Journal of Hepatocellular Carcinoma

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Patterns, Risk Factors, and Outcomes of Recurrence After Hepatectomy for Hepatocellular Carcinoma with and without Microvascular Invasion

Yang Yu[1,*], Xiao-Hui Wang[2,*], Wen-Jie Hu[1], De-Hua Chen[1], Zi-Li Hu[3], Shao-Qiang Li[1]

[1]Hepatic Pancreatobiliary Surgery Center, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, 510080, People's Republic of China; [2]Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University) Changsha, Hunan Province, 410005, People's Republic of China; [3]Department of Liver Surgery, Sun Yat-Sen University Cancer Center, Guangdong, 510060, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Shao-Qiang Li, Hepatic Pancreatobiliary Surgery Center, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, 510080, People's Republic of China, Tel +86-020-87755766-8214, Fax +86-020-87755766-8661, Email lishaoq@mail.sysu.edu.cn

Purpose: The patterns and risk factors of postsurgical recurrence of patient with hepatocellular carcinoma (HCC) with microvascular invasion (MVI) are not clarified. This study aimed to decipher and compare the postoperative recurrent patterns and the risk factors contributing to recurrence between MVI positive ($MVI^{(+)}$) and MVI negative ($MVI^{(-)}$) HCC after hepatectomy.

Patients and methods: Patients with HCC who underwent hepatectomy in three Chinese academic hospitals between January 1, 2009, and December 31, 2018, were enrolled. Recurrent patterns included early (≤2 years) or late (>2 years) recurrence, recurrent sites and number, and risk factors of recurrence were compared between the $MVI^{(+)}$and $MVI^{(-)}$ groups by propensity score–matching (PSM).

Results: Of 1756 patients included, 581 (33.1%) were $MVI^{(+)}$, and 875 (49.8%) patients developed early recurrence. Compared with the $MVI^{(-)}$ group, the $MVI^{(+)}$ group had a higher 2-year recurrence rate in the PSM cohort (hazard ratio [HR], 1.82; 95% confidence interval [CI], 1.59–2.10; $P < 0.001$), and more patients with multiple tumor recurrence. Patients with early recurrence in the $MVI^{(+)}$ group had a worse overall survival (OS) than those in the $MVI^{(-)}$ group (HR, 1.24; 95% CI, 1.02–1.50; $P = 0.034$). Resection margin (RM) ≤1.0 cm is a surgical predictor of early recurrence for the $MVI^{(+)}$ group (HR, 0.68; 95% CI, 0.54–0.87; $P = 0.002$), but not for the $MVI^{(-)}$ group.

Conclusion: Compared to $MVI^{(-)}$ HCC, $MVI^{(+)}$ HCC tends to be early, multiple recurrence and lung and lymph node metastasis after resection. RM ≤1.0 cm is a surgical risk factor of early recurrence for patient with MVI.

Keywords: hepatocellular carcinoma, microvascular invasion, recurrence patterns, risk factors, outcomes

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. It is the second leading cancer-related death in China.[1] Liver resection is the potential curative treatment for HCC with good liver function reserve. As the refinement of surgical technique and improvement of pre-operative evaluation, the postsurgical morbidity and mortality of HCC have been substantially improved.[2,3] However, the recurrent rate remains high after resection. The 5-year recurrent rate ranged from 57.7 to 70% even for patients with early HCC.[4–6]

Microvascular invasion (MVI), defined as tumor cells in the lumen covered by epithelial cells, is a malignant feature of HCC.[7] The incidence of MVI in resected HCC specimens ranged from 15 to 57.1%.[8] In the past 10 years, increasing evidence showed that MVI is a pivotal risk pathologic trait contributing to tumor recurrence after resection of HCC.[9–13]

Received: 6 September 2023
Accepted: 24 April 2024
Published: 8 May 2024

However, these previous reports mainly focused on the risk of recurrence of MVI, the patterns and risk factors of recurrence after liver resection for HCC with MVI ($MVI^{(+)}$ HCC), and whether they are different from $MVI^{(-)}$ HCC are not clarified.

In the present study, we aimed to decipher and compare the postoperative recurrent patterns and the risk factors contributing to recurrence between $MVI^{(+)}$ HCC and $MVI^{(-)}$ HCC after liver resection based on a multicenter HCC database.

Methods

Patient's Cohort

Consecutive patients with HCC who underwent initially liver resection with curative intent at three Chinese academic hospitals: the First Affiliated Hospital of Sun Yat-sen University (January 1, 2009 –December 31, 2018), the Cancer Center of Sun Yat-sen University (January 1, 2010-December, 2014) and the Hunan Provincial People's Hospital (January 1, 2010-December 31, 2016) were collected retrospectively. Only patients with Barcelona Clinic Liver Cancer (BCLC) stage 0/A-B HCC were eligible for this study, and all patients were fully evaluated for surgical safety before surgery. The exclusion criteria were as follows: (1) Patients with macroscopic portal vein or hepatic vein tumor thrombus; (2) Patients died within 30 days after operation; (3) Patients with microscopic positive resection margin (RM); (4) HCC combined with intrahepatic cholangiocarcinoma; (5) Patients had no MVI description on pathological report; (6) Patients whose recurrent information was absent. (7) Patients with any preoperative anticancer treatments.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethic Committee of the three hospitals (approval number: 2021–533). Written informed consent was obtained from adult patients and from parents or legal guardians of patients under 18 years of age. This study was censored on June 28, 2020.

Clinicopathologic Data

Baseline variables were evaluated based on patient-, tumor- and surgery-related factors. Patient-related factors included age, sex, hepatitis B virus antigen (HBsAg), presence of cirrhosis, albumin to bilirubin (ALBI) grade,[14] preoperative hemoglobin level, platelet count, alanine aminotransferase (ALT), neutrophil-to-lymphocyte ratio (NLR). NLR was obtained by neutrophil count divided by lymphocyte count. The cut-off value of NLR was determined by the Youden index calculated by the receiver operating characteristic (ROC) curve. Cirrhosis was confirmed by postoperative pathology. Tumor factors included tumor size, number, tumor capsule, tumor differentiation (histological grade), preoperative serum alpha fetoprotein (AFP), and presence of MVI. The histological grade of the tumor was assigned according to the Edmondson–Steiner grading system.[15] MVI was defined as tumor cells in the lumen covered by epithelial cells. It was confirmed by two senior pathologists. Surgical factors included type of resection (anatomical vs non-anatomical), intraoperative blood loss, blood transfusion and width of RM. Anatomical resection (AR) referred to resection of the tumor-involved segment/section, together with its portal pedicle branch. Non-anatomical resection (NAR) was defined as tumor resection with a negative tumor margin regardless of segment or section anatomy.[16] RM referred to the nearest distance from the tumor boundary to the resection plain. For patients with multiple tumors, the shortest distance from main tumor or daughter nodules to the resection plain was adopted. RM was classified into two categories: RM > 1cm and RM ≤ 1cm, which was in accordance with previous reports.[17–19] Blood transfusion referred to the transfusion of packed red blood cells during excessive intraoperative bleeding or postoperative bleeding complications. Transfusions of platelets, fresh-frozen plasma, and albumin were not included. Preoperative HCC staging was based on the BCLC staging classification.[20]

