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A wide-margin liver resection improves long-term outcomes for patients with HBV-related hepatocellular carcinoma with microvascular invasion[☆]

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ABSTRACT

Background: The impact of the resection margin on survival outcomes in patients with hepatocellular carcinoma remains to be determined. This study aimed to examine the association between the width of resection margin and the presence of microvascular invasion in hepatitis B virus–related hepatocellular carcinoma.
Methods: We reviewed data on 2,508 consecutive patients who underwent liver resection for a solitary, hepatitis B virus–related hepatocellular carcinoma for operative morbidity, tumor recurrence, and overall survival.
Results: Microvascular invasion was identified histologically in 929 patients (37.0%). A wide margin of resection (≥1 cm, $n = 384$) resulted in better 5-year recurrence and overall survival versus a narrow margin of resection (<1 cm, $n = 545$) among patients with microvascular invasion (71.1% versus 85.9%; 44.9% versus 25.0%; both $P < .001$), but not in patients without microvascular invasion ($P = .131$, .182). Similar results were identified after propensity-score matching. A wide margin resection also had a lesser incidence of early recurrence developed within the first postoperative 24 months (58.1% versus 72.7%; $P < .001$). Compared with a wide resection margin, a narrow margin was associated with worse recurrence and overall survival in patients with microvascular invasion (hazard ratio: 1.50 and 1.75). In addition, a wide or a narrow resection margin had differences in the rate of grade I–III, but not grade IV complications (31.0% versus 21.7%; $P = .017$; 3.5% versus 1.6%; $P = .147$) among cirrhotic patients with microvascular invasion.
Conclusion: The presence of microvascular invasion was associated with a worse prognosis after resection. A wide resection margin resulted in better long-term prognoses versus a narrow resection margin among patients with hepatitis B virus–related hepatocellular carcinoma with microvascular invasion.

Introduction

Hepatitis B virus (HBV) is associated closely with the development of hepatocellular carcinoma (HCC).[1,2] Liver resection (LR) remains the first-line treatment for HCC.[3] Unfortunately, long-term outcome after resection is still unsatisfactory because of a high incidence of early tumor recurrence.[3] Current studies have demonstrated that microvascular invasion (MVI), which can be found in 15.0% to 57.1% of specimens obtained after LR or liver transplan-

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tation, has been associated with an increased risk of early tumor recurrence.[4–6] Compared with non-B, non-C HCC, HBV-related HCC might be more frequently associated with microscopic intrahepatic metastasis associated with MVI.[7–11] Current experimental studies suggested strongly that HBV infection augmented the angiogenic processes through enhancing the expression of metastasis-associated protein 1 or by inhibiting immune responses against tumor cells escaping from the primary tumor, thus leading to vascular invasion.[12–14]

Some studies showed that LR with wide operative margin could decrease tumor recurrence compared with a narrow resection margin.[15,16] In contrast, several other studies failed to obtain any survival benefit from more extensive resections[17,18] or to show that a narrow resection margin might also be effective in HCC.[19] Whether a wide- or a narrow-margin LR is technically feasible and safe via assessment prehepatectomy, the effectiveness of the width of the resection margin in HCC remains controversial. Of note, a recent study reported that MVI can violate the capsule of the tumor and can invade vessels ≥1 cm from the tumor capsule.[20] If a narrow-margin resection is used for these patients, the risk of early recurrence from residual tumor embolus might be high. Therefore, is a wide-margin resection beneficial to these patients?

The current study sought to examine the impact of the width of the resection margin on short- and long-term outcomes in patients who underwent LR for HBV-related HCC with or without the presence of MVI.

Patients and Methods

Patient and study design

We reviewed prospectively collected data (February 2000–December 2013) of consecutive patients who underwent an R0 resection for histopathologically proven HCC at the Eastern Hepatobiliary Surgery Hospital (EHBH) in Shanghai, China. An R0 resection was defined as complete removal of macroscopic tumor nodules and absence of microscopic tumor tissues at the operative margin.[21] Patients were considered for the study if they had a solitary tumor, were seropositive for HBV surface antigen (HBsAg) or HBV core antibody (HBcAb) and seronegative for hepatitis C virus antibody (HCV-Ab), did not have a history of preoperative anticancer treatment or of other malignancy, and did not have macroscopic tumor thrombus in major portal/hepatic veins and bile ducts. This study was approved by the Institutional Ethics Committee of the EHBH. Informed consent was obtained from all the patients before operation for using their data for the research.

Preoperative assessment and hepatectomy

Routine preoperative examination included liver function, prothrombin time (PT), serum levels of creatinine, alpha-fetoprotein (AFP), HBV and HCV antigen/antibody, and HBV deoxyribonucleic acid (HBV-DNA). Imaging studies included chest x-ray or noncontrast computed tomography (CT), abdominal ultrasonography, and contrast-enhanced CT, or magnetic resonance imaging (MRI) of the abdomen.

Resectablity of HCC was evaluated carefully based on patient general performance, tumor stage and morphology, and liver functional reserve as reported previously.[21] All patients underwent LR, with the intention of complete removal of macroscopic tumors, provided that the volume of the future liver remnant was estimated to be sufficient on CT or magnetic resonance imaging volumetry. All operations were carried out using a conventional open approach. Intraoperative ultrasonography was used routinely. LRs based on systematic removal of one or more adjacent Couinaud segments containing the tumor together with the tumor-bearing portal vein and corresponding hepatic territory were classified as an anatomic resection, and all other resections that were not in accordance with the liver segment anatomy were classified as nonanatomic resections.[22] The resected tumors with surrounding liver tissues were examined histopathologically. Three experienced pathologists, who were blinded to any prognostic information, evaluated all sections independently, and any controversies in histopathologic findings among them were resolved by discussion. Based on the standard postoperative pathologic reports, a wide- or a narrow-resection margin was defined as the shortest distance from the edge of the tumor to the plane of LR being ≥1 or <1 cm, which was in line with the methods reported elsewhere.[15,17] Sections of nontumor-bearing liver parenchyma that were farthest away from the tumor were also examined. The presence of MVI was defined as tumors within a vascular space lined by endothelium that was visible only on microscopy.[20] The Edmondson-Steiner classification was used to determine HCC differentiation.[23] The 8th edition of the American Joint Committee on Cancer/tumor-node-metastasis system was used for tumor staging.[24]

Postoperative surveillance and end points

Patients were followed-up regularly using the protocol reported elsewhere.[21] The patient's prognostic data were gathered either from the medical records at each of the follow-up visits or from the records of telephone calls and letters for those patients who had a long survival time and failed to attend regular visits. Patients who had developed recurrence were treated with a multidisciplinary approach, which included rehepatectomy, transarterial chemoembolization, percutaneous ablation, radiotherapy, sorafenib, or conservative treatment, as discussed in our earlier reports.[25]

The end points of the study were overall survival (OS), which was measured from the date of operation to either the date of patient death or the date of last follow-up. Time to recurrence was the interval between the date of operation and the date when tumor recurrence was identified.

