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RESEARCH

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Inter-observer reliability and predictive values of triphasic computed tomography for microvascular invasion in hepatocellular carcinoma

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Abstract

Background Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor globally and a leading cause of mortality in cirrhotic patients. Our study aimed to estimate the diagnostic performance of triphasic CT and inter-observer reliability in the preoperative detection of microvascular invasion (MVI) in HCC. Two independent radiologists accomplished a retrospective analysis for 99 patients with HCC to assess the CT features for MVI in each lesion. Postoperative histopathology was considered the gold standard.

Results Multivariate regression analysis revealed that incomplete or absent tumor capsules, presence of TTPV, and absence of hypodense halo were statistically significant independent predictors of MVI. There was excellent agreement among observers in evaluating peritumoral enhancement, identifying intratumoral arteries, hypodense halo, TTPV, and macrovascular invasion. Also, our results revealed moderate agreement in assessing the tumor margin and tumor capsule.

Conclusion Triphasic CT features of MVI are reliable imaging predictors that may be helpful for standard preoperative interpretation of HCC.

Keywords Hepatocellular carcinoma, Triphasic computed tomography, Microvascular invasion, Hypodense halo

Background

Hepatocellular carcinoma (HCC) is the most prevalent primary hepatic tumor globally and a main cause of mortality in cirrhotic patients [1]. The correct and early diagnosis of HCC is fundamental for ideal management and improved long-term patient survival [2]. HCC can be assertively diagnosed through specific imaging characteristics on computed tomography (CT) or magnetic resonance imaging (MRI) therefore, imaging plays a key role in both HCC diagnosis and treatment [3]. The updated Liver Imaging Reporting and Data System (LI-RADS) has established five major features for accurate HCC detection including enhancement pattern, growth rate, and size [4].

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Hepatic resection proposes the highest chance of best survival for HCC patients. In the past decade, hepatic surgery has seen expanded indications, more intricate surgical techniques, and improved operative outcomes [5].

Vascular invasion, gross or microvascular, is a poor predictive factor in HCC [6]. Microvascular invasion (MVI) is the existence of micro-emboli of HCC deposits within liver vessels and is a critical risk factor for early recurrence occurring following curative treatment [7]. While it is feasible to detect gross vascular invasion through imaging studies, identifying MVI is often challenging and requires pathological assessment of surgical specimen [8, 9].

Previous imaging characteristics have been suggested as predictors of MVI, involving large tumor size, multifocality, irregular tumor margin or non-capsulation, and peritumoral parenchymal enhancement [10–12]. The efficacy of triphasic CT in preoperative detection of MVI has been introduced in limited studies with variable results [13–16] and still needs further validation. This study aimed to evaluate the inter-observer reliability and predictive values of triphasic CT imaging in detecting MVI in patients with HCC in correlation with postoperative pathological data.

Patients and methodology

Study population

This retrospective study has been granted by the local institutional review board with a corresponding waiver of informed consent. From January 2021 to March 2023, one hundred thirty patients with HCC underwent surgical resection and were initially enrolled. Thirty-one patients were excluded from the study. Of those, 28 had preoperative CT conducted outside our radiology unit and the other three had prior locoregional treatment. Finally, the study consisted of ninety-nine patients with HCC who underwent preoperative CT and laboratory assessment.

Clinical and laboratory data

Laboratory and clinical data were gathered for each patient. The clinical data included their age, sex, associated comorbidities, prior antiviral therapy, and the type of surgical resection (minor or major). The laboratory data included measurements of alpha-fetoprotein (AFP), serum creatinine (Cr), liver function tests (LFTs), complete blood count (CBC), and the international normalized ratio (INR).

Triphasic CT technique

All patients underwent a triphasic CT study on a 128 multidetector CT scanner (Toshiba Medical Systems Aquilion Prime ® scanner) within 2–3 weeks before the surgical resection. Patients were imaged in a craniocaudal direction with the following CT scan acquisition parameters: 120 KVp, 200–440 mAs, pitch of 0.8:1, slice thickness of 2 mm, reconstruction gap 1 mm, a field of view of 380 mm, matrix 512 × 512, and window width 150.

Non-ionic contrast medium (Omnipaque 350) was injected at a total dose of 100–120 mL with a flow rate of 3 mL/s. Triphasic CT includes three post-contrast phases: arterial phase acquired within 25–30 s after IV contrast agent injection, portal venous phase (PVP), and equilibrium phase (EP) acquired within 55 s and 3 min after IV contrast injection, respectively. Images were reconstructed utilizing a standard reconstruction algorithm in sagittal, and coronal reformats.

CT image analysis

CT image analysis was done by two independent radiologists (13 and 11 years of experience in hepatic imaging), and both radiologists were blinded to the postoperative pathological data about MVI.

Each observer separately revised CT studies to assess the following criteria for MVI: (a) The largest diameter; (b) The number of lesions; (c) The tumor margins categorized as smooth margins and non-smooth margins showing nodular tumors with smooth outline and non-nodular tumors in all imaging planes, respectively [10, 16]. The non-smooth margins were also classified into a single nodule with extranodular extension (SN EN) showing focal or crescent-like extension of nodules bulging to the hepatic parenchyma, a multinodular confluence (MN) showing multifocal outgrowths bulging into the parenchyma and infiltrative margin (d) Tumor capsule, defined as linear peripheral smooth hyperenhancement in PVP or EP and categorized as capsule complete, capsule incomplete, or no capsule [12]. (e) Peritumoral enhancement [16] is an obvious enhanced arterial part next to the tumor border, which afterward becomes isodense with the hepatic parenchyma in EP. If peritumoral enhancement is present, it is described as either irregular circumferential or wedge-shaped enhancement. (f) Intratumoral arteries were detected at the arterial phase. (g) Hypodense halo sign [13] defined as a hypoattenuating peritumoral ring of hepatic parenchyma in PVP or EP. (h) Two-trait predictor of venous invasion (TTPVI) [16] known as the detection of distinct two CT characteristics (the existence of intratumoral arteries and noncontinuous or absent hypodense halos) that can better predict MVI.(i) Hepatic capsular invasion [17] was detected by the existence of any of the following features: absent or incomplete tumor capsule; absence of hepatic parenchyma between the liver capsule and tumor, tumor growth outside the liver border or; interrupted hepatic

capsule or noticeable subcapsular effusion accumulation. CT images were also assessed for macrovascular invasion, bile duct invasion, and intratumoral fat presence.

Surgical technique

All included patients underwent a preoperative 3D visualization analysis, liver volumetry was achieved for patients who required major liver resection [18]. The surgical resection was either minor or major according to Brisbane 2000 classification [19]. Major resections were carried out for big tumors or tumors adjacent to major liver vasculature, providing an adequate remnant liver [20].

