cancer Cell. 2012;22(3):291–303.
59. Yuan SX, Yang F, Yang Y, et al. Long noncoding RNA associated with microvascular invasion in hepatocellular carcinoma promotes angiogenesis and serves as a predictor for hepatocellular carcinoma patients' poor recurrence-free survival after hepatectomy. Hepatology. 2012;56(6):2231–41.
60. Pote N, Alexandrov T, Le Faouder J, et al. Imaging mass spectrometry reveals modified forms of histone H4 as new biomarkers of microvascular invasion in hepatocellular carcinomas. Hepatology. 2013;58(3):983–94.
61. Xu L, Zhang M, Zheng X, Yi P, Lan C, Xu M. The circular RNA ciRS-7 (Cdr1as) acts as a risk factor of hepatic microvascular invasion in hepatocellular carcinoma. J Cancer Res Clin Oncol. 2017;143(1):17–27.
62. Xu ZY, Ding SM, Zhou L, et al. FOXC1 contributes to microvascular invasion in primary hepatocellular carcinoma via regulating epithelial-mesenchymal transition. Int J Biol Sci. 2012;8(8):1130–41.
63. Fransvea E, Mazzocca A, Antonaci S, Giannelli G. Targeting transforming growth factor (TGF)-betaRI inhibits activation of beta1 integrin and blocks vascular invasion in hepatocellular carcinoma. Hepatology. 2009;49(3):839–50.

64. Minguez B, Hoshida Y, Villanueva A, et al. Gene-expression signature of vascular invasion in hepatocellular carcinoma. J Hepatol. 2011;55(6):1325–31.
65. Huang KT, Kuo IY, Tsai MC, et al. Factor VII-induced microRNA-135a inhibits autophagy and is associated with poor prognosis in hepatocellular carcinoma. Mol Ther Nucleic Acids. 2017;9:274:283.
66. Lin J, Lin W, Ye Y, et al. Kindlin-2 promotes hepatocellular carcinoma invasion and metastasis by increasing Wnt/beta-catenin signaling. J Exp Clin Cancer Res. 2017;36(1):134. https://doi.org/10.1186/s13046-017-0603-4
67. Govaere O, Petz M, Wouters J, et al. The PDGFRalpha-laminin B1-keratin 19 cascade drives tumor progression at the invasive front of human hepatocellular carcinoma. Oncogene. 2017;36(47):6605–16.
68. Fu L, Chen Q, Yao T, et al. Hsa_circ_0005986 inhibits carcinogenesis by acting as a miR-129-5p sponge and is used as a novel biomarker for hepatocellular carcinoma. Oncotarget. 2017;8(27):43878–88.
69. Zhu XT, Yuan JH, Zhu TT, Li YY, Cheng XY. Long noncoding RNA glypican 3 (GPC3) antisense transcript 1 promotes hepatocellular carcinoma progression via epigenetically activating GPC3. FEBS J. 2016;283(20):3739–54.
70. Jeon Y, Kim H, Jang ES, et al. Expression profile and prognostic value of glypican-3 in post-operative South Korean hepatocellular carcinoma patients. APMIS. 2016;124(3):208–15.
71. Calderaro J, Rousseau B, Amaddeo G, et al. Programmed death ligand 1 expression in hepatocellular carcinoma: relationship with clinical and pathological features. Hepatology. 2016;64(6):2038–46.
72. Liu WT, Jing YY, Yu GF, et al. Toll like receptor 4 facilitates invasion and migration as a cancer stem cell marker in hepatocellular carcinoma. Cancer Lett. 2015;358(2):136–43.
73. Cai Z, Zeng Y, Xu B, et al. Galectin-4 serves as a prognostic biomarker for the early recurrence/metastasis of hepatocellular carcinoma. Cancer Sci. 2014;105(11):1510–7.
74. Govaere O, Komuta M, Berkers J, et al. Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. Gut. 2014;63(4):674–85.
75. Park Y, Yu E. Expression of metallothionein-1 and metallothionein-2 as a prognostic marker in hepatocellular carcinoma. J Gastroenterol Hepatol. 2013;28(9):1565–72.
