Comparative Study - Retrospective Cohort

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Significance of anatomical resection and resection margin status in patients with HBV-related hepatocellular carcinoma and microvascular invasion: a multicenter propensity score-matched study

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Background: Microvascular invasion (MVI) is a risk factor for postoperative survival outcomes for patients with hepatocellular carcinoma (HCC) after hepatectomy. This study aimed to evaluate the impact of anatomical resection (AR) versus nonanatomical resection (NAR) combined with resection margin (RM) (narrow RM <1 cm vs. wide RM ≥ 1 cm) on long-term prognosis in hepatitis B virus-related HCC patients with MVI.

Materials and methods: Data from multicenters on HCC patients with MVI who underwent hepatectomy was analyzed retrospectively. Propensity score matching analysis was performed in these patients.

Results: The 1965 enrolled patients were divided into four groups: AR with wide RM ($n = 715$), AR with narrow RM ($n = 387$), NAR with wide RM ($n = 568$), and NAR with narrow RM ($n = 295$). Narrow RM ($P < 0.001$) and NAR ($P < 0.001$) were independent risk factors for both overall survival and recurrence-free survival in these patients based on multivariate analyses. For patients in both the AR and NAR groups, wide RM resulted in significantly lower operative margin recurrence rates than those patients in the narrow RM groups after propensity score matching ($P = 0.002$ and 0.001). Patients in the AR with wide RM group had significantly the best median overall survival (78.9 vs. 51.5 vs. 48.0 vs. 36.7 months, $P < 0.001$) and recurrence-free survival (23.6 vs. 14.8 vs. 17.8 vs. 9.0 months, $P < 0.001$) than those in the AR with narrow RM, NAR with wide RM or with narrow RM groups, respectively.

Conclusions: If technically feasible and safe, AR combined with wide RM should be the recommended therapeutic strategy for HCC patients who are estimated preoperatively with a high risk of MVI.

Keywords: anatomical resection, hepatocellular carcinoma, liver resection, microvascular invasion, narrow resection margin, nonanatomical resection, overall survival, propensity score matching, recurrence-free survival, wide resection margin

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common types of cancer in China and the third-leading cause of cancer-related death all over the world[1]. Hepatitis B virus (HBV) infection is the most common cause of HCC in China[2], and liver resection (LR) still represents the first-line curative-intent strategy for HCC to date[3,4]. Nevertheless, a considerable number of patients are still prone to relapse even after curative LR, which seriously damage the long-term survival outcomes of these patients[3].

Previous studies have demonstrated that about 15–57% of HCC patients have microvascular invasion (MVI), and these patients have worse long-term survival outcomes[5,6]. Exploring the clinicopathological factors associated with MVI is expected to further improve the long-term prognosis of these patients[7,8].

Our team is highly interested in the research of HCC and MVI patients and has reported a series of related studies[9–14]. However, it remains controversial whether there is a difference between the use of anatomic resection (AR) and nonanatomic resection (NAR) in hepatectomy, and whether margin width [resection margin (RM)](narrow RM <1 cm vs. wide RM ≥1 cm) is associated with tumor recurrence and long-term survival in these patients. Several studies have shown that AR is superior to NAR in adequately clearing tumors that have spread through the portal vein system, which significantly improves long-term survival outcomes after LR[15,16]. However, Hidaka *et al.*[17] indicated that AR for HCC with MVI did not improve the long-term prognosis when compared with NAR. Additionally, Han *et al.*[18] reported concomitant narrow RM and MVI positivity increased the risks of postoperative recurrence and death; Yang *et al.*[19] revealed that wide RM (≥1 cm) resulted in better long-term survival outcomes when compared with narrow RM (<1 cm) in HBV-related HCC patients with MVI. While another study reported that AR with a negative 0 mm RM to be acceptable in patients with a single HCC, and the width of RM was not associated with the long-term survival outcomes after AR[20]. Consequently, the importance of AR and RM status in patients with HBV-related HCC and MVI should be further studied to resolve these disputes.

This study, based on a large multicenter cohort from China, aimed to assess the association between AR and RM status with tumor recurrence and long-term survival outcomes in HBV-related HCC patients with MVI, and find out perioperative prognostic factors which may impact the decision making to improve the long-term prognosis of these patients.