Histopathological analysis

An expert pathologist with 15 years of expertise in hepatic pathology assessed the surgical specimens to detect MVI. The practical guidelines for the tissue diagnosis of primary liver cancer of Liver Cancer Pathology Group of China) (LCPGC) serve as the foundation for MVI diagnosis. Presences of nests of tumor cells in the hepatic vein, portal vein, and any other vessel lined by endothelium within the tumor capsule that were only discernible under a microscope were defined as MVI [21]. All specimens were allotted into positive MVI and negative MVI groups according to the MVI bi-tiered grading system.

Follow-up

Follow-up was directed one month following surgical resection and then every 3 months consuming laboratory (CBC, serum AFP, and LFTs) and radiological findings (abdominal ultrasonography and triphasic CT or MRI). The recurrence was diagnosed based on a newly developed hepatic focal lesion on triphasic CT and elevated AFP levels.

Statistical analysis

Data were evaluated with the Statistical Package of Social Science (SPSS) program for Windows (Standard version 24). First, the data was tested for normality with a one-sample Kolmogorov–Smirnov test. Numbers and percentages were used to describe qualitative data. The association among categorical variables was tested using the Chi-square test however Monte Carlo and Fisher exact tests were performed when the assumed cell counts less than 5. The continuous variables were expressed as median (Min–Max) for non-normal data and mean ± SD (standard deviation) for normally distributed data. The two groups were compared by independent t-test (parametric data) and Mann–Whitney test (nonparametric data). The agreement between the two observers was tested using the Kappa agreement. Significant variables identified on univariate analysis were participated in the logistic regression model consuming the forward wald statistical technique to expect the most important factors. The results were counted as significant when the $p \leq 0.05$ for all statistical tests.

Results

Patients' characteristics

The study group involved 99 patients with a mean age of 62.00 ± 9.41 (73 males, and 26 females). All patients had cirrhotic liver and were classified as Child–Pugh A. The postoperative histopathological results showed that 58 patients (58.6%) tested positive for MVI, while 41 patients (41.4%) tested negative for MVI (Table 1).

Sixty-eight (86.9%) patients had received anti-HCV or HBV therapy with statistically significant association ($p = 0.041$) with negative MVI in 39 (95.1%) patients. Serum creatinine and alkaline phosphatase were statistically significantly higher in the MVI-negative than MVI-positive group ($P = 0.018$ and $P = 0.009$) respectively. There was no statistically significant association concerning other liver function tests, AFP, and MVI status of HCCs. Sixty-eight (68.7%) patients had no radiological recurrence in the first year following the operation with statistically significant association ($p = 0.033$) with MVI negative group in 33/41 (80.5%) patients.

Triphasic CT findings

Our results showed a statistically significant association between tumor margin ($p = 0.001$), tumor capsule ($p \leq 0.001$), peritumoral enhancement ($p = 0.037$), intratumoral arteries ($p = 0.008$), hypodense halo ($p \leq 0.001$), TTPV ($p \leq 0.001$) and macrovascular invasion ($p = 0.018$) and MVI. Tumor margin was multinodular in 28 (48.3%) & infiltrative in 17 (29.3%) patients of 58 positive MVI group, while margin was smooth in 22 (53.7%) patients of 41 negative MVI group.

Twenty-six (44.8%) patients of 58 positive MVI had incomplete capsules, and 19 (32.8%) patients had absent capsules. On the other side, of 41 negative MVI patients, 26 (63.4%) patients had complete capsule. Peritumoral enhancement was wedge-shaped in 13 patients (13.1%); 11 of them were positive MVI in histopathological specimens. Irregular circumferential enhancement was found in 6 (6.1%) patients; five of them also had positive MVI. While peritumoral enhancement was absent in 80 (80.8%) patients, 38 patients (92.7%) of the MVI-negative group had absent peritumoral enhancement.

In 23.2% (23/99) of the patients, intratumoral arteries were absent, and 36.6% of these patients (15/23) showed negative MVI in histopathological reports. Hypodense halo was found in 18 (18.2%) patients, 17 of them showed negative MVI and was absent in 81(81.8%)

Table 1 Patients' characteristics

	Total (no = 99)	MVI		Test of significance
		Positive (*n* = 58, 58.6%)	Negative (*n* = 41, 41.4%)	
Age (Years)				
Mean ± SD	62.00 ± 9.41	61.26 ± 9.80	63.07 ± 8.83	$t = 0.926$
Min–Max	16.00–93.00	16.00–93.00	22.00–74.00	$p = 0.357$
Sex				$\chi^2 = 1.071$
Male	73 (73.7%)	45 (77.6%)	28 (68.3%)	$p = 0.301$
Female	26 (26.3%)	13 (22.4%)	13 (31.7%)	
Diabetes				$\chi^2 = 0.476$
Yes	15 (15.2%)	10 (17.2%)	5 (12.2%)	$p = 0.490$
No	84 (84.8%)	48 (82.8%)	36 (87.8%)	
HTN				$\chi^2 = 0.580$
Yes	16 (16.2%)	8 (13.8%)	8 (19.5%)	$p = 0.446$
No	83 (83.8%)	50 (86.2%)	33 (80.5%)	
Anti-HCV or HBV therapy				$\chi^2 = 4.179$
Yes	86 (86.9%)	47 (81.0%)	39 (95.1%)	**$p = 0.041$***
No	13 (13.1%)	11 (19.0%)	2 (4.9%)	
Type of resection				$\chi^2 = 2.331$
Minor	77 (77.8%)	42 (72.4%)	35 (85.4%)	$p = 0.127$
Major	22 (22.2%)	16 (27.6%)	6 (14.6%)	
1 year follow-up (recurrence)				$\chi^2 = 4.531$
Yes	68 (68.7%)	23 (39.7%)	8 (19.5%)	**$p = 0.033$***
No	31 (31.3%)	35 (60.3%)	33 (80.5%)	
Sr. creatinine			0.83 ± 0.19	$t = 2.416$
Mean ± SD	0.78 ± 0.18	0.74 ± 0.15		**$P = 0.018$***
AFP				$Z = 0.377$
Median (Min–Max)	319 (1–2000)	294.50 (1–2000)	320 (1–2000)	$P = 0.706$
Alkaline phosphatase	7.37 ± 2.32	6.86 ± 1.97	8.09 ± 2.60	$t = 2.682$
				$P = 0.009$*
ALT				$Z = 0.496$
Median (Min–Max)	39 (20–512)	39 (20–163)	39 (20–512)	$P = 0.620$
AST				$Z = 1.146$
Median (Min–Max)	40 (20–330)	40 (20–221)	45 (20–330)	$P = 0.252$
Total bilirubin				$t = 1.160$
Mean ± SD	1.77 ± 6.67	2.43 ± 8.69	0.85 ± 0.17	$P = 0.249$
Albumin				$t = 0.033$
Mean ± SD	3.99 ± 0.36	4.00 ± 0.33	3.99 ± 0.40	$P = 0.974$
INR				$t = 0.340$
Mean ± SD	1.06 ± 0.07	1.06 ± 0.06	1.06 ± 0.09	$P = 0.734$

χ^2: Chi-square test, FET: Fisher exact test

patients, 57 of them were positive MVI in histopathological reports. TTPV was present in 66 (66.7%) patients, 47 of them showed positive MVI, while it was absent in 33 (33.3%) patients, 22 of them were negative MVI. Of 58 positive MVI patients 50 (86.2%) patients showed intratumoral arteries and 57 (98.3%) patients showed absent hypodense halo. Macrovascular invasion was identified in 15 (15.2%) patients, 13 of them showed positive MVI in histopathological specimens. The size of HCCs in all patients ranged from 2 to 20 cm. There was no significant association between other assessed triphasic CT parameters (Table 2). Demonstrative cases are illustrated at Figs. 1, 2, 3, 4.