Risk factors of recurrence were evaluated among these patient-, tumor- and surgery-related variables. Early recurrence referred to tumor recurrence within 2 years after operation, whereas late recurrence defined tumor recurrence after 2 years.[21,22]

Postoperative Follow-Up

Patients after operation were followed up every 1–2 months for the first 6 months, and every 3 months thereafter in each hospital. AFP levels and liver biochemistry were assessed, and ultrasonography was carried out in the outpatient clinic. Chest and abdominal contrast-enhanced CT were performed every 6 months. If ultrasound or CT examination revealed

a new lesion and the AFP level was raised, recurrence was considered. If ultrasonography showed a new lesion but the AFP level was normal, contrast-enhanced ultrasonography and CT or MRI were performed. If two enhanced imaging findings indicated HCC, it was defined as a recurrence. Extrahepatic metastasis was diagnosed by contrast-enhanced CT or MRI or combining with AFP. Ultrasound or CT guided biopsy was performed if necessary. Recurrent HCC was treated by radiofrequency ablation (RFA), repeated liver resection, transcatheter arterial chemoembolization (TACE) alone or combined with sorafenib or sorafenib alone, and supportive care according to the location and number of tumors, and the patient's liver function after fully discussing with patients and their families.

Statistical Analysis

Propensity score-matching (PSM) analysis was used to reduce potential confounding and the effect of selection bias by equating the two groups based on the following 18 variables: age, sex, tumor size, tumor number, cirrhosis, resection margin, type of resection, blood loss, transfusion, tumor capsule, differentiation, platelet, hemoglobin, HBsAg, AFP, ALT, NLR, ALBI grade. For propensity score matching, a nearest-neighbor 2:1 matching scheme with a caliper size of 0.2 was used (Supplementary Figure 1). HCC recurrence and overall survival (OS) were compared between the two groups in a propensity score-matched cohort using a Log rank test.

The Mann–Whitney *U*-test or student *t* test was used to compare continuous data between groups and the χ^2 test or Fisher's exact test for discrete data. Cumulative recurrence rate and OS rate were calculated by the Kaplan–Meier method. Cox proportional hazard model was used to identify risk factors associated with early and late recurrence. Variables with P values less than 0.1 on univariate analysis were selected for the multivariable analyses using a forward stepwise method. The statistical analyses were performed using the Statistical Package for the Social Science (SPSS) software (version 22.0, SPSS Inc., Chicago, IL, USA) for Windows and R software for Windows (version 3.6.4; http://www.r-project.org). P value <0.05 was considered significant difference.

Results

Demographic and Clinicopathological Data of the Cohort

A total of 2663 patients underwent liver resection for HCC in this study period. Of these, 1756 patients were included (Figure 1). Most patients (81.3%) were HBsAg positive, and 71.4% were with cirrhosis. A total of 1446 (82.3%) patients were BCLC 0-A stage. There were 581 (33.1%) patients with MVI, and they were allocated to the $MVI^{(+)}$ group, others 1175 (66.9%) patients without MVI, and they were allocated to the $MVI^{(-)}$ group. For patients in the entire cohort, the $MVI^{(+)}$ group contained more younger patients (P = 0.022); more patients with liver functions of ALBI grade 2 and 3 (P < 0.001); larger tumor (P < 0.001); higher preoperative AFP level (P < 0.001); incomplete tumor capsule (P < 0.001); poor tumor cell differentiation (P < 0.001); higher NLR (P < 0.001); and more patients needed blood transfusion (P < 0.001) compared with the $MVI^{(-)}$ group. Propensity score–matching (2:1 matching) analysis generated two new cohorts of 778 and 528 patients in the $MVI^{(-)}$ and $MVI^{(+)}$ groups, respectively, and the characteristics of the two groups were balanced, with the standardized mean difference less than 10% for all baseline variables (Supplementary Figure 2). The baseline clinicopathological data of patients in the entire cohort and in the matched cohort were shown in Table 1.

Early and Late Recurrence in the $MVI^{(+)}$ Group and $MVI^{(-)}$ Group

During a median follow-up of 32.4 months, 875 (49.8%) patients developed early recurrence, 384 (66.1%, [384/581]) patients in the $MVI^{(+)}$ group, and 491 (41.8%, [491/1175]) in the $MVI^{(-)}$ group (P < 0.001). There were 150 (39.1%, [150/384]) patients recurred within 3 months after surgery in the $MVI^{(+)}$ group, which were 1.7-fold higher than those in the $MVI^{(-)}$ group (P < 0.001) (Supplementary Figure 3). The cumulative 2-year recurrence rate of patients with MVI was markedly higher than those without MVI both in the entire cohort (Figure 2A, hazard ratio [HR], 1.96; 95% confidence interval [CI], 1.73–2.22; P < 0.001) and in the PSM cohort (Figure 2B, HR, 1.82; 95% CI, 1.59–2.10; P < 0.001). Of 687 patients with follow-up period longer than 2 years and without early recurrence in the entire cohort, 144 patients were in the $MVI^{(+)}$ group and 543 in the $MVI^{(-)}$ group. Out of 687 patients, 176 (25.6%) patients suffered from late recurrence, 40 (27.8%, [40/144]) patients in the $MVI^{(+)}$ group and 136 (25.0%, [136/543]) in the $MVI^{(-)}$ group (P = 0.504). The cumulative 5-year recurrence rates were comparable between patients