Statistical analysis

Continuous variables were described as median (range) unless stated otherwise. Categorical variables were presented as frequencies and percentages. Statistical comparison of categorical and continuous variables was conducted using the χ^2 test or the Fisher exact test and the Mann-Whitney *U* test. All analyses were 2-tailed. Survival estimates were calculated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was used in identifying independent prognostic factors of recurrence and OS. Propensity-score matching (PSM) was used to adjust for different baseline features between patients who underwent a narrow or a wide resection margin according to other reported methods.[26] A 1:1 match between the 2 groups was done using the nearest-neighbor matching method to be within a range of 0.2 standard deviation.[27] The statistical analyses were performed using SPSS 19.0 for Windows (SPSS, Chicago, IL, USA) and R software 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria). A P value < .05 was considered statistically significant.

Results

Clinicopathologic baseline

Among 3,802 consecutive patients who underwent an R0 LR during the study period, 1,294 patients were excluded from the study (Supplementary Fig 1), and the remaining 2,508 patients were included in this analysis.

In these 2,508 patients, the presence of MVI was detected histopathologically in 929 patients (37.0%); 1,057 patients (42.1%) and 1,451 patients (57.9%) received a wide or a narrow margin , respectively. Patients with MVI compared with the narrow-margin group were more likely to have Child-Pugh grade A liver function (90.6% vs 86.1%), an HBV DNA-level of $\leq 10^4$ IU/mL (78.4% vs 72.1%), tumor diameter of $\leq$ 5 cm (73.4% vs 67.3%), no cirrhosis (47.9% vs 40.7%), no portal hypertension (84.4% vs 78.5%), and received an anatomic resection (46.9% vs 40.2%; all $P < .047$). Similar results were observed in patients without MVI, except that there was no difference in HBV-DNA levels between the narrow- and wide-margin groups ($P = .085$). After PSM, the baseline features were well balanced between a narrow versus a wide margin among patients who had MVI (194 vs 194) or did not have MVI (426 vs 426) or presence (Table 1).

Operative morbidity and mortality

Among these 2,508 patients, 526 patients (21.0%) experienced operative complications (Supplementary Table 1). According to the Clavien-Dindo classification,[28] grade I–III complications occurred in 480 patients (19.1%) and grade IV in 29 patients (1.2%), respectively. A total of 22 patients (0.9%) died within 30 days of operation.

For 1,057 patients (42.1%) and 1,451 patients (57.9%) who received a wide- or a narrow-margin LR, 224 patients (21.2%) and 302 patients (20.8%) had complications, respectively ($P = .818$), with 204 patients (19.3%) and 276 patients (19.0%) having grade I–III ($P = .861$), and 14 patients (1.3%) and 16 patients (1.1%) having grade IV ($P = .501$) complications, respectively; 12 and 10 patients died of postoperative complications in the 2 groups, respectively (1.1% vs 0.7%, $P = .237$).

Impact of the width of the resection margin on recurrence and OS in patients with or without MVI

The study was censored on July 2, 2014, with a median follow-up of 69.1 (range, 3.0–167.4) months.

In the whole cohort, a wide-margin LR had a better prognosis than a narrow margin LR, with 1-, 3-, and 5-year recurrence rates being 31.6%, 52.5%, and 59.1% vs 39.0%, 60.5%, and 67.4%, respectively. The corresponding OS rates were 89.6%, 72.5%, and 58.3% vs 88.8%, 64.3%, and 49.7%, respectively (both $P < .001$; Figs 1, *A* and *B*).

In the group without MVI ($n = 1{,}579$), wide- or narrow-margin LR had similar prognoses, with 1-, 3-, and 5-year recurrence rates being 23.8%, 44.7%, and 52.0% vs 28.9%, 48.8%, and 56.4%, respectively. The corresponding OS rates were 92.1%, 79.2%, and 66.9% vs 93.9%, 75.8%, and 64.0%, respectively ($P = .131$, .182; Figs 1, *C* and *D*). In contrast, in the MVI group ($n = 929$), a wide margin LR produced a better prognosis than a narrow-margin LR, with 1-, 3-, and 5-year recurrence rates being 45.5%, 66.2%, and 71.1% vs 55.8%, 79.4%, and 85.9%, respectively. The corresponding OS rates were 85.1%, 60.9%, and 44.9% vs 78.4%, 45.0%, and 25.0%, respectively (both $P < .001$; Figs 1, *E* and *F*).

In the PSM cohort, a wide- or a narrow-margin LR had similar prognoses in the group with no MVI ($n = 852$), with 1-, 3-, and 5-year recurrence. The OS rates were 23.0%, 45.4%, and 50.0% vs 28.9%, 48.7%, and 54.9%, respectively, and 93.0%, 81.3%, and 69.9% vs 93.4%, 76.7%, and 68.6%, respectively ($P = .264$, .288; Figs 2, *A* and *B*). In contrast, in the group with MVI ($n = 388$), a wide-margin LR had better prognosis than a narrow-margin LR, with 1-, 3-, and 5-year recurrence. The OS rates were 45.1%, 64.9%, and 70.3% vs 54.1%, 75.3%, and 82.6%, respectively; and 84.5%, 60.6%, and 46.5% vs 78.4%, 48.5%, and 25.8%, respectively ($P = .008$, $< .001$) (Figs 2, *C* and *D*).

The patterns of tumor recurrence after a narrow- or a wide-margin LR are presented in Supplementary Table 2. For patients with MVI who developed recurrence, a narrow- or a wide-margin LR resulted in similar types of recurrence (eg, intra-, extra-, and synchronous intra- and extrahepatic rerecurrences), which were demonstrated in both the whole cohort, as well as in the PSM cohort ($P = .086$, $P = .058$), and a narrow-margin LR had a greater incidence of recurrence at the operative margin than a wide-margin LR (40.7% vs 27.9%; 47.7% vs 29.8%, both $P < .001$). In contrast, the differences in the types of recurrence and recurrence at the operative margin were not different among patients without MVI who underwent a narrow- or a wide-margin LR (all $P > .05$).

Independent risk factors for tumor recurrence and OS in patients with MVI

The results of univariable analysis of recurrence and OS in patients with MVI in the whole cohort are presented in Supplementary Table 3. Multivariable analysis identified a narrow margin to be independently associated with both recurrence and OS (hazard ratio [HR]: 1.62 and 1.75), in addition to AFP level $\geq$ 400 μg/L, HBV DNA level $> 10^4$ IU/mL, tumor $>$ 5 cm, and an incomplete tumor capsule. Grade III/IV tumor differentiation and portal hypertension were associated only with OS (Table 2).