Table 2 CT imaging features of MVI

	Total (no = 99)	MVI		Test of significance
		Positive ($n = 58$)	Negative ($n = 41$)	
Max dimensions (cm)				$Z = 1.573$
Median (Min–Max)	6 (2–20)	6.50 (3–15)	5 (2–20)	$P = 0.116$
Margin				MC
Smooth	31 (31.3%)	9 (15.5%)	22 (53.7%)	$\mathbf{p = 0.001}^{*}$
SN-EN	7 (7.1%)	4 (6.9%)	3 (7.3%)	
MN	41 (41.4%)	28 (48.3%)	13 (31.7%)	
Infiltrative	20 (20.2%)	17 (29.3%)	3 (7.3%)	
Tumor capsule				$\chi^2 = 17.80$
Complete	39 (39.4%)	13 (22.4%)	26 (63.4%)	$\mathbf{p \leq 0.001}$*
Incomplete	37 (37.4%)	26 (44.8%)	11 (26.8%)	
No	23 (23.2%)	19 (32.8%)	4 (9.8%)	
Peritumoral enhancement				MC
Wedge shaped	13 (13.1%)	11 (19.0%)	2 (4.9%)	$\mathbf{p = 0.037}^{*}$
Irregular	6 (6.1%)	5 (8.6%)	1 (2.4%)	
No	80 (80.8%)	42 (72.4%)	38 (92.7%)	
Intratumoral arteries				$\chi^2 = 6.99$
Yes	76 (76.8%)	50 (86.2%)	26 (63.4%)	$\mathbf{p = 0.008}$*
No	23 (23.2%)	8 (13.8%)	15 (36.6%)	
Hypodense halo				$\chi^2 = 25.49$
Yes	18 (18.2%)	1 (1.7%)	17 (41.5%)	$\mathbf{p \leq 0.001}$*
No	81 (81.8%)	57 (98.3%)	24 (58.5%)	
TTPV				$\chi^2 = 13.01$
Yes	66 (66.7%)	47 (81.0%)	19 (46.3%)	$\mathbf{p \leq 0.001}$*
No	33 (33.3%)	11 (19.0%)	22 (53.7%)	
Radiographic evidence of hepatic capsular invasion				$\chi^2 = 2.08$
Yes	66 (66.7%)	42 (72.4%)	24 (58.5%)	$p = 0.149$
No	33 (33.3%)	16 (27.6%)	17 (41.5%)	
Enhancement pattern				MC
Homogeneous	2 (2.0%)	1 (1.7%)	1 (2.4%)	$p = 0.309$
Heterogeneous	95 (96.0%)	57 (98.3%)	38 (92.7%)	
Progressive	2 (2.0%)	0 (0%)	2 (4.9%)	
Intratumoral fat				$\chi^2 = 0.580$
Yes	16 (16.2%)	8 (13.8%)	8 (19.5%)	$p = 0.446$
No	83 (83.8%)	50 (86.2%)	33 (80.5%)	
Macrovascular Invasion				$\chi^2 = 5.74$
Yes	15 (15.2%)	13 (22.4%)	2 (4.9%)	$\mathbf{p = 0.017}$*
No	84 (84.8%)	45 (77.6%)	39 (95.1%)	
Bile duct invasion				FET
Yes	6 (6.1%)	5 (8.6%)	1 (2.4%)	$p = 0.396$
No	93 (93.9%)	53 (91.4%)	40 (97.6%)	

Z: Mann Whitney test, FET: Fisher exact test, MC: Monte Carlo test

Predictors for malignancy

Univariate analysis results were infiltrative margin of tumor ($P = 0.013$, OR 5.25), incomplete or absent tumor capsule ($P = 0.002$ and ≤ 0.001 respectively, OR 4.73 and 9.5 respectively), wedge-shaped peritumoral enhancement ($P = 0.045$, OR 4.97), presence of intratumoral arteries ($P = 0.01$, OR 3.6), absence of hypodense halo ($P \leq 0.001$, OR 40.4), presence of TTPV ($P \leq 0.001$, OR 4.9) and macrovascular invasion ($P = 0.029$, OR 5.6) were independent predictors for positive MVI. After