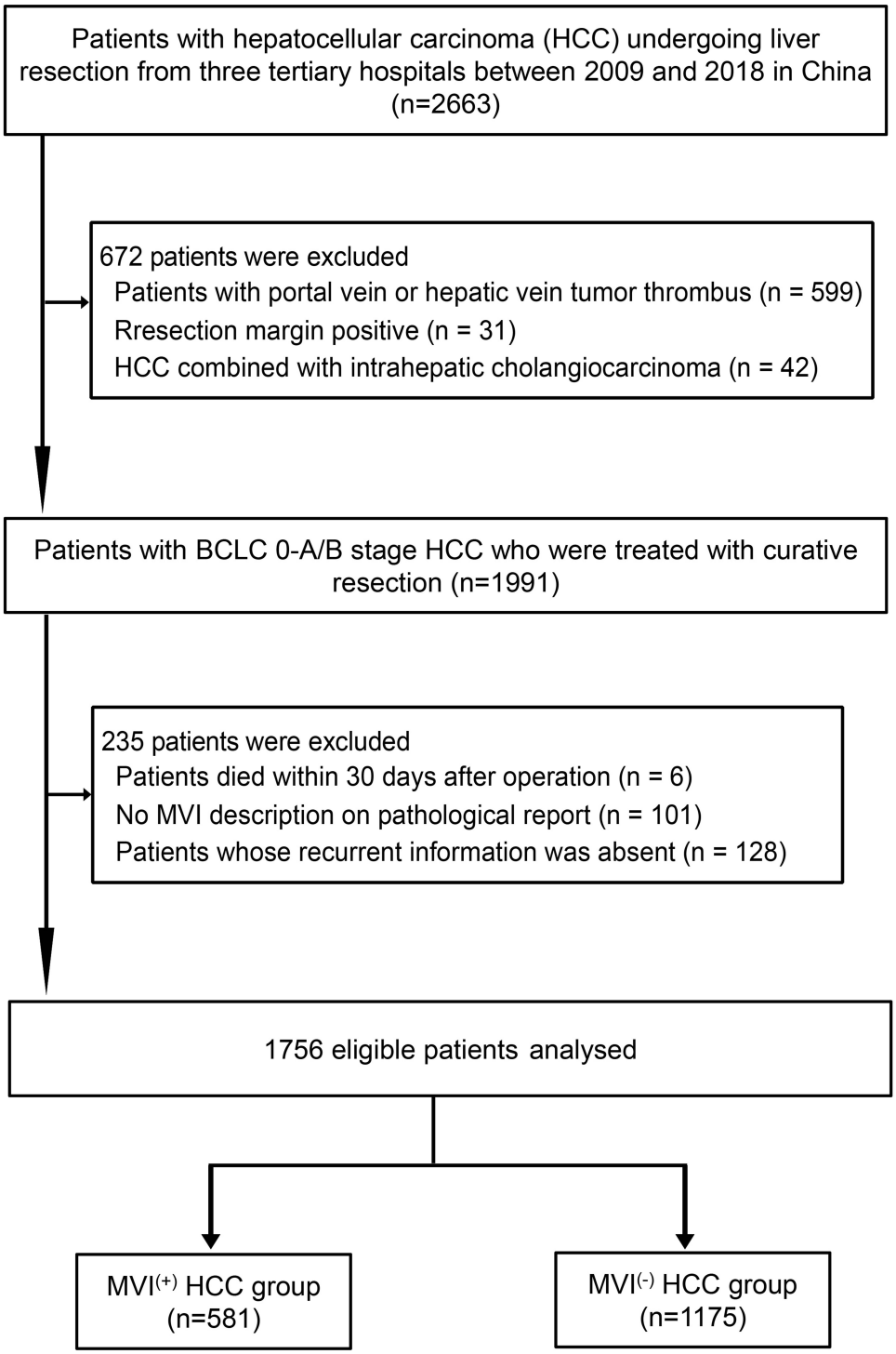

Figure 1 Flow chart of patient selection.

with MVI and those without MVI in the subset of patients without early recurrence both in the entire cohort (Figure 2C, HR, 1.35; 95% CI, 0.95–1.92; P = 0.096) and in the PSM cohort (Figure 2D, HR, 1.37; 95% CI, 0.93–2.02; P = 0.114).

Site and Number of Recurrent Tumors at Early and Late Recurrence

Of the 875 patients with early recurrence, 621 (71.0%) were only liver remnant recurrence, 94 (10.7%) were only extrahepatic metastasis, and 160 (18.3%) were both intrahepatic and extrahepatic recurrence. The recurrent sites in terms

Table 1 Baseline Characteristics of Patients with Hepatocellular Carcinoma (HCC) in Microvascular Invasion (MVI) Positive and Negative Groups

Characteristics	Entire cohort			Propensity score-matched cohort (2:1 ratio)		
	MVI(-) group (n=1175)	MVI(+) group (n=581)	*P* value	MVI(-) group (n=778)	MVI(+) group (n=528)	*P* value
Age*, years	52.0 [16–86]	50.0 [15–88]	0.022	51.0 [16–85]	50.0 [15–88]	0.488-
Sex male, n (%)	1012 (86.1)	519 (89.3)	0.073	688 (88.4)	469 (88.8)	0.826
HBsAg positive, n (%)	949 (80.8)	479 (82.4)	0.396	634 (81.5)	434 (82.2)	0.746
Cirrhosis yes, n (%)	835 (71.1)	419 (72.1)	0.646	552 (71.0)	377 (71.4)	0.860
ALT*, U/L	36.5 [6.8–280.2]	37.0 [7.5–305.3]	0.328	36.8 [8.0–280.2]	37.0 [7.5–305.3]	0.645
CRE*, μmol/L	71.2[32.0–127.3]	71.6[32.5–145.8]	0.306	71.2[32.0–127.3]	70.3[31.5–140.0]	0.712
Hemoglobin*, g/dL	14.0 [10.0–19.6]	13.9 [9.8–19.1]	0.317	14.0 [10.0–19.6]	14.0 [10.2–19.1]	0.957
Platelet*, 10^9/L	179 [65–468]	197 [77–565]	<0.001	186 [65–468]	191 [77–565]	0.308
NLR*	1.83 [0.2–7.9]	2.11 [0.1–8.6]	0.037	1.91 [0.2–7.9]	2.01 [0.1–8.1]	0.469
Blood loss *, mL	300[100–1500]	300[100–1800]	<0.001	300[100–1500]	300[100–1800]	0.130
Tumor size *, cm	6.0 [1.0–22.0]	7.4 [1.0–23.0]	<0.001	6.8 [1.0–22.0]	7.0 [1.0–22.0]	0.170
Tumor number, n (%)			0.374			0.241
Solitary	965 (82.1)	467 (80.3)		646 (83.0)	425 (80.5)	
multiple	210 (17.9)	114 (19.7)		132 (17.0)	103 (19.5)	
Tumor capsule, n (%)			<0.001			0.375
Complete	899 (76.5)	348 (59.9)		518 (66.6)	339 (64.2)	
Incomplete	276 (23.5)	233 (40.1)		260 (33.4)	189 (35.7)	
ALBI grade, n (%)			<0.001			0.223
Grade 1	762 (64.9)	297 (51.1)		455 (58.5)	286 (54.2)	
Grade 2	411 (35.0)	284 (48.9)		321 (41.3)	239 (45.3)	
Grade 3	2 (0.1)	9 (1.5)		2 (0.2)	3 (0.5)	
AFP, n (%)			<0.001			0.423
≤400 μg /L	810 (68.9)	286 (54.2)		433 (55.7)	282 (53.4)	
>400 μg /L	365 (31.1)	242 (45.8)		345 (44.3)	246 (46.6)	
BCLC stage, n (%)			0.323			0.255
0-A	975 (83.0)	471 (81.2)		651 (83.7)	429 (81.3)	
B	200 (17.0)	110 (18.9)		127 (16.3)	99 (18.7)	
Type of resection, n (%)			<0.001			0.403
Anatomic	396 (33.7)	262 (45.1)		312 (40.1)	224 (42.4)	
Non-anatomic	779 (66.3)	319 (54.9)		466 (59.9)	304 (57.6)	
Resection margin, n (%)			0.713			0.807
≤1.0 cm	805 (68.5)	393 (67.6)		521 (67.0)	357 (67.6)	
>1.0 cm	370 (31.5)	188 (32.4)		257 (33.0)	171 (32.4)	
Blood transfusion, n (%)			<0.001			0.282
No	968 (82.3)	429 (73.8)		612 (78.6)	402 (76.1)	
Yes	207 (17.7)	152 (26.2)		166 (21.4)	126 (23.9)	
Differentiation, n (%)			<0.001			0.240
I-II	1059 (90.1)	444 (76.4) 137 (23.6)		653 (83.9)	430 (81.4)	
III-IV	116 (9.9)			125 (16.1)	98 (18.6)	

Notes: Data are n (%) and ranges. *Presented as median and ranges.