In the PSM cohort, the results of univariable analysis of recurrence and OS are presented in Supplementary Table 4. On multivariable analysis, a narrow operative margin was also associated with worse recurrence and OS compared with a wide operative margin (HR: 1.60 and 1.81; Table 2).

Impact of operative margin on early tumor recurrence in patients with or without MVI

Of these 2,508 patients, 1,204 (48.1%) developed early recurrence within the first postoperative 24 months after LR.[29] For the MVI group, a wide-margin LR decreased early recurrence rate when compared with a narrow-margin LR (58.1% vs 72.7%, $P < .001$). In contrast, the 2 procedures had a similar result in the group without MVI (35.4% vs 38.3%, $P = .232$; Table 3).

The univariable analyses of early recurrence in the MVI group are presented in Supplementary Table 5. Multivariable analysis revealed that a narrow operative margin was significantly associated with early recurrence (HR: 1.50) in addition to HBV DNA level $> 10^4$ IU/mL, AFP level $>$ 400 ug/L, tumor $>$ 5 cm, and incomplete tumor capsule (Table 4).

Impact of operative margin on short- and long-term prognoses in cirrhotic patients with MVI

Of these 2,508 patients, 523 patients had cirrhosis and MVI. Among them, 200 patients (38.2%) and 323 patients (61.8%) underwent a wide- or a narrow-margin LR, respectively. Operative complications developed in 72 (36.0%) vs 81 (25.1%) of these 2 groups ($P = .008$), however, such differences occurred only for grade I–III, but not grade IV complications (31.0% vs 21.7%, $P = .017$; 3.5% vs 1.6%, $P = .147$). The operative mortality was not different between the 2 groups (3 patients [1.5%] vs 7 patients [2.2%], $P = .582$).

The long-term prognosis was also better after a wide-margin LR in these patients. The 1-, 3- and 5-year recurrence rates for the

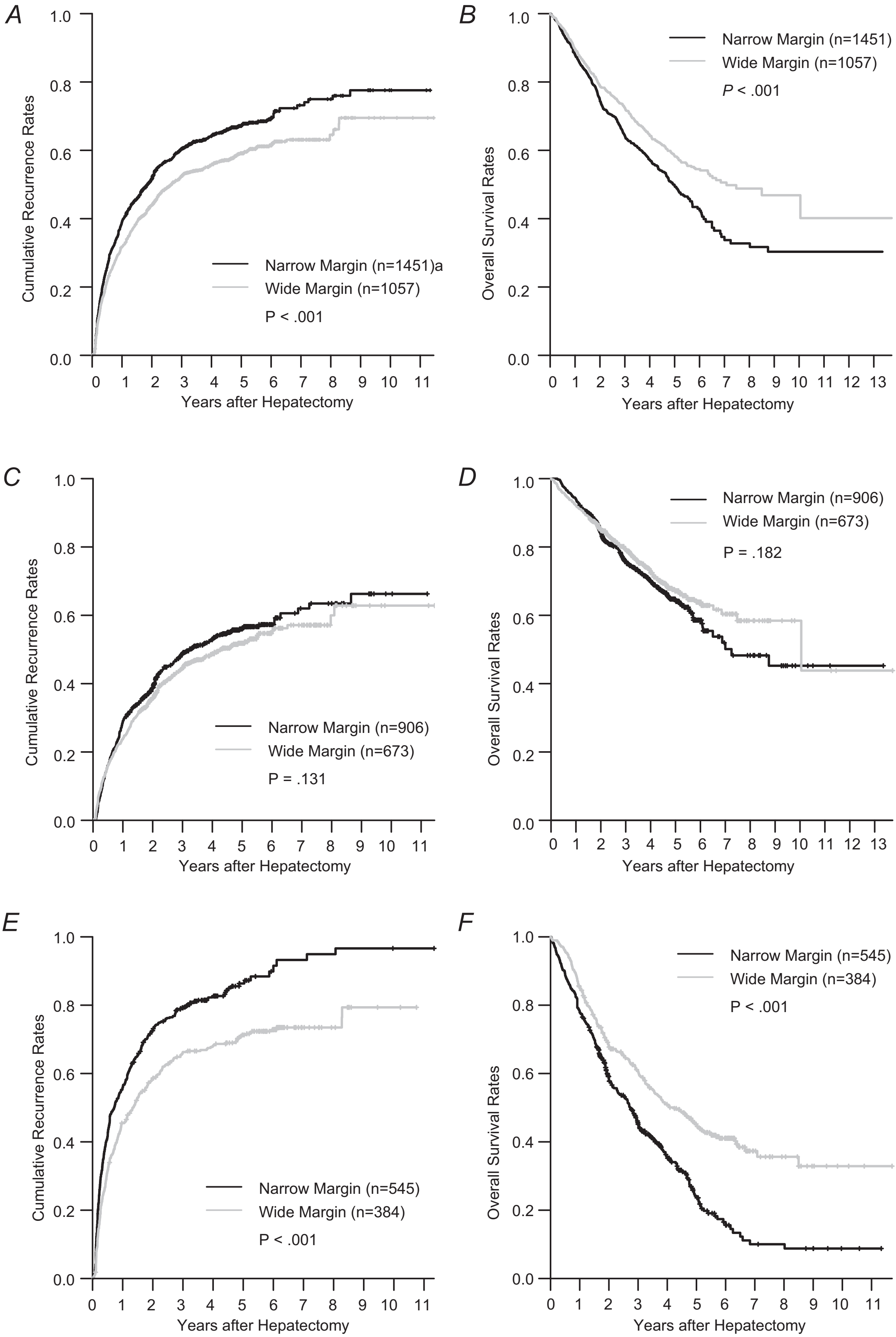

Fig 1. Tumor recurrence and overall survival (OS) after a narrow versus a wide operative margin after liver resection for hepatocellular carcinoma (HCC) patients in the whole cohort. (*A*) Tumor recurrence, (*B*) OS, (*C*) tumor recurrence in patients without microvascular invasion (MVI), (*D*) OS in patients without MVI, (*E*) tumor recurrence in patients with MVI, and (*F*) OS in patients with MVI.