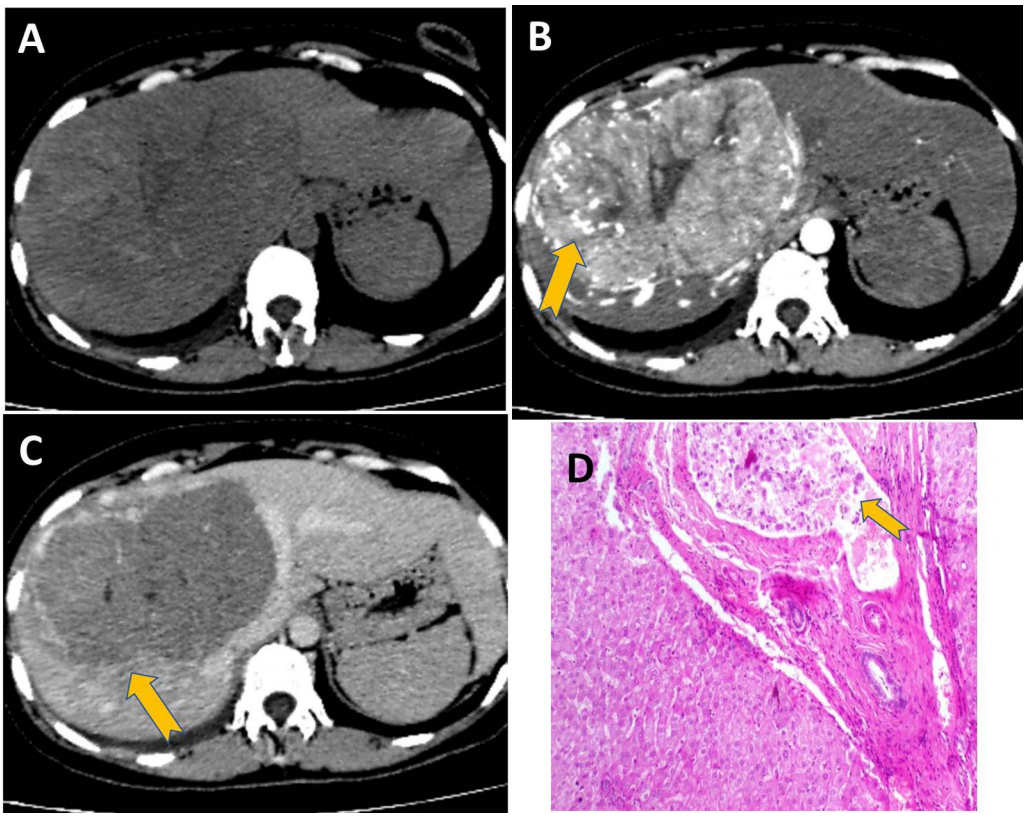

Fig. 1 38-year-old female with solitary hepatocellular carcinoma (HCC) occupying segment VIII of the liver who underwent minor resection. **A** Axial non-contrast CT image shows a hypodense focal lesion at segment VIII. **B** Axial arterial phase CT image shows heterogeneous enhancement of the lesion with intratumoral arteries (arrow). **C** Axial equilibrium phase CT image shows washout of contrast and the lesion shows smooth margins, incomplete capsule (arrow), but no hypodense halo. TTPVI of positive intratumoral arteries and negative hypodense halo is indicative of positive MVI. **D** Histopathologic examination revealed frequent microvascular emboli in the portal tract (yellow arrow), magnification × 100

multivariate analysis, the most significant predictor factors for positive MVI were incomplete and absent tumor capsule ($P=0.053$ and 0.027 respectively), absence of hypodense halo ($P=0.002$), and the existence of TTPV ($P=0.017$) (Table 3).

Inter-observer agreement

An excellent inter-observer agreement was detected in the evaluation of peritumoral enhancement, identification of intratumoral arteries, hypodense halo, TTPV, and macrovascular invasion. Furthermore, there was moderate inter-observer agreement regarding the tumor margin and tumor capsule (Table 4).

Discussion

Recently MVI has aroused worldwide attention as a chief risk factor for poor survival and recurrence in patients with HCCs. It means early invasion of tumor vessels by tumor cells [22]. Detection of MVI in imaging studies is generally challenging [11]. So, we targeted to study the reliability and performance of some proposed CT features to MVI.

Our results revealed a significant association between Anti HBV and HCV therapy and the negativity of MVI in our results. This is explained by the effect of antiviral therapy in controlling liver inflammation; one of the primary contributors to develop HCC. Rationally it may affect the aggressiveness of the tumor. So, it can decrease the development of HCC as well as the post-surgical recurrence [23]. Chou et al. [10] showed no significant relation between chronic viral hepatitis and microvascular invasion, despite that, patients with chronic viral hepatitis were higher in number in the MVI-positive group compared to the MVI-negative group.

In this study, the non-smooth margin of the tumor was correlated with positive MVI, it has been further subclassified into single nodule with extra nodular extension, multinodular margin & infiltrative margin with increasing incidence of MVI, respectively. That was in concordance with prior studies [10] [13, 16, 17]. Zhang et al. [17] reported that nodular borders in were gorgeous in blood

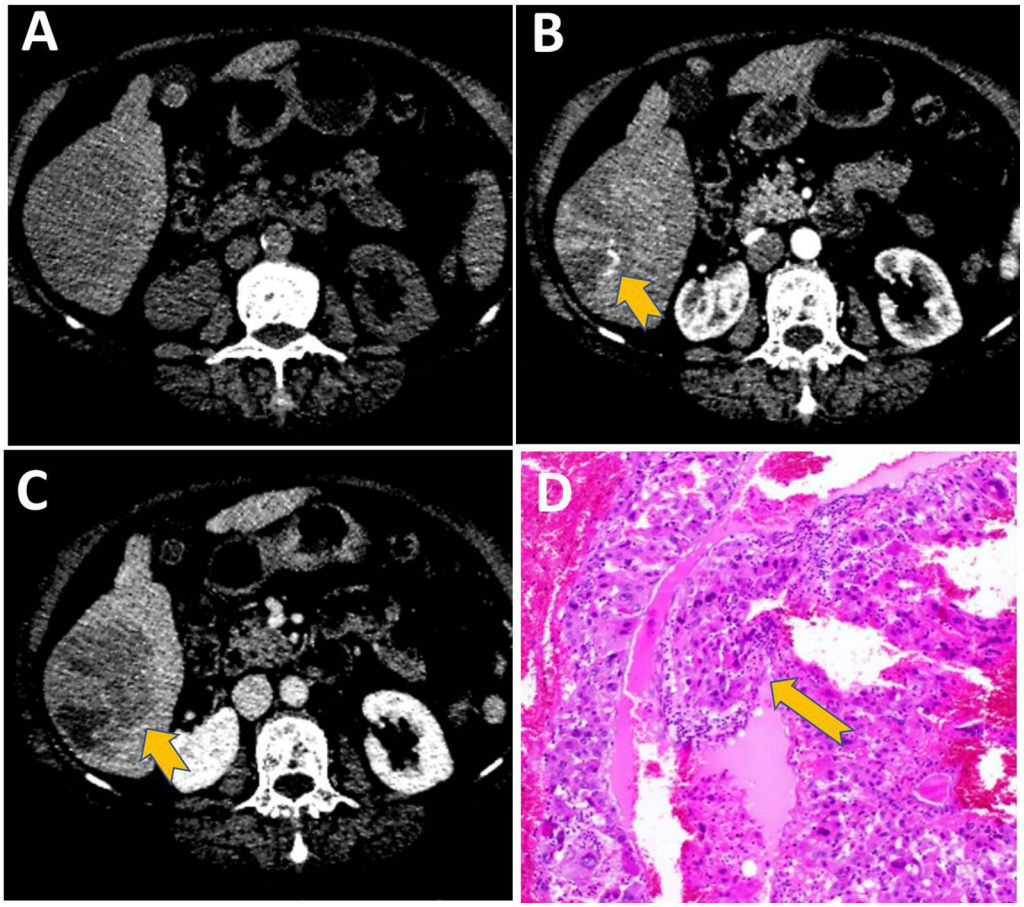

Fig. 2 A 73-year-old man with solitary hepatocellular carcinoma (HCC) at segment VI of the liver underwent minor resection. **A** Axial non-contrast CT image shows a hypodense focal lesion at segment VI. **B** Axial arterial phase CT image shows heterogeneous enhancement of the lesion with intratumoral arteries (arrow). **C** Axial equilibrium phase CT image shows washout of contrast and the lesion shows micronodular margins, incomplete capsule (arrow), but no hypodense halo. TTPVI of positive intratumoral arteries and negative hypodense halo is indicative of positive MVI. **D** Histopathologic examination revealed frequent microvascular emboli with protruding tumor cells into vessel lumen (yellow arrow), magnification × 100

vessels to predict MVI in a detailed evaluation of margin pathology. It has been previously reported by Chou et al. [10] that site of MVI occurs frequently at the location of extranodular involvement.