76. Shim JH, Lee HC, Han S, Kang HJ, Yu E, Lee SG. Hepatocyte nuclear factor 1beta is a novel prognostic marker independent of the Milan criteria in transplantable hepatocellular carcinoma: a retrospective analysis based on tissue microarrays. Liver Transplant. 2013;19(3):336–45.
77. Chung KY, Cheng IK, Ching AK, Chu JH, Lai PB, Wong N. Block of proliferation 1 (BOP1) plays an oncogenic role in hepatocellular carcinoma by promoting epithelial-to-mesenchymal transition. hepatology. 2011;54(1):307–18.
78. Yang B, Liu Y, Zhao J, et al. Ectopic overexpression of filamin C scaffolds MEK1/2 and ERK1/2 to promote the progression of human hepatocellular carcinoma. Cancer Lett. 2017;388:167–76.
79. Liu Z, Chang Q, Yang F, et al. Long non-coding RNA NEAT1 overexpression is associated with unfavorable prognosis in patients with hepatocellular carcinoma after hepatectomy: a Chinese population-based study. Eur J Surg Oncol. 2017;43(9):1697–703.
80. Zhou ZJ, Dai Z, Zhou SL, et al. Overexpression of HnRNP A1 promotes tumor invasion through regulating CD44v6 and indicates poor prognosis for hepatocellular carcinoma. Int J Cancer. 2013;132(5):1080–9.
81. Zhuang LK, Yang YT, Ma X, et al. MicroRNA-92b promotes hepatocellular carcinoma progression by targeting Smad7 and is mediated by long non-coding RNA XIST. Cell Death Dis. 2016;7:e2203.
82. Xiao C, Wang C, Cheng S, et al. The significance of low levels of LINC RP1130-1 expression in human hepatocellular carcinoma. Biosci Trends. 2016;10(5):378–85.
83. Nault JC, Galle PR, Marquardt JU. The role of molecular enrichment on future therapies in hepatocellular carcinoma. J Hepatol. 2018;69(1):237–47.
84. Yamashita Y, Shirabe K, Aishima S, Maehara Y. Predictors of microvascular invasion in hepatocellular carcinoma. Dig Dis. 2015;33(5):655–60.
85. Agopian VG, Harlander-Locke M, Zarrinpar A, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg. 2015;220(4):416–27.
86. Yamashita YI, Imai K, Yusa T, et al. Microvascular invasion of single small hepatocellular carcinoma ⟨/=3 cm: Predictors and optimal treatments. Ann Gastroenterol Surg. 2018;2(3):197–203.
87. Zhao H, Hua Y, Lu Z, et al. Prognostic value and preoperative predictors of microvascular invasion in solitary hepatocellular carcinoma ⟨/= 5 cm without macrovascular invasion. Oncotarget. 2017;8(37):61203–14.
88. Cucchetti A, Piscaglia F, Grigioni AD, et al. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study. J Hepatol. 2010;52(6):880–8.
89. Lei Z, Li J, Wu D, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. JAMA Surg. 2016;151(4):356–63.
90. Lai Q, Nicolini D, Inostroza Nunez M, et al. A novel prognostic index in patients with hepatocellular cancer waiting for liver transplantation: time-radiological-response-alpha-fetoprotein-INflammation (TRAIN) score. Ann Surg. 2016;264(5):787–96.
91. Pote N, Cauchy F, Albuquerque M, et al. Contribution of virtual biopsy to the screening of microvascular invasion in hepatocellular carcinoma: A pilot study. Liver Int. 2018;38(4):687–94.
92. Lim KC, Chow PK, Allen JC, et al. Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg. 2011;254(1):108–13.
93. Bockhorn M, Sotiropoulos G, Neuhaus J, et al. Prognostic impact of intrahepatic lymphatic and microvascular involvement in cases of colorectal liver metastases. Int J Colorectal Dis. 2009;24(7):845–50.