Table 1
Clinicopathologic characteristics of patients in the cohort before and after PSM

Variable	Total	Before PSM (%)						After PSM (%)					
		MVI absence			MVI presence			MVI absence			MVI presence		
		Narrow margin (*n*=906)	Wide margin (*n* = 673)	*P* value*	Narrow margin (*n* = 545)	Wide margin (*n* = 384)	*P* value†	Narrow margin (*n* = 426)	Wide margin (*n* = 426)	*P* value*	Narrow margin (*n* = 194)	Wide margin (*n* = 194)	*P* value†
Age, years													
≤ 65	2224 (88.7)	795 (87.7)	601 (89.3)	.340	493 (90.5)	335 (87.2)	.121	394 (92.5)	392 (92.0)	.798	180 (92.8)	183 (94.3)	.535
> 65	284 (11.3)	111 (12.3)	72(10.7)		52 (9.5)	49 (12.8)		32 (7.51)	34 (7.98)		14 (7.22)	11 (5.67)	
Sex													
Female	365 (14.4)	134 (14.8)	103 (15.3)	.777	72 (13.2)	53 (13.8)	.884	70 (16.4)	59 (13.8)	.293	25 (12.9)	28 (14.4)	.657
Male	2,147 (85.6)	772 (85.2)	570 (84.7)		473 (86.8)	331 (86.2)		356 (83.6)	367 (86.2)		169 (87.1)	166 (85.6)	
HBsAg													
Negative	365 (14.6)	136 (15.0)	106 (15.8)	.687	70 (12.8)	53 (13.8)	.757	72 (16.9)	71 (16.7)	.927	29 (14.9)	23 (11.9)	.371
Positive	2,143 (85.4)	770 (85.0)	567 (84.2)		475 (87.2)	331 (86.2)		354 (83.1)	355 (83.3)		165 (85.1)	171 (88.1)	
HBcAb													
Positive	2,446 (97.5)	882 (97.4)	660 (98.1)	.351	529 (97.1)	375 (97.7)	.583	415 (97.4)	421 (98.8)	.130	190 (97.9)	191 (98.5)	.703
Negative	62 (2.5)	24 (2.6)	13 (1.9)		16 (2.9)	9 (2.3)		11 (2.58)	5 (1.17)		4 (2.06)	3 (1.55)	
HBeAg													
Negative	1,787 (71.3)	645 (71.2)	503 (74.7)	.118	365 (67.0)	274 (71.4)	.156	329 (77.2)	329 (77.2)	1.000	147 (75.8)	151 (77.8)	.630
Positive	721 (28.7)	261 (28.8)	170 (25.3)		180 (33.0)	110 (28.6)		97 (22.8)	97 (22.8)		47 (24.2)	43 (22.2)	
Child-Pugh grade													
A	2,211 (88.2)	784 (86.5)	610 (90.6)	.012	469 (86.1)	348 (90.6)	.035	396 (93.0)	394 (92.5)	.792	181 (93.3)	182 (93.8)	.836
B	297 (11.8)	122 (13.5)	63 (9.4)		76 (13.9)	36 (9.4)		30 (7.04)	32 (7.51)		13 (6.70)	12 (6.19)	
Varices													
No	2,170 (86.5)	769 (84.9)	594 (88.3)	.053	468 (85.9)	339 (88.3)	.284	394 (92.5)	394 (92.5)	1.000	181 (93.3)	180 (92.8)	.842
Yes	338 (13.5)	137 (15.1)	79 (11.7)		77 (14.1)	45 (11.7)		32 (7.51)	32 (7.51)		13 (6.70)	14 (7.22)	
Portal hypertension													
No	2,034 (81.1)	719 (79.4)	563 (83.7)	.031	428 (78.5)	324(84.4)	.026	381 (89.4)	380 (89.2)	.912	179 (92.3)	176 (90.7)	.585
Yes	474 (18.9)	187 (20.6)	110 (16.3)		117 (21.5)	60 (15.6)		45 (10.6)	46 (10.8)		15 (7.73)	18 (9.28)	
HBV DNA, IU/mL													
≤ 104	1,933 (77.1)	697 (76.9)	542 (80.5)	.085	393 (72.1)	301 (78.4)	.030	357 (83.8)	360 (84.5)	.778	154 (79.4)	153 (78.9)	.901
> 104	575 (22.9)	209 (23.1)	131 (19.5)		152 (27.9)	83 (21.6)		69 (16.2)	66 (15.5)		40 (20.6)	41 (21.1)	
AFP, ug/L													
≤ 400	1,835 (73.2)	661 (73.0)	493 (73.3)	.896	408 (74.9)	273 (71.1)	.201	315 (73.9)	314 (73.7)	.938	144 (74.2)	134 (69.1)	.260
> 400	673 (26.8)	245 (27.0)	180 (26.7)		137 (25.1)	111 (28.9%)		111 (26.1)	112 (26.3)		50 (25.8)	60 (30.9)	
PT, seconds													
≤ 13	1,983 (79.1)	725 (80.0)	547 (81.3)	.533	429 (78.7)	282 (73.4)	.062	377 (88.5)	378 (88.7)	.914	170 (87.6)	170 (87.6)	1.000
> 13	525 (20.9)	181 (20.0)	126 (18.7)		116 (21.3)	102 (26.6)		49 (11.5)	48 (11.3)		24 (12.4)	24 (12.4)	