In the present study, the infiltrative margin has been added and had the highest incidence of MVI. Similarly, Renzulli et al. [16] determined that the infiltrative margin was the most pattern closely associated with MVI. It has been suggested that treatment of HCC having non-smooth margins could be remodeled by either extensive surgical resection or postoperative treatment to reach a complete response or elongated tumor-free survival [13].

Incomplete or absent tumor capsule is significantly correlated with MVI in the current study. Though, the relationship between tumor capsule and MVI stays debatable in previous studies [13]. Histologically, a fibrous capsule is comprised of two layers; inner fibrous-rich layer and an outer layer rich in small vessels and a newly formed bile duct [12]. Our results were in line with some authors who considered the fibrous capsule to be a favorable predictive factor since it precludes invasion of normal surrounding liver parenchyma [13, 24]. Also, Ariizumi et al. [25] showed a significant association between the incomplete capsule and MVI. On the contrary, Witjes et al. and Adachi et al. [26, 27] considered tumor capsule is predictive for vascular invasion, explained by the frequent invasion of the blood vessels within the fibrous capsule by tumor cells.

Irregular circumferential or wedge-shaped peritumoral enhancement was significantly related to MVI in this study. This is mostly attributed to peritumoral hemodynamic changes in the form of arterial hyperperfusion in areas with reduced portal flow secondary to minute portal branch occlusion by tumor thrombi [28]. This was in

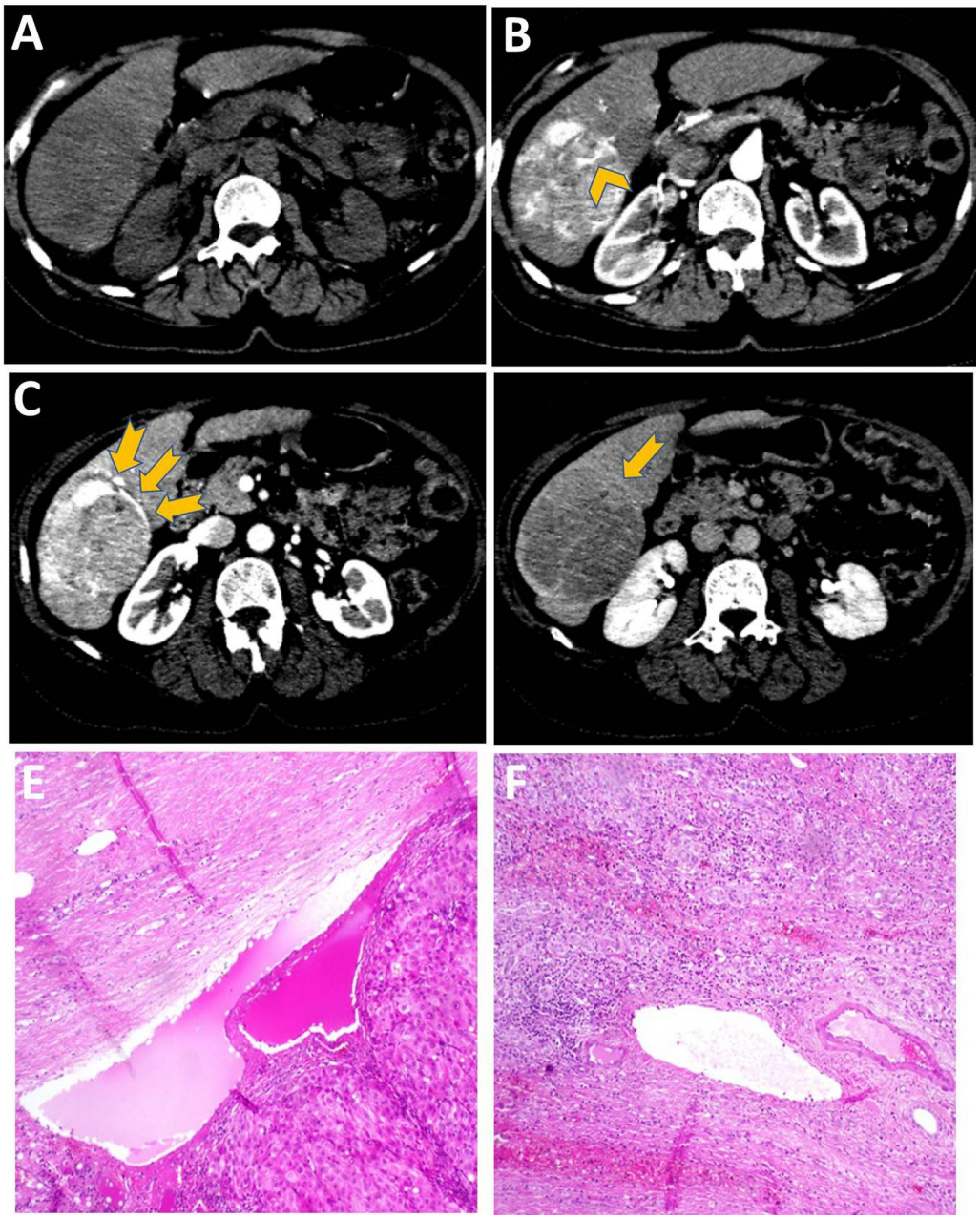

Fig. 3 51-year-old female with solitary hepatocellular carcinoma (HCC) at segment VI of the liver who underwent minor resection. **A** Axial non-contrast CT image shows hypodense focal lesion at segment VI. **B** Axial arterial phase CT image shows heterogeneous enhancement of the lesion with intratumoral arteries (arrowhead). **C**, Axial PVP CT image shows evident hypodense halo (arrows). TTPVI of positive both intratumoral arteries and hypodense halo is indicative of absent MVI. **D** Axial equilibrium phase CT image shows washout of the contrast and the lesion shows smooth margins, and a complete capsule (arrow). **E**, **F** Histopathologic examination failed to detect any microvascular emboli neither in the capsule (**E**) nor in the portal tract (**F**), magnification × 100

keeping with previous studies as Kim et al., and Miyata et al. [29, 30] using different imaging modalities and different CT angiographic technique.