Abbreviations: HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; CRE, creatinine; NLR, neutrophil to lymphocyte ratio; ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer;

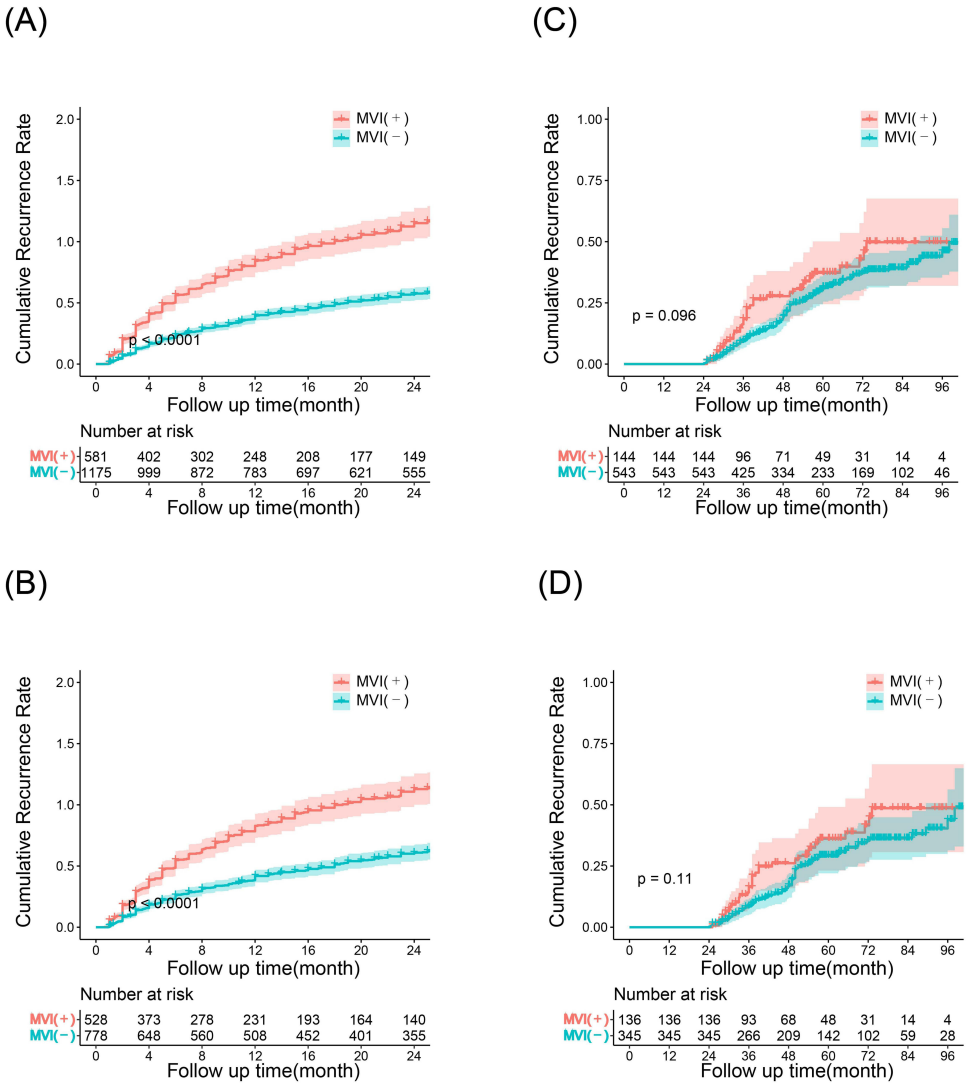

Figure 2 Cumulative recurrence curves of hepatocellular carcinoma (HCC) patients with or without microvascular invasion (MVI). The cumulative 2-year recurrence rate of patients with and without MVI in the entire cohort (Figure 2A) and in the propensity score-matched cohort (Figure 2B), and the cumulative 5-year recurrence rates of patients with late recurrence in the entire cohort (Figure 2C) and in the propensity score-matched cohort (Figure 2D).

of intrahepatic, extrahepatic and both intrahepatic and extrahepatic recurrence between the $MVI^{(+)}$ group and $MVI^{(-)}$ group were no difference (P = 0.097). A total of 308 (35.2%) patients were solitary recurrence, the proportion of patients with solitary recurrent tumor was lower (30.2% vs 39.4%), but multiple recurrent foci (>3) was markedly higher (53.4% vs 38.5%, P < 0.001) in the $MVI^{(+)}$ group than in the $MVI^{(-)}$ group (Table 2).

Of 176 patients developed late recurrence, the occurrence rate of intrahepatic, extrahepatic and both intrahepatic and extrahepatic recurrence of patients with MVI and without MVI were also no difference (P = 0.504). A total of 104 (59.1%) patients whose late recurrent tumor were solitary. The proportion of patients with multiple recurrent foci (>3) was low and comparable between patients with MVI and those without MVI (17.5% vs 20.5%, P = 0.684) (Table 2).

A total of 149 (8.5%), 67 (3.8%), and 49 (2.8%) patients developed lung, peritoneal organs (peritoneum, omentum, adrenal grand) and regional lymph node metastasis in the entire cohort, respectively. Lung and regional lymph node metastasis was significantly higher in the $MVI^{(+)}$ group than in the $MVI^{(-)}$ group (lung: 14.3% vs 5.6%, P < 0.001; lymph node: 4.3% vs 2.0%, P = 0.007) (Supplementary Table 1).