PLT, 10^9/L													
≥ 100	1,908 (76.1)	725 (80.0)	547 (81.3)	.784	411 (75.4)	287 (74.7)	.815	337 (79.1)	343 (80.5)	.609	157 (80.9)	155 (79.9)	.798
< 100	600 (23.9)	181 (20.0)	126 (18.7)		134 (24.6)	97 (25.3)		89 (20.9)	83 (19.5)		37 (19.1)	39 (20.1)	
TBIL, mol/L													
≤ 17	1,801 (71.8)	653 (72.1)	506 (75.2)	.167	376 (69.0)	266 (69.3)	.928	354 (83.1)	345 (81.0)	.422	151 (77.8)	151 (77.8)	1.000
> 17	707 (28.2)	253 (27.9)	167 (24.8)		169 (31.0)	118 (30.7)		72 (16.9)	81 (19.0)		43 (22.2)	43 (22.2)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Total	Before PSM (%)						After PSM (%)					
		MVI absence			MVI presence			MVI absence			MVI presence		
		Narrow margin (*n*=906)	Wide margin (*n* = 673)	*P* value[*]	Narrow margin (*n* = 545)	Wide margin (*n* = 384)	*P* value[†]	Narrow margin (*n* = 426)	Wide margin (*n* = 426)	*P* value[*]	Narrow margin (*n* = 194)	Wide margin (*n* = 194)	*P* value[†]
ALB, g/L													
> 35	2,461 (98.1)	884 (97.6)	663 (98.5)	.189	535 (98.2)	379 (98.7)	.526	424 (99.5)	426 (100)	.157	192 (99.0)	193 (99.5)	.562
≤ 35	47 (1.9)	22 (2.4)	10 (1.5)		10 (1.8)	5 (1.3)		2 (0.47)	0 (0.00)		2 (1.03)	1 (0.52)	
ALT, U/L													
≤ 44	1,478 (58.9)	524 (57.8)	421 (62.6)	.059	323 (59.3)	210 (54.7)	.165	281 (66.0)	283 (66.4)	.885	114 (58.8)	114 (58.8)	1.000
> 44	1,030 (41.1)	382 (42.2)	252 (37.4)		222 (40.7)	174 (45.3)		145 (34.0)	143 (33.6)		80 (41.2)	80 (41.2)	
Type of hepatectomy													
Anatomic	1,116 (44.5)	392 (43.3)	325 (48.3)	.047	219 (40.2)	180 (46.9)	.042	181 (42.5)	180 (42.3)	.945	83 (42.8)	83 (42.8)	1.000
Nonanatomic	1,392 (55.5)	514 (56.7)	348 (51.7)		326 (59.8)	204 (53.1)		245 (57.5)	246 (57.7)		111 (57.2)	111 (57.2)	
Blood transfusion													
No	2,156 (86.0)	788 (87.0)	575 (85.4)	.379	474 (87.0)	319 (83.1)	.098	387 (90.8)	389 (91.3)	.810	175 (90.2)	173 (89.2)	.738
Yes	352 (14.0)	118 (13.0)	98 (14.6)		71 (13.0)	65 (16.9)		39 (9.15)	37 (8.69%)		19 (9.79)	21 (10.8)	
Tumor diameter, cm													
≤ 5	1,871 (74.6)	680 (75.1)	542 (80.5)	.010	367 (67.3)	282 (73.4)	.046	347 (81.5)	344 (80.8)	.793	142 (73.2)	147 (75.8)	.560
> 5	637 (25.4)	226 (24.9)	131 (19.5)		178 (32.7)	102 (26.6)		79 (18.5)	82 (19.2)		52 (26.8)	47 (24.2)	
Tumor capsule													
Incomplete	1,214 (48.4)	415 (45.8)	317 (47.1)	.609	276 (50.6)	206 (53.6)	.367	186 (43.7)	199 (46.7)	.371	93 (47.9)	111 (57.2)	.067
Complete	1,294 (51.6)	491 (54.2)	356 (52.9)		269 (49.4)	178 (46.4)		240 (56.3)	227 (53.3)		101 (52.1)	83 (42.8)	
Cirrhosis													
No	1,110 (44.3)	375 (41.4)	329 (48.9)	.003	222 (40.7)	184 (47.9)	.030	190 (44.6)	198 (46.5)	.582	86 (44.3)	86 (44.3)	1.000
Yes	1,398 (55.7)	531 (58.6)	344 (51.1)		323 (59.3)	200 (52.1)		236 (55.4)	228 (53.5)		108 (55.7)	108 (55.7)	
Edmondson-Steiner grade													
I/II	777 (31.0)	375 (41.4)	329 (48.9)	.252	134 (24.6)	97 (25.3)	.815	163 (38.3)	139 (32.6)	.086	46 (23.7)	53 (27.3)	.415
III/IV	1,731 (69.0)	531 (58.6)	344 (51.1)		411 (75.4)	287 (74.7)		263 (61.7)	287 (67.4)		148 (76.3)	141 (72.7)	
TNM stage[‡]													
I/II	2,409 (96.0)	881 (97.2)	648 (96.3)	.284	515 (94.5)	365 (95.1)	.709	409 (96.0)	408 (95.8)	.863	183 (94.3)	187 (96.4)	.334
III/IV	99 (4.0)	25 (2.8)	25 (3.7)		30 (5.5)	19 (4.9)		17 (4.0)	18 (4.2)		11 (5.7)	7 (3.6)	