Irregular circumferential peritumoral enhancement was significantly associated with MVI rather than wedge-shaped pattern in studies done by Yoneda et al. [12] and Nishie et al. [31] who stated that the size of peritumoral enhancement was found to be a significant risk factor for MVI by CT arterioportography, while Renzulli et al. [16] suggested assessment of peritumoral

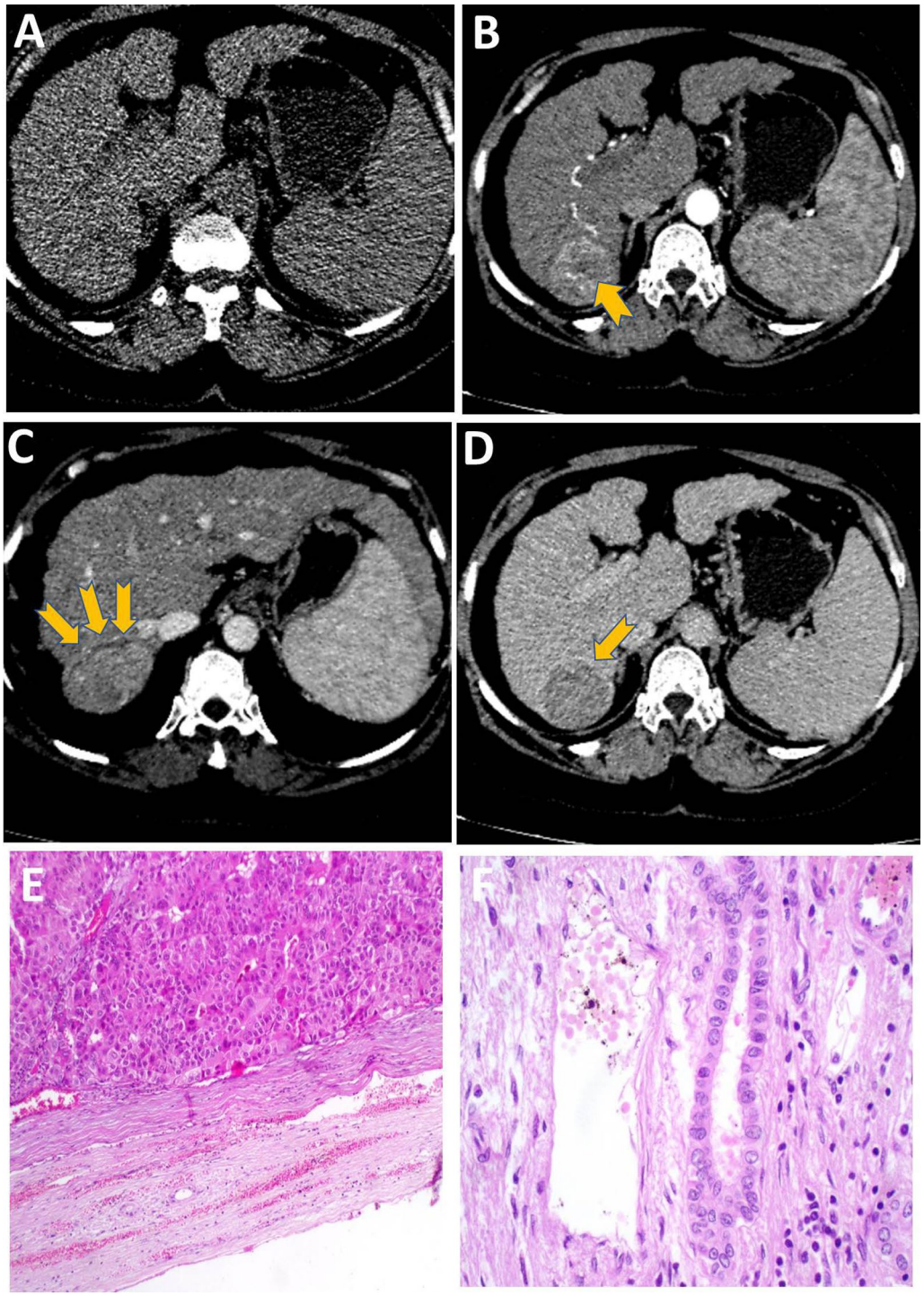

Fig. 4 59-year-old female with solitary hepatocellular carcinoma (HCC) at segment VI of the liver who underwent minor resection. **A** Axial non-contrast CT image shows hypodense focal lesion at segment VI. **B** Axial arterial phase CT image shows heterogeneous enhancement of the lesion with intratumoral arteries (arrow). **C** Axial PVP CT image at different levels shows evident incomplete hypodense halo (arrows). **D** axial equilibrium phase CT image shows washout of contrast and the lesion shows smooth margins and complete capsule. **E**, **F** Histopathologic examination failed to detect any microvascular emboli neither in the capsule (**E**) nor in the portal tract (**F**), magnification × 100

Table 3 Multivariate logistic regression analysis for independent predictors of MVI

	Univariate regression		Multivariate regression	
	***P* value**	**OR (95%) CI**	***P* value**	**OR (95%) CI**
Margin	0.013	5.25 (1.42–19.3)	–	–
Infiltrative				
Others (r)				
Tumor capsule			–	1
Complete (r)	–	1	0.053	3.1 (0.98–3.06)
Incomplete	0.002	4.73 (1.8–12.5)	**0.027**	6.9 (1.25–6.97)
No	≤ 0.001	9.5 (2.7–33.7)		
Peritumoral enhancement			–	–
Wedge-shaped				
Irregular	0.045	4.97 (1.03–23.9)		
No	0.177	4.52 (0.51–40.4)		
	–	1		
Intratumoral arteries	0.01	3.6 (1.4–9.6)	–	–
No hypodense halo	≤ 0.001	40.4 (5.1–320)	**0.002**	67 (4.5–1000)
TTPV	≤ 0.001	4.9 (2.01–12.2)	**0.017**	3.5 (1.2–10)
Macrovascular Invasion	0.029	5.6 (1.2–26.5)	–	–

(r): reference group, *CI* confidence interval

enhancement by noninvasive, commonly used imaging methods, such as CT or dynamic MRI.

The association between imaging features and HCC-precise "venous invasion" gene mark was named radiogenomic venous invasion in some reports or two-trait predictor of venous invasion (TTPVI) in others. It depends on the detection of intratumoral arteries and peritumoral hypodense halos in CT studies. It was suggested to have a strong association with histologic MVI [11, 16, 32].

Our results showed a significant association between the presence of TTPVI and MVI positivity in pathological reports. That was in agreement with Renzulli et al. [16] who considered it as one of three significant features to expect MVI on both CT and MRI with high positive predictive values (PPV) > 95%. Nevertheless, the identification of hypodense halo and internal arteries are challenging in small HCCs [11].

Macrovascular invasion reduces the therapeutic alternatives and signifies a contraindication to liver transplantation. While macrovascular invasion often coexists with lesions with an infiltrative appearance that refers to the permeative growth pattern throughout cirrhotic parenchyma, unsurprisingly, it should be associated with MVI as resulted in the present study [33].