Table 2 Characteristics and Treatments of Recurrent Tumors

Variables	Early Recurrence				Late Recurrence			
	Total No. (n=875)	$MVI^{(+)}$ (n=384)	$MVI^{(-)}$ (n=491)	*P* value	Total No. (n=176)	$MVI^{(+)}$ (n=40)	$MVI^{(-)}$ (n=136)	*P* value
Site of recurrence								
Intrahepatic	621 (71.0)	262 (68.2)	359 (73.1)	0.097	124 (73.9)	27 (67.5)	104 (76.4)	0.504
Extrahepatic	94 (10.7)	40 (10.4)	55 (11.2)		23 (13.1)	7 (17.5)	16 (11.8)	
Both	160 (18.3)	82 (21.6)	77 (15.7)		29 (13.0)	6 (15.0)	16 (11.8)	
Total number of recurrent foci								
Solitary	308 (35.2)	116 (30.2)	193 (39.3)	<0.001	104 (59.1)	26 (65.0)	78 (57.4)	0.684
2–3	171 (19.5)	63 (16.4)	109 (22.2)		37 (21.0)	7 (17.5)	30 (22.1)	
>3	389 (45.3)	205 (53.4)	189 (38.5)		35 (19.9)	7 (17.5)	28 (20.5)	
Treatment for recurrent tumor								
Curative treatment	300 (34.3)	112 (29.2)	189 (38.5) ‡	0.015	99 (56.3)	22 (55.0)	77 (56.6)§	0.925
Palliative treatment	398 (45.5)	187 (48.7)	210 (42.8)		55 (33.0)	13 (32.5)	45 (33.1)	
Supportive care	177 (20.2)	85 (22.1)	92 (18.7)		22 (10.7)	5 (12.5)	14 (10.3)	

Note: Curative treatment includes repeat resection, radiofrequency ablation and salvage liver transplantation; Palliative treatment includes transcatheter arterial chemoembolization (TACE) alone or with sorafenib or sorafenib only; ‡included 1 patient underwent liver transplantation. § included 2 patients underwent salvage liver transplantation. Values in parentheses are percentage.

Impact of Early and Late Recurrence on OS in the $MVI^{(+)}$ Group and $MVI^{(-)}$group

In the subset of patients with early recurrence in the entire cohort, the proportion of patients with MVI receiving curative treatments was lower than those without MVI (29.2% vs 38.5%, P = 0.015) (Table 2). The 5-year OS rate of patients with MVI was significantly lower than those without MVI both in the entire cohort (Figure 3A, HR, 1.27; 95% CI, 1.07–1.52; P = 0.007) and in the PSM cohort (Figure 3B, HR, 1.24; 95% CI, 1.02–1.50; P = 0.034). In the subset of patients with late recurrence, more patients were solitary recurrence compared to those with early recurrence. The proportion of patients received curative treatments was comparable (55.0% vs 55.6%), thereby achieving good comparable 5-year OS rates between patients with and without MVI both in the entire cohort (Figure 3C, HR, 1.84; 95% CI, 0.90–3.76; P = 0.091) and in the PSM cohort (Figure 3D, HR, 1.96; 95% CI, 0.90–4.28; P = 0.087).

Risk Factors Associated with Recurrence of $MVI^{(+)}$ HCC and $MVI^{(-)}$ HCC

Univariate and multivariate Cox regression models were performed to investigate the risk factors contributing to recurrence in the entire cohort (Supplementary Table 2). Multivariate Cox analysis identified that distinct risk factors contribute to early and late recurrence. Patient factors (age > 50 years, HBsAg positive, NLR > 1.9), tumor factors (AFP > 400 μg/L, tumor size >5.0cm, multiple tumors, poor tumor differentiation and MVI positive), and surgical factors (RM ≤ 1.0 cm and blood transfusion) were independent predictors of early recurrence. Male patients, cirrhosis, ALBI grade of 2 and 3, AFP > 400 μg/L, poor tumor differentiation were risk factors related to late recurrence. Among these factors, MVI was the most potential risk factor contributing to early recurrence (HR, 1.66; 95% CI, 1.44–1.91; P < 0.001). Cirrhosis was the key independent risk factor for late recurrence (HR, 1.97; 95% CI, 1.43–2.72; P < 0.001) (Table 3).

Subgroup univariate (Supplementary Table 3 and Table 4) and multivariate analysis (Table 3) for the $MVI^{(+)}$ group and $MVI^{(-)}$ group showed that tumor traits (AFP, tumor size and tumor number) as the predictors of early recurrence were the same in both groups. Among patient factors, age <50 years and cirrhosis were the independent risk factors contributing to early recurrence in the $MVI^{(+)}$ group; whereas age, HBsAg and NLR were the predictors of early recurrence in the $MVI^{(-)}$ group. As to the surgical factors, only RM ≤1.0cm was the risk factor of early recurrence for patients with MVI, and blood transfusion was the only surgical risk factor for those without MVI. Cirrhosis and tumor differentiation were the independent risk factors for late recurrence in the $MVI^{(+)}$ group. Patient-related factors (age, sex, HBsAg, cirrhosis, ALBI grade) and AFP were the predictors for late recurrence in the $MVI^{(-)}$ group. Cirrhosis was still the most potential risk factor for late recurrence in both $MVI^{(+)}$ group and $MVI^{(-)}$ group (Table 3).