HBsAg, hepatitis B surface antigen; *HBcAb*, hepatitis B core antibody; *HBeAg*, hepatitis B e antigen; *PLT*, platelet; *TBIL*, total bilirubin; *ALB*, albumin; *ALT*, alanine aminotransferase; *TNM*, tumor-node-metastasis.

[*] Comparison between the narrow and wide operative margin groups in patients with MVI absence.

[†] Comparison between the narrow and wide operative margin groups in patients with MVI presence.

[‡] Patients who were classified as III/IV stage had IIIC diseases with direct tumor invasion to adjacent tissues or organs, and IVA diseases with nodal metastases.

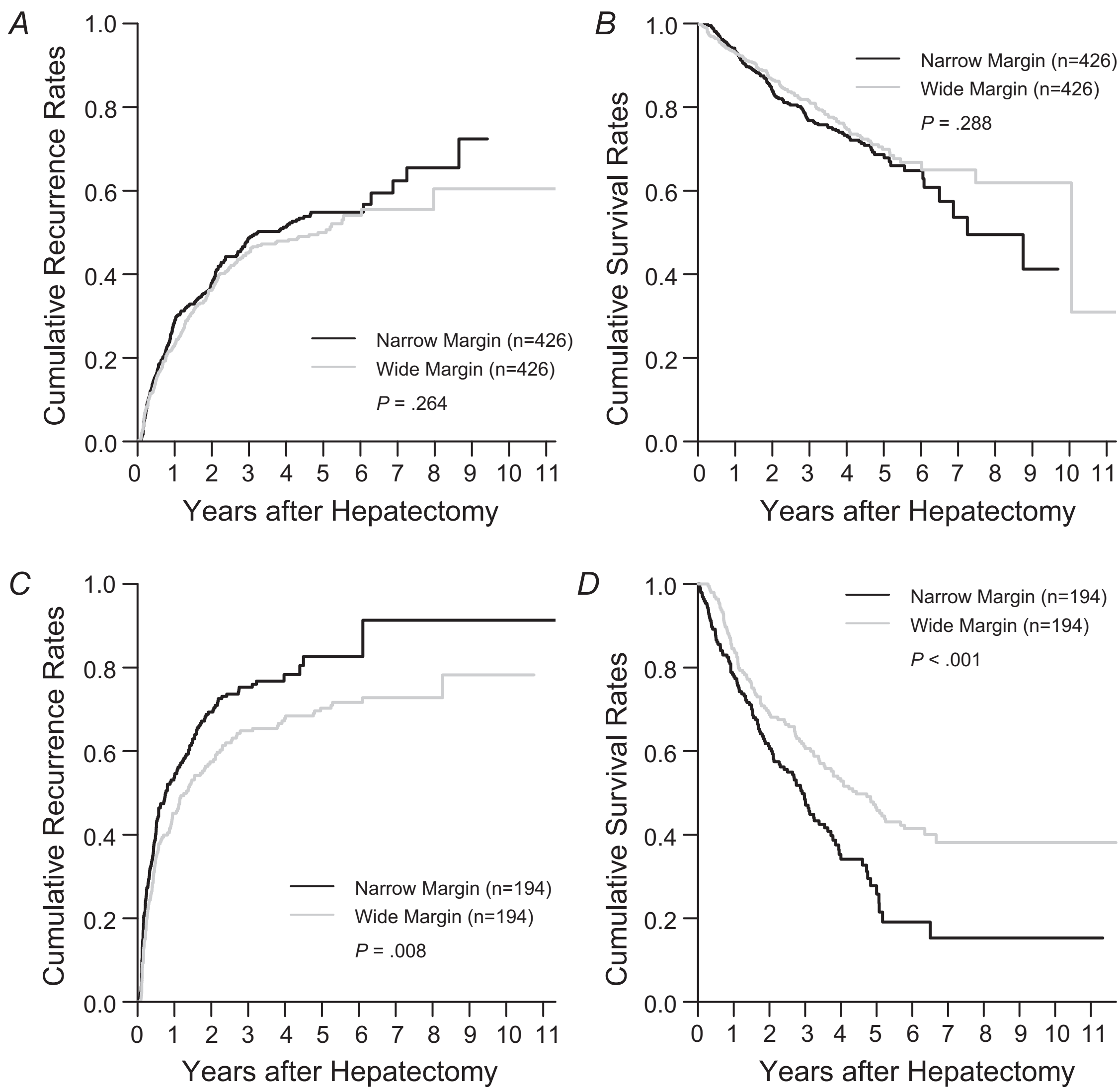

Fig 2. Tumor recurrence and overall survival (OS) after a narrow versus a wide operative margin after liver resection for hepatocellular carcinoma (HCC) patients in the propensity-score matching (PSM) cohort. (*A*) Tumor recurrence in patients without microvascular invasion (MVI), (*B*) OS in patients without MVI, and (*C*) tumor recurrence in patients with MVI, and (*D*) OS in patients with MVI.

Table 2
Multivariable analysis of tumor recurrence and OS in patients with MVI

Variable	Tumor recurrence				OS			
	P value	HR	95% CI		*P* value	HR	95% CI	
Whole cohort ($n = 929$)								
AFP, μg/L, ≥ versus<400	.019	1.22	1.03	1.45	.030	1.23	1.02	1.48
HBV DNA, IU/mL, > versus ≤ 10^4	.003	1.29	1.09	1.53	.012	1.29	1.06	1.56
Portal hypertension, yes versus no	—	—	—	—	.025	1.28	1.03	1.58
Resection margin, narrow versus wide	< .001	1.62	1.38	1.89	< .001	1.73	1.45	2.07
Tumor diameter, cm, ≤ versus > 5	.005	1.27	1.08	1.49	< .001	1.53	1.28	1.84
Tumor capsule, complete versus incomplete	< .001	1.68	1.44	1.96	< .001	1.45	1.23	1.72
Edmondson-Steiner grade, III/IV versus. I/II	—	—	—	—	< .001	1.67	1.33	2.11
PSM cohort ($n = 388$)								
Resection margin, narrow versus wide	< .001	1.6	1.26	2.03	< .001	1.81	1.38	2.37
Tumor diameter, cm, ≤ versus > 5	.004	1.46	1.12	1.89	< .001	1.69	1.27	2.24
Tumor capsule, complete versus incomplete	< .001	2.01	1.57	2.57	< .001	1.72	1.31	2.26
Edmondson-Steiner grade, III/IV versus I/II	—	—	—	—	< .001	2.04	1.4	2.98

CI, confidence interval; AFP, alpha fetoprotein.

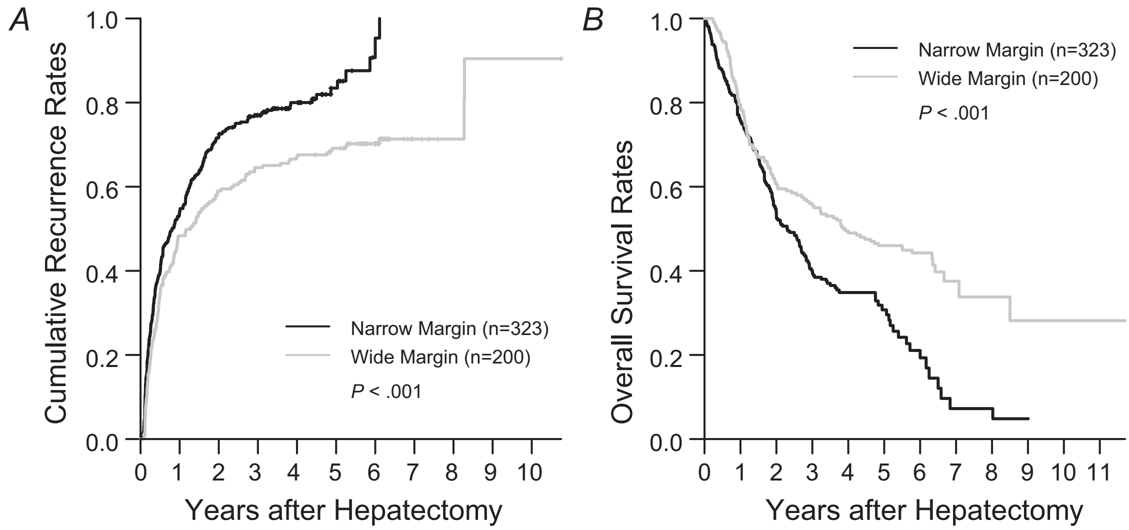

Fig 3. Tumor recurrence and overall survival (OS) after a narrow versus a wide operative margin liver resection for hepatocellular patients with cirrhosis and macrovascular invasion presence. (*A*) Tumor recurrence and (*B*) OS.

Table 3
Relation between operative margin and early tumor recurrence after liver resection

Operative margin	Tumor recurrence, *n* (%)*		*P* value
	Early	Late	
MVI presence			
Wide ($n=384$)	223 (58.1)	161 (41.9)	< .001
Narrow ($n=545$)	396 (72.7)	149 (27.3)	
MVI absence			
Wide ($n=673$)	238 (35.4)	435 (64.6)	.232
Narrow ($n=906$)	347 (38.3)	559 (61.7)	

* Tumor recurrence that developed within 24 months was defined as early recurrence, otherwise as late recurrence.