Table 4 Inter-observer agreement

	Observer 1	Observer 2	Kappa agreement %
Margin			58.60
Smooth	31 (31.3%)	17 (17.2%)	
SN-EN	7 (7.1%)	19 (19.2%)	
MN	41 (41.4%)	35 (35.4%)	
Infiltrative	20 (20.2%)	28 (28.3%)	
Tumor capsule			59.60
Complete	39 (39.4%)	18 (18.2%)	
Incomplete	37 (37.4%)	47 (47.5%)	
No	23 (23.2%)	34 (34.3%)	
Peritumoral enhancement			92.90
Wedge-shaped	13 (13.1%)	10 (10.1%)	
Irregular circumferential	6 (6.1%)	8 (8.1%)	
No	80 (80.8%)	81 (81.8%)	
Intratumoral arteries			92.90
Yes	76 (76.8%)	75 (75.8%)	
No	23 (23.2%)	24 (24.2%)	
Hypodense halo			88.90
Yes	18 (18.2%)	15 (15.2%)	
No	81 (81.8%)	84 (84.8%)	
TTPV	66 (66.7%)	62 (62.6%)	81.80
Yes	33 (33.3%)	37 (37.4%)	
No			
Radiographic evidence of hepatic capsular invasion			82.80
Yes	66 (66.7%)	57 (57.6%)	
No	33 (33.3%)	42 (42.4%)	
Enhancement pattern			99.00
Homogeneous	2 (2.0%)	1 (1.0%)	
Heterogeneous	95 (96.0%)	96 (97.0%)	
Progressive	2 (2.0%)	2 (2.0%)	
Intratumoral fat			99.00
Yes	16 (16.2%)	15 (15.2%)	
No	83 (83.8%)	84 (84.8%)	
Macrovascular Invasion			96.90
Yes	15 (15.2%)	12 (12.1%)	
No	84 (84.8%)	87 (87.9%)	
Bile duct invasion			99.00
Yes	6 (6.1%)	5 (5.1%)	
No	93 (93.9%)	94 (94.9%)	

In the current study, there was no significant association between MVI status and hepatic capsular invasion. This disagrees with Zhang et al. [17] who showed an association between this CT feature and MVI. This may be explained by common but less specific radiological criteria that were used to determine hepatic capsular invasion by authors.

Also, our results revealed no significant association concerning the enhancement pattern, presence of intratumoral fat, or bile duct invasion with MVI. This may be attributed to selection bias of patients that had already undergone liver resection.

Serum AFP is one of the most frequently used tumor markers for HCC, current study showed higher AFP in the MVI-positive compared to the MVI-negative group but with no detected significant difference between both studied groups. Eguchi et al. [34] stated that the AFP level could be employed as a predictor of MVI and early recurrence. Zhang et al. [17] used AFP and tumor size (> or < 5 cm) in stratified analysis of HCC for the prediction of MVI. However, our results were in line with Chou et al. [10]. This discrepancy in results could be exerted by possibility of the presence of non-AFP-secreting tumors.

Univariate analysis of this study revealed that infiltrative tumor margin, incomplete or absent tumor capsule, wedge-shaped peritumoral enhancement, existence of intratumoral arteries, lack of hypodense halo, presence of TTPV, and macrovascular invasion were independent predictors for MVI. Despite of that, multivariate analysis showed that incomplete and absent tumor capsule, the absence of hypodense halo, and the presence of TTPV are the most strong independent predictors for MVI.

Renzulli et al. [16] described TTPV involving the absence of hypodense halo is one of three worrisome features with a high predictive value for MVI. Other two features included non-smooth margin and peritumoral enhancement. Ueda et al. [35] reported that intact or complete capsule can avoid tumor spread.

Non-smooth or irregular margin was reported in prior studies [10, 13, 16] as a strong independent risk for MVI. Chou et al. [10] reported that a non-smooth margin was the single significant predictor for MVI in their multivariate analysis. The difference in results between this study and others may be attributed to tumor size that was non-significantly different between our studied groups. It was difficult to assess tumor margin in small liver tumors.

Similar to Renzulli et al. [16], the current study showed excellent inter-observer agreement in the assessment of peritumoral enhancement, identification of intratumoral arteries, hypodense halo, and TTPV. While moderate agreement was detected during assessment of tumor margin and tumor capsule. This also could be explained by variability in tumor size as; tumor margin and capsule are easier to be assessed in large tumors than in small ones.

This study had a few limitations. Firstly, the selection bias of surgical candidates besides retrospective design may cause inadequate expression of HCC radiologic characteristics, a prospective study is recommended in the future. Another limitation is the lack of incorporation of histologic features, e.g., grading of liver fibrosis. Thirdly, lack of adding of MRI examination, so, further combining CT and MRI in the future may be beneficial. Additionally, further quantitative or textural image analysis is recommended, may impact study results.

Conclusion

Incomplete or absent tumor capsule, presence of TTPV, and absence of hypodense halo are independent radiological predictors for MVI that may be helpful for standard preoperative interpretation of HCC.

Abbreviations

CT	Computed Tomography
EP	Equilibrium phase
HCC	Hepatocellular carcinoma
MN	Multinodular confluence
MVI	Microvascular invasion
PVP	Porto venous phase
SN EN	Single nodule with extranodular extension
TTPVI	Two-trait predictor of venous invasion

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Author contributions

All authors have read & approved the manuscript. Study concept and design was proposed by GAS and FAD. Database search by MAA, MM, and GAS. Image analysis and interpretation of data: GAS and MM. Clinical assessment: AS, MS, MAA. Pathological analysis: KMA. Revision of the manuscript; GAS, MM and FAD. Technical, or material support; AS, MS and GAS.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board of Mansoura University (Approval No: R.23.12.2407.R1).

Consent for publication

Written informed consent was waived by the Institutional Review Board.

Competing interests

The authors declare that they have no conflict of interest.

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References

1. Konyn P, Ahmed A, Kim D (2021) Current epidemiology in hepatocellular carcinoma. Expert Rev Gastroenterol Hepatol 15(11):1295–1307