HIGHLIGHTS

- The first multicenter study compared anatomical resection or nonanatomical resection and resection margin status in hepatocellular carcinoma with microvascular invasion to resolve disputes.
- Anatomical resection combined with wide resection margin should be the recommended therapeutic strategy for hepatocellular carcinoma patients who are estimated preoperatively with a high risk of microvascular invasion.

Materials and methods

Patients

A retrospective study was conducted on HBV-related HCC patients who underwent LR from January 2009 to December 2019 at seven large cancer centers: Chinese People's Liberation Army (PLA) General Hospital of Beijing, Eastern Hepatobiliary Surgery Hospital (EHBH) of Shanghai, Affiliated Hospital of Guizhou Medical University of Guizhou, Fujian Provincial Hospital of Fujian, Affiliated Hospital of Binzhou Medical College (AHBMC) of Shandong, Northern Theater General Hospital of Liaoning, and Wenzhou People's Hospital (WZPH) of Zhejiang. Patients were divided into four groups according to different hepatectomy method and RM status (AR with wide RM, AR with narrow RM, NAR with wide RM, and NAR with narrow RM). The study was approved by the individual Ethics Committee of all of the hospitals included. As patient identities were anonymized, the requirement for informed consent was waived by the Ethics Committee. The retrospective cohort study was registered with ResearchRegitry.com (Unique Identification Number: researchregistry 6089). The work was reported in accordance with the STROCSS criteria[21], Supplemental Digital Content 1, http://links.lww.com/JS9/A132.

Inclusion and exclusion criteria

The inclusion criteria were patients with (1) histopathological diagnosis of HCC with MVI; (2) good liver function with a Child–Pugh A grading/selected B (score ≤7); (3) radical LR as an initial treatment, with no residual tumors on gross inspection and histological examination of resected specimens; (4) no macrovascular invasion or extrahepatic metastasis; and (5) complete clinical and follow-up data. The exclusion criteria were (1) data missing or lost to follow-up; (2) patients with extrahepatic metastases; or (3) accompanied with other malignancies. MVI is defined as the presence of tumor cells in a portal vein, hepatic vein, or large capillary vessel of surrounding hepatic tissue lined with endothelium that is visible only on microscopy.

Preoperative investigations and liver resection

Routine preoperative investigations include imaging and serological tests. All patients underwent standard liver imaging protocols that included abdominal ultrasound, contrast-enhanced MRI and/or computed tomography (CT) scan of the abdomen, and plain radiography or noncontrast CT scan of the chest. Routine preoperative laboratory investigations included complete blood counts, liver and kidney function tests, hepatitis B and C serology, HBV DNA load, and serum α-fetoprotein (AFP) levels.

Resectability of HCC was carefully evaluated by experienced liver surgeons based on patient general performance, tumor staging and morphology, and liver functional reserve as previously reported[22]. LRs based on resection of one or more adjacent Couinaud liver segments containing the tumor together with the tumor-bearing portal venous and the corresponding hepatic arterial territory were classified as AR. All other liver resections that were not in accordance with the liver segmental anatomy were classified as NAR[15]. The resected tumor and its surrounding liver tissue were examined by three experienced pathologists. Based on the standard postoperative pathological reports, a wide-RM or a narrow-RM was defined as the shortest distance from the edge of the tumor to the plane of LR being

greater than or equal to 1 or less than 1 cm, which was in line with the methods used in previous reports[19,23].

Postoperative follow-up

Investigations at follow-up included serum AFP, liver function, HBV DNA load, and contrast-enhanced CT or MRI every 2–3 months for the first and second years, and then every 6 months until death or dropout from follow-up. Tumor recurrence was diagnosed based on elevated serum AFP levels and MRI or CT imaging findings. When tumor recurrence was diagnosed, patients were subjected to appropriate treatments including percutaneous ethanol injection, radiofrequency ablation, transarterial chemoembolization, or LR, depending on the general condition of the patient, the liver functional reserve, and the pattern of tumor recurrence[10]. The primary endpoints of this study were overall survival (OS) and recurrence-free survival (RFS). OS was calculated from the date of LR to the date of death or last follow-up, while RFS was calculated from the date of LR to the date of first diagnosis of tumor recurrence.