Table 4
Multivariable analysis of early tumor recurrence in patients with MVI

Variable	Early recurrence			
	P value	HR	95% CI	
HBV DNA, IU/mL, > versus $\leq 10^4$	< .001	1.39	1.16	1.66
AFP, μg/L, ≥ versus <400	.011	1.26	1.06	1.51
Resection margin, narrow versus wide	< .001	1.50	1.27	1.77
Tumor diameter, cm, ≤ versus >5	.013	1.25	1.05	1.49
Tumor capsule, complete versus incomplete	< .001	1.76	1.49	2.09

CI, confidence interval; *AFP*, alpha fetoprotein.

wide- and narrow-margin groups were 48.2%, 64.5%, and 69.1% vs 69.1%, 77.2%, and 82.9%, respectively. The corresponding OS rates were 79.0%, 56.0%, and 46.0% vs 75.9%, 39.6%, and 31.0%, (both $P <$ .001; Fig 3, *A* and *B*).

The univariable analysis of recurrence and OS is presented in Supplementary Table 6. Multivariable analysis showed that a narrow operative margin was an independent risk factor of both recurrence and OS after LR for cirrhotic patients with MVI (HR: 1.49 and 1.65; Table 5).

Discussion

In this study, MVI was histologically present in 37.0% patients who underwent LR for an HBV-related solitary HCC. The width of the resection margin did not show a significant impact on operative complication rates (including severity of complication) or operative mortality. A significant difference in long-term prognosis between a wide- versus a narrow-margin LR was only identified in patients with MVI, in whom a narrow-margin LR significantly increased the risk of early recurrence. These results were identified in the studied populations both before or after PSM. Although a wide resection margin increased operative morbidity in cirrhotic patients, it was a favorable factor for the long-term prognosis in these patients with MVI.

For achieving a curative resection, LR with a wide operative margin is usually considered for HCCs that show locally aggressive features, such as tumors with an incomplete capsule or without a capsule and tumors fused by multiple nodules.[30] Even for patients without these features and for tumors that have been resected with a tumor-free margin, postoperative tumor-recurrence rates remain high. The presence of MVI appears to contribute greatly to this phenomenon.[3] Although MVI is mainly found in intratumoral microvessels, it can invade beyond the capsules of HCCs.[20] If an operative margin is narrow, intrahepatic metastases caused by residual MVI can result in early recurrence. Our results demonstrated that a wide-margin LR decreased early recurrence only in patients with MVI and not in patients without MVI. A narrow-margin LR increased the risk of early recurrence in patients with MVI.

Cirrhosis is a limiting factor for the more extensive LRs for HCC. In 523 cirrhotic patients with MVI, a wide-margin resection increased the grade I–III complication rate but did not increase grade IV complications or operative mortality. Wide resection margins also were associated with a better long-term prognosis, and a narrow resection margin was an independent risk factor for recurrence and OS (HR: 1.50 and 1.65). The use of a wide-margin LR in these patients with cirrhosis should be assessed carefully to obtain adequate liver functional reserve after LR.

Because a decision on resection margin based on the presence of MVI has to be made before hepatectomy, the key point thus becomes whether it is possible to accurately predict the presence of MVI preoperatively. Liver biopsy is not an effective method for the diagnosis of MVI,[31] however, the preoperative prediction of MVI has quickly been developed during the past decade. The predictive tools include new imaging techniques,[32–35] biomarkers such as protein induced by vitamin K absence/antagonism II and AFP-L3,[30,36,37] and predictive models such as artificial neural networks.[38] For predicting the presence of MVI in HBV-related

Table 5
Multivariable analysis of tumor recurrence and OS in cirrhotic patients with MVI

Variable	Tumor recurrence				OS			
	P value	HR	95% CI		*P* value	HR	95% CI	
Child-Pugh grade, A versus B	–	–	–	–	.007	1.61	1.14	2.27
AFP, μg/L, ≥ versus < 400	.0043	1.40	1.12	1.74	.004	1.42	1.12	1.81
Resection margin, narrow versus wide	< .001	1.50	1.21	1.86	< .001	1.65	1.30	2.10
Tumor diameter, cm, ≤ versus > 5	.022	1.29	1.04	1.60	.014	1.35	1.06	1.71
Tumor capsule, complete versus incomplete	< .001	1.67	1.35	2.07	< .001	1.63	1.30	2.06

CI, confidence interval; *AFP*, alpha fetoprotein.

HCC, we recently developed a MVI nomogram which incorporated clinicopathologic variables including HBV-DNA level.[39] Although a highly specific tool is still lacking, accumulating results suggest that preoperative identification of patients at high risk of having MVI is becoming increasingly possible. For patients who are estimated to have a high risk of MVI according to preoperative prediction, a wide-margin LR should be obtained if technically feasible and safe.

MVI status is not the only factor in determining the extent of the resection margin in HCC. Large tumor size, unfavorable tumor location, cirrhosis, and small liver remnants are the main limiting factors to achieve a wide operative margin.[19,40,41] In some of these situations, aiming at an R0 resection with a narrow margin to preserve more liver parenchyma and to protect important intrahepatic structures becomes a good strategy to balance between operative safety and treatment effectiveness.

This study had several limitations. First, patients with multiple HCCs were not studied because the different distances of resection margins among the tumor nodules removed made the analysis difficult. In addition, this study focused on patients with HBV infection, and whether the results can be applied to patients with other etiologies of HCC remains to be determined. We know that the presence of MVI is a troubling prognostic indicator in HCV-related and other etiologies of HCC.[42,43] Third, although a wide-margin resection was associated with a decreased risk of recurrence in patients with MVI compared with a narrow-margin resection, the wide margin could not completely eliminate the risk of MVI for the prognosis after LR for HCC. Finally, this study is not a randomized controlled trail and therefore biases in patient's selection may exist.

In conclusion, our study showed that the presence of MVI was identified in 37% of patients with HBV-related HCC and was associated with a worse prognosis. A wide margin of resection improved long-term survival of patients who had HBV-related HCC with MVI.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.09.016.