2. Guan M-C, Wang M-D, Liu S-Y, Ouyang W, Liang L, Pawlik TM et al (2021) Early diagnosis and therapeutic strategies for hepatocellular carcinoma: from bench to bedside. World J Gastrointest Oncol 13(4):197
3. Lee S, Kim Y-Y, Shin J, Hwang SH, Roh YH, Chung YE et al (2020) CT and MRI liver imaging reporting and data system version 2018 for hepatocellular carcinoma: a systematic review with meta-analysis. J Am Coll Radiol 17(10):1199–1206
4. Abdel Razek AAK, El-Serougy LG, Saleh GA, Shabana W, Abd E-W (2020) Liver imaging reporting and data system version 2018: what radiologists need to know. J Comput Assist Tomogr 44(2):168–177
5. Cloyd JM, Mizuno T, Kawaguchi Y, Lillemoe HA, Karagkounis G, Omichi K et al (2020) Comprehensive complication index validates improved outcomes over time despite increased complexity in 3707 consecutive hepatectomies. Ann Surg 271(4):724–731
6. Bruix J, Reig M, Sherman M (2016) Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 150(4):835–853
7. Erstad DJ, Tanabe KK (2019) Prognostic and therapeutic implications of microvascular invasion in hepatocellular carcinoma. Ann Surg Oncol 26:1474–1493
8. Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK (2013) A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 20:325–339
9. Griffin N, Addley H, Sala E, Shaw AS, Grant LA, Eldaly H et al (2012) Vascular invasion in hepatocellular carcinoma: is there a correlation with MRI? Br J Radiol 85(1014):736–744
10. Chou C-T, Chen R-C, Lin W-C, Ko C-J, Chen C-B, Chen Y-L (2014) Prediction of microvascular invasion of hepatocellular carcinoma: preoperative CT and histopathologic correlation. Am J Roentgenol 203(3):W253–W259
11. An C, Kim M-J (2019) Imaging features related with prognosis of hepatocellular carcinoma. Abdom Radiol 44(2):509–516
12. Yoneda N, Matsui O, Kobayashi S, Kitao A, Kozaka K, Inoue D et al (2019) Current status of imaging biomarkers predicting the biological nature of hepatocellular carcinoma. Jpn J Radiol 37:191–208
13. Reginelli A, Vanzulli A, Sgrazzutti C, Caschera L, Serra N, Raucci A et al (2017) Vascular microinvasion from hepatocellular carcinoma: CT findings and pathologic correlation for the best therapeutic strategies. Med Oncol 34:1–8
14. Kim BK, Han KH, Park YN, Park MS, Kim KS, Choi JS et al (2008) Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol 97(3):246–252
15. Banerjee S, Wang DS, Kim HJ, Sirlin CB, Chan MG, Korn RL et al (2015) A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology 62(3):792–800
16. Renzulli M, Brocchi S, Cucchetti A, Mazzotti F, Mosconi C, Sportoletti C et al (2016) Can current preoperative imaging be used to detect microvascular invasion of hepatocellular carcinoma? Radiology 279(2):432–442
17. Zhang W, Liu L, Wang P, Wang L, Liu L, Chen J et al (2018) Preoperative computed tomography and serum α-fetoprotein to predict microvascular invasion in hepatocellular carcinoma. Medicine (Baltimore) 97(27):e11402
18. Shehta A, Farouk A, Elghawalby AN, Elshobary M, Aboelenin A, Fouad A et al (2021) Outcomes of hepatic resection for hepatocellular carcinoma associated with portal vein invasion. J Surg Res 266:269–283
19. Strasberg SM, Phillips C (2013) Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg 257(3):377–382
20. Elhanafy E, Aboelinin M, Said R, Elmahdy Y, Aboelenin A, Fouad A et al (2023) Outcomes of liver resection for huge hepatocellular carcinoma exceeding 10 cm in size: a single center experience. Am J Surg 225(6):1013–1021
21. Cong W-M, Bu H, Chen J, Dong H, Zhu Y-Y, Feng L-H et al (2016) Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. World J Gastroenterol 22(42):9279
22. Granata V, Fusco R, Setola SV, Picone C, Vallone P, Belli A, Incollingo P, Albino V, Tatangelo F, Izzo F, Petrillo A (2019) Microvascular invasion and grading in hepatocellular carcinoma: correlation with major and ancillary features according to LIRADS. Abdominal Radiol 15(44):2788–2800
23. Wu S, Yang L, Bi X, Lin Y, Deng W, Jiang T, Li M, Xie Y (2023) Attach importance to antiviral therapy in patients with hepatocellular carcinoma caused by hepatitis virus. Gastroenterol Endosc 1(1):5–10
24. Wu TH, Yu MC, Chen TC, Lee CF, Chan KM, Wu TJ, Chou HS, Lee WC, Chen MF (2012) Encapsulation is a significant prognostic factor for better outcome in large hepatocellular carcinoma. J Surg Oncol 105(1):85–90
25. Ariizumi SI, Kitagawa K, Kotera Y, Takahashi Y, Katagiri S, Kuwatsuru R, Yamamoto M (2011) A non-smooth tumor margin in the hepatobiliary phase of gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging predicts microscopic portal vein invasion, intrahepatic metastasis, and early recurrence after hepatectomy in patients with hepatocellular carcinoma. J Hepatobiliary Pancreat Sci 18(4):575–585
26. Adachi E, Maeda T, Kajiyama K, Kinukawa N, Matsumata T, Sugimachi K, Tsuneyoshi M (1996) Factors correlated with portal venous invasion by hepatocellular carcinoma: univariate and multivariate analyses of 232 resected cases without preoperative treatments. Cancer Interdiscip Int J Am Cancer Soc 77(10):2022–2031
27 Witjes CD, Willemssen FE, Verheij J, Van Der Veer SJ, Hansen BE, Verhoef C, de Man RA, IJzermans JN (2012) Histological differentiation grade and microvascular invasion of hepatocellular carcinoma predicted by dynamic contrast-enhanced MRI. J Magn Reson Imaging 36(3):641–647
28. Matsui O, Kobayashi S, Sanada J, Kouda W, Ryu Y, Kozaka K, Kitao A, Nakamura K, Gabata T (2011) Hepatocelluar nodules in liver cirrhosis: hemodynamic evaluation (angiography-assisted CT) with special reference to multi-step hepatocarcinogenesis. Abdom Imaging 36:264–272
29. Kim H, Park MS, Choi JY, Park YN, Kim MJ, Kim KS, Choi JS, Han KH, Kim E, Kim KW (2009) Can microvessel invasion of hepatocellular carcinoma be predicted by pre-operative MRI? Eur Radiol 19:1744–1751
30. Miyata R, Tanimoto A, Wakabayashi G, Shimazu M, Nakatsuka S, Mukai M, Kitajima M (2006) Accuracy of preoperative prediction of microinvasion of portal vein in hepatocellular carcinoma using superparamagnetic iron oxide-enhanced magnetic resonance imaging and computed tomography during hepatic angiography. J Gastroenterol 41:987–995
31. Nishie A, Yoshimitsu K, Asayama Y, Irie H, Tajima T, Hirakawa M, Ishigami K, Nakayama T, Kakihara D, Nishihara Y, Taketomi A (2008) Radiologic detectability of minute portal venous invasion in hepatocellular carcinoma. Am J Roentgenol 190(1):81–87
32. Banerjee S, Wang DS, Kim HJ, Sirlin CB, Chan MG, Korn RL, Rutman AM, Siripongsakun S, Lu D, Imanbayev G, Kuo MD (2015) A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology 62(3):792–800
33. Cannella R, Taibbi A, Porrello G, Burgio MD, Cabibbo G, Bartolotta TV (2020) Hepatocellular carcinoma with macrovascular invasion: multimodality imaging features for the diagnosis. Diagn Interv Radiol 26(6):531
34. Eguchi S, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, Kanematsu T (2010) Predictor for histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. World J Surg 34:1034–1038
35. Ueda K, Matsui O, Kawamori Y, Nakanuma Y, Kadoya M, Yoshikawa J, Gabata T, Nonomura A, Takashima T (1998) Hypervascular hepatocellular carcinoma: evaluation of hemodynamics with dynamic CT during hepatic arteriography. Radiology 206(1):161–166

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