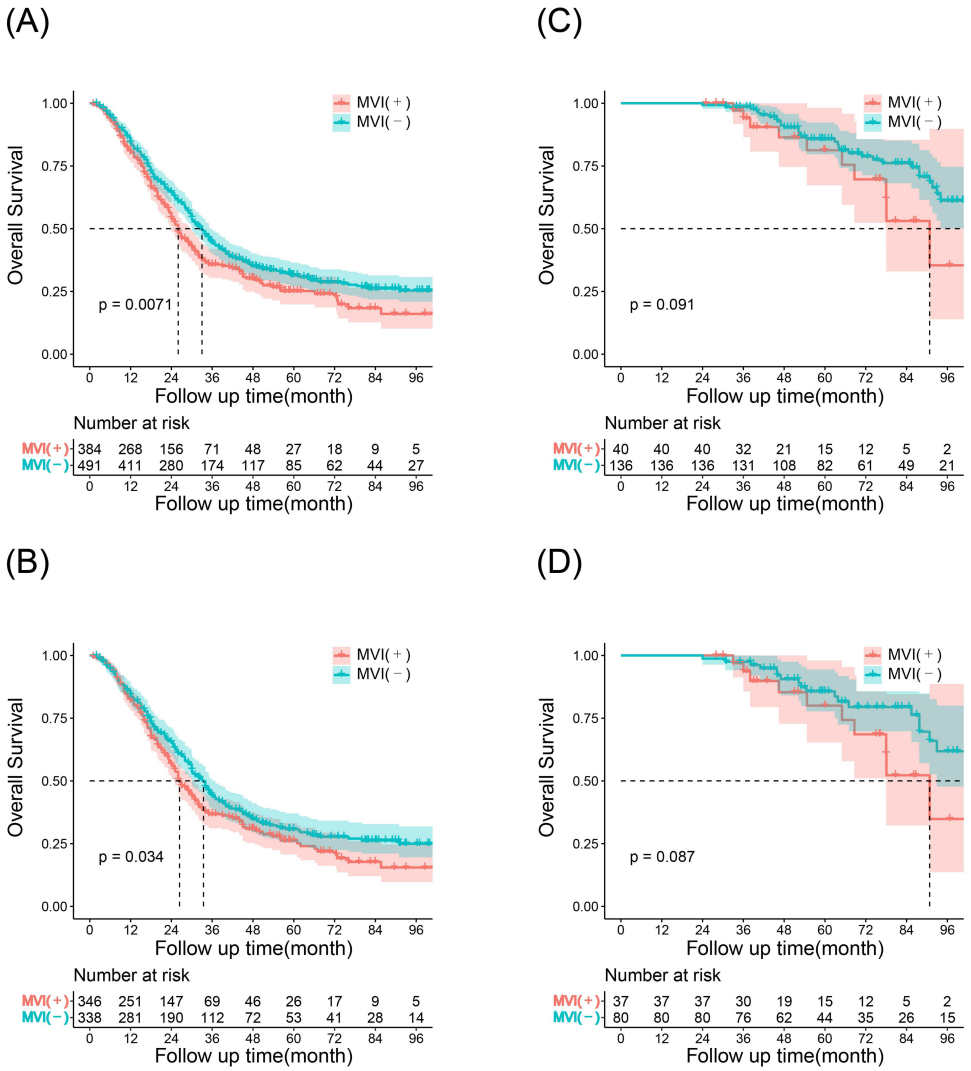

Figure 3 Overall survival (OS) curves of patients with early and late recurrence in the subset of patients with or without microvascular invasion. Overall survival in the entire cohort (**3A**) and in the propensity score-matched cohort (**3B**) of patients with early recurrence, and overall survival in the entire cohort (**3C**) and in the propensity score-matched cohort (**3D**) of patients with late recurrence.

Discussion

In this large cohort of patients with BCLC stage 0-A/B HCC, the occurrence rate of MVI was 33.1%. MVI was a potential risk factor contributing to early recurrence, but not to late recurrence after resection, which was consistently observed in unadjusted, propensity score-matched, multivariable and competing risk analyses.

The recurrent time mode can be classified into two distinct types: early and late recurrence. There is no consensus regarding the time point between early and late recurrence.[23,24] A 2-year after resection was the predominant threshold in clinical practice.[21,22] The multivariable analyses of the present study showed that tumor factors and surgical factors independently affected recurrence within 2 years after resection, liver underlying diseases (mainly cirrhosis) are the key risk factors of late recurrence (Table 3). This evidence supported the notion that early recurrence was caused by micro-metastasis of the primary tumor, and late recurrence was mainly caused by a new tumor with different clone originated in the diseased liver.[25] Therefore, 2-year as the cut-off value to clinically differentiate early and late recurrence is reasonable.

In the present study, our results showed that 875 (49.8%) patients developed early recurrence, and the 2-year recurrence rate was 66.1% in the $MVI^{(+)}$ group. Notably, there were 150 (39.1%) patients suffered from recurrence within 3 months after resection in the $MVI^{(+)}$ group. All of these were significantly higher than those in the $MVI^{(-)}$ group.

Table 3 Risk Factors Associated with Early and Late Tumor Recurrence Identified by Cox Multivariate Analysis in the Entire Cohort, $MVI^{(+)}$ and $MVI^{(-)}$ Subset

Variables	Entire cohort (n=1756)		$MVI^{(+)}$ group (n=581)		$MVI^{(-)}$ group (n=1175)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Early recurrence						
Age (year), ≤50 vs >50	0.806 (0.703–0.924)	0.020	0.809 (0.661–0.991)	0.040	0.798 (0.664–0.959)	0.016
HBsAg, positive vs negative	1.229 (1.021–1.480)	0.029	NA		1.396 (1.083–1.799)	0.010
Cirrhosis, yes vs no	NA		1.765 (1.253–1.982)	<0.001	NA	
NLR, >1.9 vs ≤1.9†	1.230 (1.067–1.417)	0.004	NA		1.505 (1.250–1.811)	<0.001
AFP (μg/L), >400 vs ≤400	1.376 (1.195–1.585)	<0.001	1.422 (1.161–1.742)	0.001	1.000 (1.000–1.000)	<0.001
Tumor size (cm), >5 vs ≤5	1.448 (1.223–1.715)	<0.001	1.469 (1.124–1.919)	0.005	1.314 (1.067–1.618)	0.001
Tumor number, multiple vs solitary	1.541 (1.310–1.813)	<0.001	1.222 (1.056–1.416)	0.007	1.542 (1.340–1.773)	<0.001
Differentiation, III-IV vs I-II	1.352 (1.215–1.504)	<0.001	NA		NA	
MVI, positive vs negative	1.655 (1.435–1.909)	<0.001	-		-	
Blood transfusion, yes vs no	1.307 (1.115–1.531)	0.001	NA		1.658 (1.336–2.058)	<0.001
Resection margin, >1cm vs ≤1cm	0.816 (0.701–0.955)	0.010	0.684 (0.538–0.870)	0.002	NA	
Late recurrence						
AFP (μg/L), >400 vs ≤400	0.415 (0.279–0.618)	<0.001	NA		0.350 (0.209–0.586)	<0.001
Differentiation, III-IV vs I-II	1.644 (1.274–2.132)	<0.001	1.687 (1.255–1.973)	0.041	NA	
Sex, male vs female	0.517 (0.291–0.919)	0.024	NA		0.485 (0.253–0.927)	0.029
HBsAg, positive vs negative	NA		NA		1.940 (1.171–3.215)	0.010
Cirrhosis, yes vs no	1.970 (1.428–2.717)	<0.001	2.753 (1.380–5.492)	0.004	2.014 (1.413–20,871)	<0.001
ALBI grade, 2–3 vs 1	1.585 (1.161–2.164)	0.004	NA		1.703 (1.184–2.449)	0.004

Notes: †1.9 was the median value of NLR in the primary cohort.
Abbreviations: HR, hazard ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein, MVI, microvascular invasion; ALBI, albumin to bilirubin.

These indicated that $MVI^{(+)}$ HCCs are prone to be early recurrence, especially the first 3-month after liver resection. Follow-up protocol of every 3–4 months for the first year after operation recommended by the European Association for the Study of the Liver (EASL)[26] may not be suitable for patients with $MVI^{(+)}$ HCC, a more stringent postoperative surveillance for early recurrence of $MVI^{(+)}$ HCC should be considered.

Liver remnant is the most common site of HCC recurrence, accounting for 54% to 80.1% of patients with recurrence.[23,27–29] In the patients with early recurrence, 71.0% of recurrence involved liver only and 18.3% was both intrahepatic and extrahepatic recurrence in this study. The occurrence of both intrahepatic and extrahepatic early recurrence was higher in the $MVI^{(+)}$ group than in the $MVI^{(-)}$ group (21.6% vs 15.6%), but it was no statistical difference (P = 0.097). However, the proportion of patients with early multiple recurrence (>3) was significantly higher in the $MVI^{(+)}$ group than in the $MVI^{(-)}$ group (53.4% vs 38.5%).