Statistical analysis

Continuous variables were described as median (interquartile 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 Fisher's exact test and the Mann–Whitney *U*-test. 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 RFS and OS. Propensity score matching (PSM) was used to adjust for different baseline features between patients who underwent narrow or wide RM. A 1 : 1 match between groups was performed using the nearest-neighbor matching method to be within a range of 0.2 SD. All analyses were two-tailed and a *P* value less than 0.05 was considered statistically significant. The statistical analyses were performed using SPSS (version 25.0; IBM) and R program (version 3.6.3, R Foundation for Statistical Computing).

Results

Patient characteristics

The 1965 patients with HCC and MVI who met the inclusion criteria were divided into four groups according to the different hepatectomy methods and RM status: AR with wide RM, AR with narrow RM, NAR with wide RM, and NAR with narrow RM (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). The baseline characteristics of these patients are showed in Table 1. There were significant differences in the number of tumors, tumor diameter, satellite lesions, tumor capsule, and Edmondson–Steiner grading among these groups. All the variables in these groups showed no significant difference after PSM (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A133 and Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/A133).

Univariate and multivariate cox regression analyses on survival outcomes

The results of univariate analyses for OS and RFS of HCC patients with MVI after hepatectomy before or after PSM are shown in Supplementary Tables 3–5, Supplemental Digital Content 2, http://links.lww.com/JS9/A133. Before PSM, the independent risk factors for OS or RFS in all HCC patients with MVI were: HBV DNA level (OS, $P < 0.001$; RFS, $P < 0.001$), AFP level (OS, $P < 0.001$; RFS, $P < 0.001$), number of tumors (OS, $P = 0.023$; RFS, $P = 0.014$), tumor diameter (OS, $P < 0.001$; RFS, $P < 0.001$), satellite lesions (OS, $P < 0.001$; RFS, $P < 0.001$), tumor encapsulation (OS, $P < 0.001$; RFS, $P < 0.001$), Edmondson–Steiner grading (OS, $P < 0.001$), RM status (OS, $P < 0.001$; RFS, $P < 0.001$), and hepatectomy methods (OS, $P < 0.001$; RFS, $P < 0.001$) (Table 2). After PSM was adjusted for either the RM status ($n = 1292$) or the hepatectomy methods ($n = 1584$), the RM status and the hepatectomy methods were both determined to be independent risk factors of OS or RFS (all $P < 0.001$). The details are shown in Table 2 and Supplementary Tables 3–5, Supplemental Digital Content 2, http://links.lww.com/JS9/A133.

Impact of AR or NAR combined with different RM status on the timings and patterns of tumor recurrence

Table 3 demonstrates that 1423 of 1965 patients with HCC and MVI (72.9%) developed tumor recurrence on follow-up, and early recurrence developed in the four groups ranged from 52.4 to 68.6%. Patients in the AR with wide RM group had a significantly lower early recurrence rate, while patients in the NAR with narrow RM group had a significantly higher early recurrence rate when compared with the other two groups before PSM ($P = 0.003$). However, the types of recurrence (intrahepatic, extrahepatic, and intraplus extrahepatic) showed no significant differences among the four groups ($P = 0.391$). When considering the sites of intrahepatic recurrence, patients who underwent wide RM in both the AR and NAR groups had significantly lower operative margin recurrence but higher distal liver segmental recurrence rates when compared with patients who underwent narrow RM in both the AR and NAR groups ($P < 0.001$ before PSM). As shown in Supplementary Table 6, Supplemental Digital Content 2, http://links.lww.com/JS9/A133 after PSM, patients in the NAR with wide RM group had significantly lower early recurrence and intrahepatic recurrence rates than those patients in the NAR with narrow RM group ($P = 0.020$ and 0.015). No matter whether the patients were in the AR group or NAR group, wide RM resulted in significantly lower operative margin recurrence rates than those patients in the narrow RM groups ($P = 0.002$ and 0.001). Furthermore, for patients who underwent narrow RM, AR still resulted in significantly lower adjacent intrahepatic segmental recurrence and higher distal segmental recurrence rates when compared with those patients who underwent NAR ($P = 0.047$).