94. Ho CM, Hu RH, Lee PH, Wu YM, Ho MC. Long-term survival in patients with T2 hepatocellular carcinoma after primary curative resection can be further stratified by tumor size. Medicine. 2014;93(27):e203.
95. Grat M, Stypulkowski J, Patkowski W, et al. Limitations of predicting microvascular invasion in patients with hepatocellular cancer prior to liver transplantation. Sci Rep. 2017;7:39881.
96. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35–43.
97. Vitale A, Huo TL, Cucchetti A, et al. Survival benefit of liver transplantation versus resection for Hepatocellular carcinoma: impact of MELD score. Ann Surg Oncol. 2015;22(6):1901–7.

98. El-Fattah MA. Hepatocellular carcinoma biology predicts survival outcome after liver transplantation in the USA. Indian J Gastroenterol. 2017;36(2):117–25.
99. Vitale A, Cucchetti A, Qiao GL, et al. Is resectable hepatocellular carcinoma a contraindication to liver transplantation? A novel decision model based on "number of patients needed to transplant" as measure of transplant benefit. J Hepatol. 2014;60(6):1165–71.
100. Jiang JH, Guo Z, Lu HF, et al. Adjuvant transarterial chemoembolization after curative resection of hepatocellular carcinoma: propensity score analysis. World J Gastroenterol. 2015;21(15):4627–34.
101. Goh BK, Chow PK, Teo JY, et al. Number of nodules, Child-Pugh status, margin positivity, and microvascular invasion, but not tumor size, are prognostic factors of survival after liver resection for multifocal hepatocellular carcinoma. J Gastrointest Surg. 2014;18(8):1477–85.
102. Nishikawa H, Arimoto A, Wakasa T, Kita R, Kimura T, Osaki Y. Effect of transcatheter arterial chemoembolization prior to surgical resection for hepatocellular carcinoma. Int J Oncol. 2013;42(1):151–60.
103. Renzulli M, Buonfiglioli F, Conti F, et al. Imaging features of microvascular invasion in hepatocellular carcinoma developed after direct-acting antiviral therapy in HCV-related cirrhosis. Eur Radiol. 2018;28(2):506–13.
104. Li Z, Lei Z, Xia Y, et al. Association of preoperative antiviral treatment with Incidences of microvascular invasion and early tumor recurrence in hepatitis B virus-related hepatocellular carcinoma. JAMA Surg. 2018; https://doi.org/10.1001/jamasurg.2018.2721.
105. Braunwarth E, Stattner S, Fodor M, et al. Surgical techniques and strategies for the treatment of primary liver tumours: hepatocellular and cholangiocellular carcinoma. Eur Surg. 2018;50(3):100–12.
106. Pereyra D, Starlinger P. Shaping the future of liver surgery: Implementation of experimental insights into liver regeneration. Eur Surg. 2018;50(3):132–6.
107. Zhou Y, Xu D, Wu L, Li B. Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. Langenbecks Arch Surg. 2011;396(7):1109–17.
108. Okamura Y, Ito T, Sugiura T, Mori K, Uesaka K. Anatomic versus nonanatomic hepatectomy for a solitary hepatocellular carcinoma : a case-controlled study with propensity score matching. J Gastrointest Surg. 2014;18(11):1994–2002.
109. Cucchetti A, Qiao GL, Cescon M, et al. Anatomic versus nonanatomic resection in cirrhotic patients with early hepatocellular carcinoma. Surgery. 2014;155(3):512–21.
110. Zhao H, Chen C, Fu X, et al. Prognostic value of a novel risk classification of microvascular invasion in patients with hepatocellular carcinoma after resection. Oncotarget. 2017;8(3):5474–86.
111. Marubashi S, Gotoh K, Akita H, et al. Anatomical versus non-anatomical resection for hepatocellular carcinoma. Br J Surg. 2015;102(7):776–84.
112. Kishi Y, Hasegawa K, Kaneko J, et al. Resection of segment VIII for hepatocellular carcinoma. Br J Surg. 2012;99(8):1105–12.