In the patients with late recurrence, nearly 60% of patients whose recurrent tumors were solitary. The proportion of patients with multiple recurrence (>3) was low and comparable between the $MVI^{(+)}$ group and the $MVI^{(-)}$ group. The cumulative 5-year recurrence rates were also comparable between patients with MVI and those without MVI both in the entire cohort (HR, 1.35; 95% CI, 0.95–1.92; P = 0.096) and in the PSM cohort (HR, 1.37; 95% CI, 0.93–2.02; P = 0.114). The sites of recurrence and the number of patients with solitary recurrence of the two groups were similar. Of note, there were 13.1% patients who suffered from late recurrence presenting only extrahepatic metastasis. This was different from the study by Xu et al, in which they reported that no late recurrence patient developed only extrahepatic metastasis.[30] Although Lee et al reported that primary tumor-related factors independently influenced recurrence from only 2 years after resection,[31] we identified that poor tumor differentiation for the $MVI^{(+)}$ group and high AFP level for the $MVI^{(-)}$ group were the independent risk factors for late recurrence. Poor differentiated HCC cells are likely to produce AFP.[32] High AFP level was significantly associated with poor cell differentiation.[33] In this regard, tumor cell differentiation and AFP level may have the same function of outcome prediction. Poor differentiated tumor cells possess cancer stem cells or

dormancy cell properties.[34] They may disseminate from the primary tumor and implant to extrahepatic organs before resection, thereby possibly growing metastatic lesion in a favorable micro-environment months or years later.[35] This might be another source of late recurrence.

The most common extrahepatic metastatic organ after liver resection was the lung (8.5%), following by the peritoneal organs (3.8%) and lymph node (2.8%) in the primary cohort during the follow-up. Lung metastasis was the most common site of extrahepatic spread after liver resection.[29,36,37] The occurrence rates of lung and lymph node metastasis were over 2-fold higher in the $MVI^{(+)}$ group than in $MVI^{(-)}$ group (Supplementary Table 1). This reflected the high metastatic potential of $MVI^{(+)}$ HCC. Regular surveillance by imaging examinations targeting both remnant liver and extrahepatic organs is necessary.

Because more patients with early recurrence had heavy tumor burden or extrahepatic metastasis, lesser patients had chance of curative treatment (repeated resection or RFA) for recurrent tumors in the $MVI^{(+)}$ group compared with the $MVI^{(-)}$ group (Table 2). This probably explains why OS of patients with MVI was worse than those without MVI in the subgroup of patients with early recurrence in PSM cohort (Figure 3B, HR, 1.24; 95% CI, 1.02–1.50; P = 0.034). On the contrary, in patients with late recurrence, the burden of recurrent tumor was lower, and more patients could receive curative treatments than those with early recurrence. Therefore, the OS of patients with late recurrence was better than those with early recurrence. The proportion of patients received curative treatment was no different, thereby achieving good and comparable OS between the patients with MVI and those without MVI.

We further evaluated whether the risk factors related to early recurrence were different between $MVI^{(+)}$ HCC and $MVI^{(-)}$ HCC. Multivariate analysis showed that the patient-, tumor-related risk factors were similar between $MVI^{(+)}$ HCC and $MVI^{(-)}$ HCC (Table 3). However, different surgical risk factor influenced early recurrence in these two subsets of HCC. RM ≤1.0 cm was the only independent surgical predictor of early recurrence for patients with MVI, but it was not a predictor for those without MVI. RM >1.0 cm reduced 31.6% risk of early recurrence for $MVI^{(+)}$ HCC (HR, 0.684).

Previous studies documented that most of micro-metastasises are found within 1.0 cm, and rarely more than 2.0 cm from the tumor.[38–40] Roayaie et al reported that 87.8% (115/131) of MVI occurred in para-tumor tissue ≤1.0 cm from the tumor.[7] Another pathologic study on 125 HCC specimens revealed that the median farthest distance of MVI was 3.5 mm from the tumor, and 81.6% of MVI were found within 1.0 cm from the main tumor.[41] Therefore, an RM >1.0 cm could decrease recurrence for $MVI^{(+)}$ HCC by eradicating the majority of micro-metastasises or MVI. Since the patient- and tumor-related risk factors could not be altered at diagnosis, an RM >1.0 cm is preferred to reduce early recurrence if it is technically feasible and the liver remnant is sufficient for $MVI^{(+)}$ HCC.

The present study possesses two major limitations. First, it is a retrospective study, patients selection bias existed, although it consisted of multicenter large number of patients, but we tried to minimize such limitation by PSM. Second, most patients with HCC recruited in this study are HBV-related, whether the results can be recommended to patient with other etiologies remains to be determined.

Conclusion

In summary, we have deciphered and compared the post-resection recurrent pattern between $MVI^{(+)}$ HCC and $MVI^{(-)}$ HCC. $MVI^{(+)}$ HCC tends to be early recurrence with multiple foci, and lung and regional lymph node metastasis after liver resection. A stringent surveillance for early recurrence is recommended. MVI is the most potential risk factor contributing to early recurrence, and cirrhosis is a key risk factor of late recurrence. Patient- and tumor-related risk factors of early recurrence are similar in patient with MVI and those without MVI. However, RM ≤1.0 cm is a critical surgical predictor of early recurrence only for patients with MVI. An RM >1.0 cm should be performed for HCC with high risk of MVI when it is technically feasible and safe.