Impact of AR or NAR combined with different RM status on OS and RFS before PSM

The four groups of patients with HCC and MVI who underwent different hepatectomy methods with different RM status showed significantly different OS and RFS rates before PSM ($P < 0.001$) (Fig. 1). Patients in the AR with wide RM group had significantly

Table 1

The clinicopathological characteristics of all HCC patients with MVI among different groups before PSM ($n = 1965$)

Variables	Total	AR and wide RM group ($n = 715$)	AR and narrow RM group ($n = 387$)	NAR and wide RM group ($n = 568$)	NAR and narrow RM group ($n = 295$)	*P*
Age, years						
≤ 60	1447 (73.6)	527 (73.7)	284 (73.4)	403 (71.0)	233 (79.0)	0.091
> 60	518 (26.4)	188 (26.3)	103 (26.6)	165 (29.0)	62 (21.0)	
Sex						
Female	298 (15.2)	105 (14.7)	66 (17.1)	87 (15.3)	40 (13.6)	0.614
Male	1667 (84.8)	610 (85.3)	321 (82.9)	481 (84.7)	255 (86.4)	
HBeAg						
Negative	1376 (70.0)	518 (72.4)	258 (66.7)	396 (69.7)	204 (69.2)	0.240
Positive	589 (30.0)	197 (27.6)	129 (33.3)	172 (30.3)	91 (30.8)	
HBV DNA, IU/ml						
$\leq 10^4$	1154 (58.7)	423 (59.2)	231 (59.7)	325 (57.2)	175 (59.3)	0.854
$> 10^4$	811 (41.3)	292 (40.8)	156 (40.3)	243 (42.8)	120 (40.7)	
AFP, ng/ml						
≤ 400	1320 (67.2)	488 (68.3)	257 (66.4)	385 (67.8)	190 (64.4)	0.660
> 400	645 (32.8)	227 (31.7)	130 (33.6)	183 (32.2)	105 (35.6)	
ALB, g/l						
< 35	172 (8.8)	53 (7.4)	31 (8.0)	62 (10.9)	26 (8.8)	0.158
≥ 35	1793 (91.2)	662 (92.6)	356 (92.0)	506 (89.1)	269 (91.2)	
ALT, U/l						
≤ 44	1250 (63.6)	478 (66.9)	230 (59.4)	379 (66.7)	163 (55.3)	**0.001**
> 44	715 (36.4)	237 (33.1)	157 (40.6)	189 (33.3)	132 (44.7)	
TBIL, mol/l						
≤ 17	1431 (72.8)	527 (73.7)	275 (71.1)	401 (70.6)	228 (77.3)	0.152
> 17	534 (27.2)	188 (26.3)	112 (28.9)	167 (29.4)	67 (22.7)	
PT, s						
≤ 13	1464 (74.5)	533 (74.5)	293 (75.7)	416 (73.2)	222 (75.3)	0.834
> 13	501 (25.5)	182 (25.5)	94 (24.3)	152 (26.8)	73 (24.7)	
PLT, 10^9/l						
< 100	393 (20.0)	131 (18.3)	91 (23.5)	123 (21.7)	48 (16.3)	0.051
≥ 100	1572 (80.0)	584 (81.7)	296 (76.5)	445 (78.3)	247 (83.7)	
Child–Pugh grade						
A	1755 (89.3)	642 (89.8)	335 (86.6)	519 (91.4)	259 (87.8)	0.091
B	210 (10.7)	73 (10.2)	52 (13.4)	49 (8.6)	36 (12.2)	
Varices						
Absent	1716 (87.3)	622 (87.0)	325 (84.0)	510 (89.8)	259 (87.8)	0.067
Present	249 (12.7)	93 (13.0)	62 (16.0)	58 (10.2)	36 (12.2)	
Cirrhosis						
No	504 (25.6)	175 (24.5)	113 (29.2)	133 (23.4)	83 (28.1)	0.138
Yes	1461 (74.4)	540 (75.5)	274 (70.8)	435 (76.6)	212 (71.9)	
Number of tumors						
Solitary	1763 (89.7)	661 (92.4)	351 (90.7)	503 (88.6)	248 (84.1)	**0.001**
Multiple	202 (10.3)	54 (7.6)	36 (9.3)	65 (11.4)	47 (15.9)	
Tumor diameter, cm						
≤ 5	1110 (56.5)	443 (62.0)	215 (55.6)	320 (56.3)	132 (44.7)	< **0.001**
> 5	855 (43.5)	272 (38.0)	172 (44.4)	248 (43.7)	163 (55.3)	
Satellite lesions						
Absent	1383 (70.4)	533 (74.5)	255 (65.9)	394 (69.4)	201 (68.1)	**0.014**
Present	582 (29.6)	182 (25.5)	132 (34.1)	174 (30.6)	94 (31.9)	
Tumor capsule						
Complete	960 (48.9)	385 (53.8)	165 (42.6)	280 (49.3)	130 (44.1)	**0.001**
Incomplete	416 (21.1)	147 (20.6)	78 (20.2)	117 (20.6)	74 (25.1)	
Absent	589 (30.0)	183 (25.6)	144 (37.2)	171 (30.1)	91 (30.8)	
Edmondson–Steiner grade						
≤ II	680 (34.6)	265 (37.1)	123 (31.8)	208 (36.6)	84 (28.5)	**0.027**
≥ III	1285 (65.4)	450 (62.9)	264 (68.2)	360 (63.4)	211 (71.5)	