References

1. Stewart BW, Wild CP, eds. *World Cancer Report 2014*. Lyon, France: International Agency for Research on Cancer; 2014; 403–413.
2. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142:1264–1273.
3. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. *Hepatology*. 2011;53:1020–1022.
4. 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;20:325–339.
5. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology*. 2014;146:1691–1700.
6. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: A retrospective, exploratory analysis. *Lancet Oncol*. 2009;10:35–43.
7. Utsunomiya T, Shimada M, Kudo M, Ichida T, Matsui O, Izumi N, et al. A comparison of the surgical outcomes among patients with HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: A nationwide study of 11,950 patients. *Ann Surg*. 2015;261:513–520.
8. Kaibori M, Ishizaki M, Matsui K, Kwon AH. Clinicopathologic characteristics of patients with non-B non-C hepatitis virus hepatocellular carcinoma after hepatectomy. *Am J Surg*. 2012;204:300–307.
9. Omichi K, Shindoh J, Yamamoto S, Matsuyama Y, Akamatsu N, Arita J, et al. Postoperative outcomes for patients with non-B non-C hepatocellular carcinoma: A subgroup analysis of patients with a history of hepatitis B infection. *Ann Surg Oncol*. 2015;22(Suppl 3):S1034–S1040.
10. Kao WY, Su CW, Chau GY, Lui WY, Wu CW, Wu JC. A comparison of prognosis between patients with hepatitis B and C virus-related hepatocellular carcinoma undergoing resection surgery. *World J Surg*. 2011;35:858–867.
11. Sasaki K, Matsuda M, Ohkura Y, Kawamura Y, Hashimoto M, Ikeda K, et al. Minimum resection margin should be based on tumor size in hepatectomy for hepatocellular carcinoma in hepatoviral infection patients. *Hepatol Res*. 2013;43:1295–1303.
12. Ryu SH, Chung YH, Lee H, Kim JA, Shin HD, Min HJ, et al. Metastatic tumor antigen 1 is closely associated with frequent postoperative recurrence and poor survival in patients with hepatocellular carcinoma. *Hepatology*. 2008;47:929–936.
13. Bui-Nguyen TM, Pakala SB, Sirigiri RD, Xia W, Hung MC, Sarin SK, et al. NF-kappa B signaling mediates the induction of MTA1 by hepatitis B virus transactivator protein HBx. *Oncogene*. 2010;29:1179–1189.
14. Yang P, Li QJ, Feng Y, Zhang Y, Markowitz GJ, Ning S, et al. TGF–beta-miR-34a-CCL22 signaling-induced Treg cell recruitment promotes venous metastases of HBV-positive hepatocellular carcinoma. *Cancer Cell*. 2012;22:291–303.
15. Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: A prospective randomized trial. *Ann Surg*. 2007;245:36–43.
16. Laurent C, Blanc JF, Nobili S, Sa Cunha A, le Bail B, Bioulac-Sage P, et al. Prognostic factors and longterm survival after hepatic resection for hepatocellular carcinoma originating from noncirrhotic liver. *J Am Coll Surg*. 2005;201:656–662.
17. 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.
18. Lee KT, Wang SN, Su RW, Chen HY, Shi HY, Ker CG, et al. Is wider surgical margin justified for better clinical outcomes in patients with resectable hepatocellular carcinoma? *J Formos Med Assoc*. 2012;111:160–170.
19. Dahiya D, Wu TJ, Lee CF, Chan KM, Lee WC, Chen MF. Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: A 20-year experience. *Surgery*. 2010;147:676–685.
20. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. *Gastroenterology*. 2009;137:850–855.
21. Wang K, Liu J, Yan ZL, Li J, Shi LH, Cong WM, et al. Overexpression of aspartyl-(asparaginyl)-beta-hydroxylase in hepatocellular carcinoma is associated with worse surgical outcome. *Hepatology*. 2010;52:164–173.
22. Strasberg SM, Phillips C. Use and dissemination of the Brisbane 2000 nomenclature of liver anatomy and resections. *Ann Surg*. 2013;257:377–382.
23. Edmondson HA, Steiner PE. Primary carcinoma of the liver: A study of 100 cases among 48,900 necropsies. *Cancer*. 1954;7:462–503.
24. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al.. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer International Publishing; 2017.
25. Yang T, Lu JH, Lau WY, Zhang TY, Zhang H, Shen YN, et al. Perioperative blood transfusion does not influence recurrence-free and overall survivals after curative resection for hepatocellular carcinoma: A propensity score matching analysis. *J Hepatol*. 2016;64:583–593.
26. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc*. 1984;79:516–524.
27. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265–2281.
28. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009;250:187–196.

29. Cheng Z, Yang P, Qu S, Zhou J, Yang J, Yang X, et al. Risk factors and management for early and late intrahepatic recurrence of solitary hepatocellular carcinoma after curative resection. *HPB (Oxford)*. 2015;17:422–427.
30. 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.
31. Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: A systematic review and meta-analysis. *Gut*. 2008;57:1592–1596.
32. Kaibori M, Ishizaki M, Matsui K, Kwon AH. Predictors of microvascular invasion before hepatectomy for hepatocellular carcinoma. *J Surg Oncol*. 2010;102:462–468.
33. Witjes CD, Willemssen FE, Verheij J, van der Veer SJ, Hansen BE, Verhoef C, et al. Histological differentiation grade and microvascular invasion of hepatocellular carcinoma predicted by dynamic contrast-enhanced MRI. *J Magn Reson Imaging*. 2012;36:641–647.
34. Choi YS, Rhee H, Choi JY, Chung YE, Park YN, Kim KW, et al. Histological characteristics of small hepatocellular carcinomas showing atypical enhancement patterns on gadoxetic acid-enhanced MR imaging. *J Magn Reson Imaging*. 2013;37:1384–1391.
35. Banerjee S, Wang DS, Kim HJ, Sirlin CB, Chan MG, Korn RL, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. *Hepatology*. 2015;62:792–800.
36. Pawlik TM, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl*. 2005;11:1086–1092.
37. Ding ZB, Shi YH, Zhou J, Shi GM, Ke AW, Qiu SJ, et al. Liver-intestine cadherin predicts microvascular invasion and poor prognosis of hepatitis B virus-positive hepatocellular carcinoma. *Cancer*. 2009;115:4753–4765.
38. Cucchetti A, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanello M, 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;52:880–888.
39. Lei Z, Li J, Wu D, Xia Y, Wang Q1, Si A, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. *JAMA Surg*. 2016;151:356–363.
40. Sasaki K, Shindoh J, Nishioka Y, Margonis GA, Sugawara T, Andreatos N, et al. Impact of viral etiology on postoperative de novo recurrence after hepatectomy for hepatocellular carcinoma in cirrhotic patients. *J Gastrointest Surg*. 2017;21:487–495.
41. Matsui Y, Terakawa N, Satoi S, Kaibori M, Kitade H, Takai S, et al. Postoperative outcomes in patients with hepatocellular carcinomas resected with exposure of the tumor surface: Clinical role of the no-margin resection. *Arch Surg*. 2007;142:596–602.
42. Vigano L, Conci S, Cescon M, Fava C, Capelli P, D'Errico A, et al. Liver resection for hepatocellular carcinoma in patients with metabolic syndrome: A multicenter matched analysis with HCV-related HCC. *J Hepatol*. 2015;63:93–101.
43. Nathan H, Schulick RD, Choti MA, Pawlik TM. Predictors of survival after resection of early hepatocellular carcinoma. *Ann Surg*. 2009;249:799–805.