Acknowledgments

This study was partially supported by the grant of National Natural Science Foundation of China (No. 82072663), and Hunan Provincial Natural Science Foundation of China (2023JJ40382).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca a Cancer J Clinicians*. 2021;71:209–249. doi:10.3322/caac.21660
2. Fan ST, Mau Lo C, Poon RT, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. *Ann Surg*. 2011;253:745–758. doi:10.1097/SLA.0b013e3182111195
3. Goh BKP, Chua DW, Koh YX, et al. Continuous improvements in short and long-term outcomes after partial hepatectomy for hepatocellular carcinoma in the 21st century: Single institution experience with 1300 resections over 18 years. *Surg Oncol*. 2021;38:101609. doi:10.1016/j.suronc.2021.101609
4. Pompili M, Saviano A, de Matthaeis N, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤3 cm. Results of a multicenter Italian survey. *J Hepatol*. 2013;59:89–97. doi:10.1016/j.jhep.2013.03.009
5. Roayaie S, Obeidat K, Sposito C, et al. Resection of hepatocellular cancer ≤2 cm: results from two Western centers. *Hepatology*. 2013;57:1426–1435. doi:10.1002/hep.25832
6. Hwang S, Lee YJ, Kim KH, et al. The impact of tumor size on long-term survival outcomes after resection of solitary hepatocellular carcinoma: single-institution experience with 2558 patients. *J Gastrointestinal Surg*. 2015;19:1281–1290. doi:10.1007/s11605-015-2849-5
7. 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;137:850–855. doi:10.1053/j.gastro.2009.06.003
8. Rodríguez-Perálvarez 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;20:325–339. doi:10.1245/s10434-012-2513-1
9. Shindoh J, Kobayashi Y, Kawamura Y, et al. Microvascular invasion and a size cutoff value of 2 cm predict long-term oncological outcome in multiple hepatocellular carcinoma: reappraisal of the American Joint Committee on Cancer staging system and validation using the surveillance, epidemiology, and end-results database. *Liver Can*. 2020;9:156–166. doi:10.1159/000504193
10. Zhang XP, Wang K, Wei XB, et al. An Eastern hepatobiliary surgery hospital microvascular invasion scoring system in predicting prognosis of patients with hepatocellular carcinoma and microvascular invasion after r0 liver resection: a large-scale, multicenter study. *oncologist*. 2019;24:e1476–e88. doi:10.1634/theoncologist.2018-0868
11. Lee S, Kang TW, Song KD, et al. Effect of microvascular invasion risk on early recurrence of hepatocellular carcinoma after surgery and radiofrequency ablation. *Ann Surg*. 2021;273:564–571. doi:10.1097/SLA.0000000000003268
12. Nitta H, Allard MA, Sebagh M, et al. Prognostic value and prediction of extratumoral microvascular invasion for hepatocellular carcinoma. *Ann Surg Oncol*. 2019;26:2568–2576. doi:10.1245/s10434-019-07365-0
13. Jung SM, Kim JM, Choi GS, et al. Characteristics of early recurrence after curative liver resection for solitary hepatocellular carcinoma. *J Gastrointestinal Surg*. 2019;23:304–311. doi:10.1007/s11605-018-3927-2
14. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-The ALBI grade. *J Clinical Oncology*. 2015;33:550–558. doi:10.1200/JCO.2014.57.9151
15. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7:462–503. doi:10.1002/1097-0142(195405)7:3<462::AID-CNCR2820070308>3.0.CO;2-E
16. Li SQ, Huang T, Shen SL, et al. Anatomical versus non-anatomical liver resection for hepatocellular carcinoma exceeding Milan criteria. *Br J Surg*. 2017;104:118–127. doi:10.1002/bjs.10311
17. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Ann Surg*. 2007;245:36–43. doi:10.1097/01.sla.0000231758.07868.71
18. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg*. 2000;231:544–551. doi:10.1097/00000658-200004000-00014
19. Shimada K, Sakamoto Y, Esaki M, Kosuge T. Role of the width of the surgical margin in a hepatectomy for small hepatocellular carcinomas eligible for percutaneous local ablative therapy. *American Journal of Surgery*. 2008;195:775–781. doi:10.1016/j.amjsurg.2007.06.033
20. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dise*. 2010;30:61–74. doi:10.1055/s-0030-1247133
21. Portolani N, Coniglio A, Ghidoni S, et al. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg*. 2006;243:229–235. doi:10.1097/01.sla.0000197706.21803.a1
22. Sherman M. Recurrence of hepatocellular carcinoma. *New Engl J Med*. 2008;359:2045–2047. doi:10.1056/NEJMe0807581
23. Lee KF, Chong CCN, Fong AKW, et al. Pattern of disease recurrence and its implications for postoperative surveillance after curative hepatectomy for hepatocellular carcinoma: experience from a single center. *Hepatobiliary Surg Nutr*. 2018;7:320–330. doi:10.21037/hbsn.2018.03.17
24. Shah SA, Greig PD, Gallinger S, et al. Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. *J American Coll Surg*. 2006;202:275–283. doi:10.1016/j.jamcollsurg.2005.10.005
25. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*. 2003;38:200–207. doi:10.1016/S0168-8278(02)00360-4
26. European Association For The Study Of The Liver and other. EASL clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182–236. doi:10.1016/j.jhep.2018.03.019
27. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J American Coll Surg*. 2003;197:753–758. doi:10.1016/j.jamcollsurg.2003.07.003
28. Kim H, Rhim H, Choi D, et al. Recurrence and treatment pattern in long-term survivors with hepatocellular carcinoma: a comparison between radiofrequency ablation and surgery as a first-line treatment. *World j Surg*. 2010;34:1881–1886. doi:10.1007/s00268-010-0533-1
29. Yoh T, Seo S, Taura K, et al. Surgery for recurrent hepatocellular carcinoma: Achieving long-term survival. *Ann Surg*. 2021;273:792–799. doi:10.1097/SLA.0000000000003358

30. Xu XF, Xing H, Han J, et al. Risk factors, patterns, and outcomes of late recurrence after liver resection for hepatocellular carcinoma: a multicenter study from China. *JAMA Surgery*. 2019;154:209–217. doi:10.1001/jamasurg.2018.4334
31. Lee HA, Lee YS, Kim BK, et al. Change in the recurrence pattern and predictors over time after complete cure of hepatocellular carcinoma. *Gut Liver*. 2021;15:420–429. doi:10.5009/gnl20101
32. Agopian VG, Harlander-Locke MP, Markovic D, et al. Evaluation of patients with hepatocellular carcinomas that do not produce α-Fetoprotein. *JAMA Surgery*. 2017;152:55–64. doi:10.1001/jamasurg.2016.3310
33. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012;143:986–94.e3; quiz e14–5. doi:10.1053/j.gastro.2012.05.052
34. Ben-Porath I, Thomson MW, Carey VJ, et al. An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. *Nature Genet*. 2008;40:499–507. doi:10.1038/ng.127
35. Attaran S, Bissell MJ. The role of tumor microenvironment and exosomes in dormancy and relapse. *Semi Cancer Biol*. 2022;78:35–44. doi:10.1016/j.semcancer.2021.09.008
36. Li J, Liu Y, Yan Z, et al. A nomogram predicting pulmonary metastasis of hepatocellular carcinoma following partial hepatectomy. *Br. J. Cancer*. 2014;110:1110–1117. doi:10.1038/bjc.2014.19
37. Ochiai T, Ikoma H, Okamoto K, Kokuba Y, Sonoyama T, Otsuji E. Clinicopathologic features and risk factors for extrahepatic recurrences of hepatocellular carcinoma after curative resection. *World j Surg*. 2012;36:136–143. doi:10.1007/s00268-011-1317-y
38. Nakashima Y, Nakashima O, Tanaka M, Okuda K, Nakashima M, Kojiro M. Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. *Hepatology res*. 2003;26:142–147. doi:10.1016/S1386-6346(03)00007-X
39. Shi M, Zhang CQ, Zhang YQ, Liang XM, Li JQ. Micrometastases of solitary hepatocellular carcinoma and appropriate resection margin. *World j Surg*. 2004;28:376–381. doi:10.1007/s00268-003-7308-x
40. Sasaki A, Kai S, Iwashita Y, Hirano S, Ohta M, Kitano S. Microsatellite distribution and indication for locoregional therapy in small hepatocellular carcinoma. *Cancer*. 2005;103:299–306. doi:10.1002/cncr.20798
41. Fujita N, Aishima S, Iguchi T, et al. Histologic classification of microscopic portal venous invasion to predict prognosis in hepatocellular carcinoma. *Human Pathol*. 2011;42:1531–1538. doi:10.1016/j.humpath.2010.12.016