Data are presented as *n* (%).

Bold text hinted that these variables were statistically significant.

AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AR, anatomical resection; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma, MVI, microvascular invasion; NAR, nonanatomical resection; PSM, propensity score matching; PLT, platelet; PT, prothrombin time; RM, resection margin.

Table 2

Multivariate analysis for OS and RFS in HCC patients with MVI before and after PSM

Cohort	Variables	OS			RFS		
		B	HR (95% CI)	*P*	*B*	HR (95% CI)	*P*
	HBeAg, positive vs. negative	–	–	–	0.060	1.061 (0.945–1.192)	0.313
	HBV DNA, IU/ml, $>10^4$ vs. $\leq 10^4$	0.402	1.494 (1.305–1.711)	**<0.001**	0.259	1.296 (1.160–1.447)	**<0.001**
	AFP, ng/ml, >400 vs. ≤400	0.302	1.353 (1.176–1.557)	**<0.001**	0.226	1.253 (1.119–1.405)	**<0.001**
	ALB, g/l, ≥35.vs. <35	–	–	–	-0.106	0.900 (0.753–1.075)	0.244
	ALT, U/l, >44.vs. ≤44	0.060	1.061 (0.925–1.218)	0.396	0.059	1.060 (0.948–1.186)	0.306
Before PSM	Number of tumors, multiple vs. solitary	0.228	1.256 (1.032–1.528)	**0.023**	0.207	1.230 (1.043–1.449)	**0.014**
(*n*=1965)	Tumor diameter, cm, >5.vs. ≤5	0.472	1.603 (1.397–1.838)	**<0.001**	0.351	1.421 (1.273–1.585)	**<0.001**
	Satellite lesions, present vs. absent	0.351	1.420 (1.235–1.634)	**<0.001**	0.226	1.253 (1.118–1.405)	**<0.001**
	Tumor capsule						
	Incomplete vs. complete	0.433	1.542 (1.302–1.826)	**<0.001**	0.302	1.352 (1.180–1.550)	**<0.001**
	Absent vs. complete	0.323	1.381 (1.186–1.607)	**<0.001**	0.199	1.220 (1.081–1.378)	**0.001**
	Edmondson–Steiner grade, ≥III vs. <II	0.302	1.353 (1.163–1.575)	**<0.001**	0.111	1.117 (0.996–1.254)	0.060
	RM, narrow vs. wide	0.309	1.363 (1.189–1.561)	**<0.001**	0.299	1.348 (1.208–1.505)	**<0.001**
	Hepatectomy method, NAR vs. AR	0.315	1.370 (1.201–1.564)	**<0.001**	0.271	1.311 (1.180–1.457)	**<0.001**
	HBeAg, positive vs. negative	0.061	1.063 (0.892–1.267)	0.493	0.091	1.095 (0.952–1.260)	0.202
	HBV DNA, IU/ml, $>10^4$ vs. $\leq 10^4$	0.429	1.535 (1.293–1.823)	**<0.001**	0.244	1.276 (1.113–1.464)	**<0.001**
	AFP, ng/ml, >400 vs. ≤400	0.276	1.318 (1.113–1.561)	**0.001**	0.239	1.270 (1.108–1.457)	**0.001**
	ALT, U/l, >44.vs. ≤44	0.062	1.064 (0.899–1.260)	0.472	0.118	1.125 (0.983–1.288)	0.088
After PSM for RM status	Number of tumors, multiple vs. solitary	0.263	1.301 (1.029–1.646)	**0.028**	0.181	1.198 (0.984–1.459)	0.072
(*n*=1292)	Tumor diameter, cm, >5.vs. ≤5	0.513	1.671 (1.410–1.979)	**<0.001**	0.321	1.378 (1.206–1.574)	**<0.001**
	Satellite lesions, present vs. absent	0.365	1.440 (1.219–1.702)	**<0.001**	0.262	1.299 (1.134–1.489)	**<0.001**
	Tumor capsule						
	Incomplete vs. complete	0.538	1.713 (1.392–2.109)	**<0.001**	0.351	1.420 (1.201–1.680)	**<0.001**
	Absent vs. complete	0.442	1.556 (1.291–1.875)	**<0.001**	0.287	1.332 (1.150–1.544)	**<0.001**
	Edmondson–Steiner grade, ≥III vs. <II	0.527	1.694 (1.385–2.071)	**<0.001**	0.203	1.225 (1.058–1.419)	**0.007**
	RM, narrow vs. wide	0.389	1.476 (1.255–1.736)	**<0.001**	0.345	1.413 (1.242–1.606)	**<0.001**
	Hepatectomy method, NAR vs. AR	0.313	1.367 (1.161–1.610)	**<0.001**	0.263	1.301 (1.142–1.483)	**<0.001**
	HBV DNA, IU/ml, $>10^4$ vs. $\leq 10^4$	0.432	1.540 (1.324–1.792)	**<0.001**	0.306	1.358 (1.203–1.534)	**<0.001**
	AFP, ng/ml, >400 vs. ≤400	0.256	1.292 (1.106–1.509)	**0.001**	0.233	1.262 (1.113–1.431)	**<0.001**
	ALT, U/l, >44.vs. ≤44	0.030	1.030 (0.883–1.202)	0.705	0.074	1.076 (0.951–1.219)	0.245
	Number of tumors, multiple vs. solitary	0.288	1.334 (1.076–1.654)	**0.009**	0.260	1.298 (1.084–1.553)	**0.004**
After PSM for hepatectomy method	Tumor diameter, cm, >5.vs. ≤5	0.451	1.570 (1.349–1.828)	**<0.001**	0.333	1.395 (1.237–1.573)	**<0.001**
(*n*=1584)							
	Satellite lesions, present vs. absent	0.338	1.402 (1.200–1.638)	**<0.001**	0.245	1.277 (1.125–1.450)	**<0.001**
	Tumor capsule						
	Incomplete vs. complete	0.421	1.524 (1.263–1.838)	**<0.001**	0.345	1.412 (1.214–1.642)	**<0.001**
	Absent vs. complete	0.287	1.332 (1.126–1.576)	**0.001**	0.185	1.203 (1.052–1.375)	**0.007**
	Edmondson–Steiner grade, ≥III vs. <II	0.302	1.353 (1.145–1.598)	**<0.001**	0.084	1.087 (0.958–1.234)	0.196
	RM, narrow vs. wide	0.322	1.380 (1.184–1.607)	**<0.001**	0.329	1.390 (1.229–1.572)	**<0.001**
	Hepatectomy method, NAR vs. AR	0.322	1.380 (1.193–1.596)	**<0.001**	0.268	1.307 (1.164–1.467)	**<0.001**