113. Hirokawa F, Hayashi M, Miyamoto Y, et al. Outcomes and predictors of microvascular invasion of solitary hepatocellular carcinoma. Hepatol Res. 2014;44(8):846–53.
114. Hou YF, Li B, Wei YG, et al. Second Hepatectomy improves survival in patients with microvascular invasive hepatocellular carcinoma meeting the Milan criteria. Medicine. 2015;94(48):e2070.
115. Mehta N, Heimbach J, Harnois DM, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for Hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol. 2017;3(4):493–500.
116. Suh SW, Lee JM, You T, et al. Hepatic venous congestion in living donor grafts in liver transplantation: is there an effect on hepatocellular carcinoma recurrence? Liver Transplant. 2014;20(7):784–90.
117. Sun JJ, Wang K, Zhang CZ, et al. Postoperative adjuvant transcatheter arterial chemoembolization after R0 hepatectomy improves outcomes of patients who have hepatocellular carcinoma with Microvascular invasion. Ann Surg Oncol. 2016;23(4):1344–51.
118. Jin YJ, Lee JW, Lee OH, et al. Transarterial chemoembolization versus surgery/radiofrequency ablation for recurrent hepatocellular carcinoma with or without microvascular invasion. J Gastroenterol Hepatol. 2014;29(5):1056–64.
119. Gao Z, Du G, Pang Y, et al. Adjuvant transarterial chemoembolization after radical resection contributed to the outcomes of hepatocellular carcinoma patients with high-risk factors. Medicine. 2017;96(33):e7426.
120. Wang L, Wang W, Yao X, et al. Postoperative adjuvant radiotherapy is associated with improved survival in hepatocellular carcinoma with microvascular invasion. Oncotarget. 2017;8(45):79971–81.
121. Kadam PD, Chuan HH. Erratum to: rectocutaneous fistula with transmigration of the suture: a rare delayed complication of vault fixation with the sacrospinous ligament. Int Urogynecol J Pelvic Floor Dysfunct. 2016;27(3):505.
122. Finn RS, Zhu AX, Farah W, et al. Therapies for advanced stage hepatocellular carcinoma with macrovascular invasion or metastatic disease: a systematic review and meta-analysis. Hepatology. 2018;67(1):422–35.
123. Wang SN, Chuang SC, Lee KT. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: a pilot study. Hepatol Res. 2014;44(5):523–31.
124. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2015;16(13):1344–54.
125. Elewa MA, Al-Gayyar MM, Schaalan MF, Abd El Galil KH, Ebrahim MA, El-Shishtawy MM. Hepatoprotective and anti-tumor effects of targeting MMP-9 in hepatocellular carcinoma and its relation to vascular invasion markers. Clin Exp Metastasis. 2015;32(5):479–93.
126. Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer. 2014;120(22):3527–35.
127. Mazzaferro V, Romito R, Schiavo M, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 2006;44(6):1543–54.
128. Chen R, Yu H, An Y-L, Chen H-J, Teng G-J. Endothelial progenitor cells combined with cytosine deaminase-endostatin for suppression of liver carcinoma. J Biomed Nanotechnol. 2016;12(6):1174–82.
129. Chen K, Xia Y, Wang H, Xiao F, Xiang G, Shen F. Adjuvant iodine-125 brachytherapy for hepatocellular carcinoma after complete hepatectomy: a randomized controlled trial. PLoS ONE. 2013;8(2):e57397.
130. Imai K, Yamashita YI, Yusa T, et al. Microvascular invasion in small-sized hepatocellular carcinoma: significance for outcomes following hepatectomy and radiofrequency ablation. Anticancer Res. 2018;38(2):1053–60.
131. Meniconi RL, Komatsu S, Perdigao F, Boelle PY, Soubrane O, Scatton O. Recurrent hepatocellular carcinoma: a Western strategy that emphasizes the impact of pathologic profile of the first resection. Surgery. 2015;157(3):454–62.