Bold text hinted that these variables were statistically significant.

AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AR, anatomical resection; B, Coefficient; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; MVI, microvascular invasion; NAR, nonanatomical resection; OS, overall survival; RFS, recurrence-free survival; RM, resection margin.

better OS rates than those in the AR with narrow RM group. The 1-year, 3-year, and 5-year OS rates for AR with wide RM, the AR with narrow RM, the NAR with wide RM and the NAR with narrow RM groups were 1-year OS: 91.3% vs. 83.4% vs. 84.6% vs. 75.3%; 3-year OS: 69.9% vs. 56.9% vs. 62.1% vs. 50.8%; 5-year OS: 56.7% vs. 46.6% vs. 44.4% vs. 34.1%; median OS 78.9 vs. 51.5 vs. 48.0 vs. 36.7 months, respectively, $P<0.001$) (Fig. 1A and Supplementary Table 7, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). For the RFS rates of these four groups of patients, the AR with wide RM group also had significantly better 1-year, 3-year, and 5-year RFS rates than three those groups (Fig. 1B and Supplementary Table 7, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). There were no significant differences in the OS and RFS rates between the AR with narrow RM and NAR with wide RM groups ($P=0.969$ and 0.735) (Supplementary Table 7, Supplemental Digital Content 2, http://links.lww.com/JS9/A133).

Impact of AR or NAR combined with different RM status on OS and RFS after PSM

As shown in Fig. 2, patients who underwent AR with narrow RM had significantly worse OS and RFS rates when compared to those patients who underwent AR with wide RM after PSM (median OS 53.1 vs. 75.7 months, $P=0.002$; median RFS 15.4 vs. 24.1 months, $P<0.001$, Fig. 2A-B and Supplementary Table 8, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). Similarly, patients who underwent NAR with narrow RM had significantly worse OS and RFS rates than those patients

Table 3

Time and patterns of tumor recurrence in HCC patients with MVI among different groups before PSM ($n = 1423$)

Characteristics	Total ($n = 1423$)	AR and wide RM group ($n = 466$)	AR and narrow RM group ($n = 292$)	NAR and wide RM group ($n = 426$)	NAR and narrow RM group ($n = 239$)	*P*
Time to recurrence						
Recurrence in 12 months	821 (57.7)	244 (52.4)	177 (60.6)	236 (55.4)	164 (68.6)	0.003
Recurrence in 12–24 months	276 (19.4)	105 (22.5)	50 (17.1)	88 (20.7)	33 (13.8)	
Recurrence over 24 months	326 (22.9)	117 (25.1)	65 (22.3)	102 (23.9)	42 (17.6)	
Type of recurrence						
Intrahepatic	958 (67.3)	302 (64.8)	199 (68.2)	283 (66.4)	174 (72.8)	0.391
Extrahepatic	247 (17.4)	89 (19.1)	47 (16.1)	80 (18.8)	31 (13.0)	
Intrahepatic plus extrahepatic	218 (15.3)	75 (16.1)	46 (15.8)	63 (14.8)	34 (14.2)	
Site of intrahepatic recurrencea	1176 (82.6)	377 (80.9)	245 (83.9)	346 (81.2)	208 (87.0)	
Operative margin	377 (32.1)	106 (28.1)	92 (37.6)	96 (27.7)	83 (39.9)	< 0.001
Adjacent segment	192 (16.3)	57 (15.1)	36 (14.7)	60 (17.3)	39 (18.8)	
Distal segment	255 (21.7)	100 (26.5)	43 (17.5)	81 (23.4)	31 (14.9)	
Multisegments	352 (29.9)	114 (30.3)	74 (30.2)	109 (31.5)	55 (26.4)	

Operative margin recurrence: any recurrence located within 2 cm of the operative margin, irrespective of any additional recurrence in other parts of the liver; adjacent segment recurrence: any recurrence located in the adjacent segment or in the same segment after subsegmentectomy, but with 2 cm away from the operative margin; distal segment recurrence: any recurrence did not locate in the adjacent segment or in the contralateral hemi-liver; multi-segments recurrence: recurrences involving multiple hepatic segments.

AR, anatomical resection; HCC, hepatocellular carcinoma; MVI, microvascular invasion; NAR, nonanatomical resection; PSM, propensity score matching; RM, resection margin.

alncluded intrahepatic only and intrahepatic plus extrahepatic recurrences.

with wide RM (median OS 36.7 vs. 46.7 months, $P = 0.002$; median RFS 9.1 vs. 17.6 months, $P = 0.005$; Figs 2C–D and Supplementary Table 8, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). Moreover, patients with wide RM who underwent AR had significantly better OS and RFS rates than those who underwent NAR after PSM for the same hepatectomy method (median OS 75.7 vs. 50.2 months, $P = 0.001$; median RFS 22.9 vs. 17.9 months, $P < 0.001$, Figs 3A, B and Supplementary Table 9, Supplemental Digital Content 2, http://links.lww.com/JS9/A133). Also, patients with narrow RM in the AR group had significantly better OS and RFS rates than those patients in the NAR group (median OS 47.3 vs. 38.3 months, $P = 0.004$; median RFS 13.6 vs. 9.3 months, $P = 0.009$, Figs 3C, D and Supplementary Table 9, Supplemental Digital Content 2, http://links.lww.com/JS9/A133).

Discussion

Over the past several decades, controversies exist on the effectiveness of AR and RM status in preventing HCC recurrence and the patterns of recurrence after LR for HCC[16,19,20]. The presence of MVI is known to be associated with worse surgical outcomes in patients with HCC after LR[10,13,24]. According to

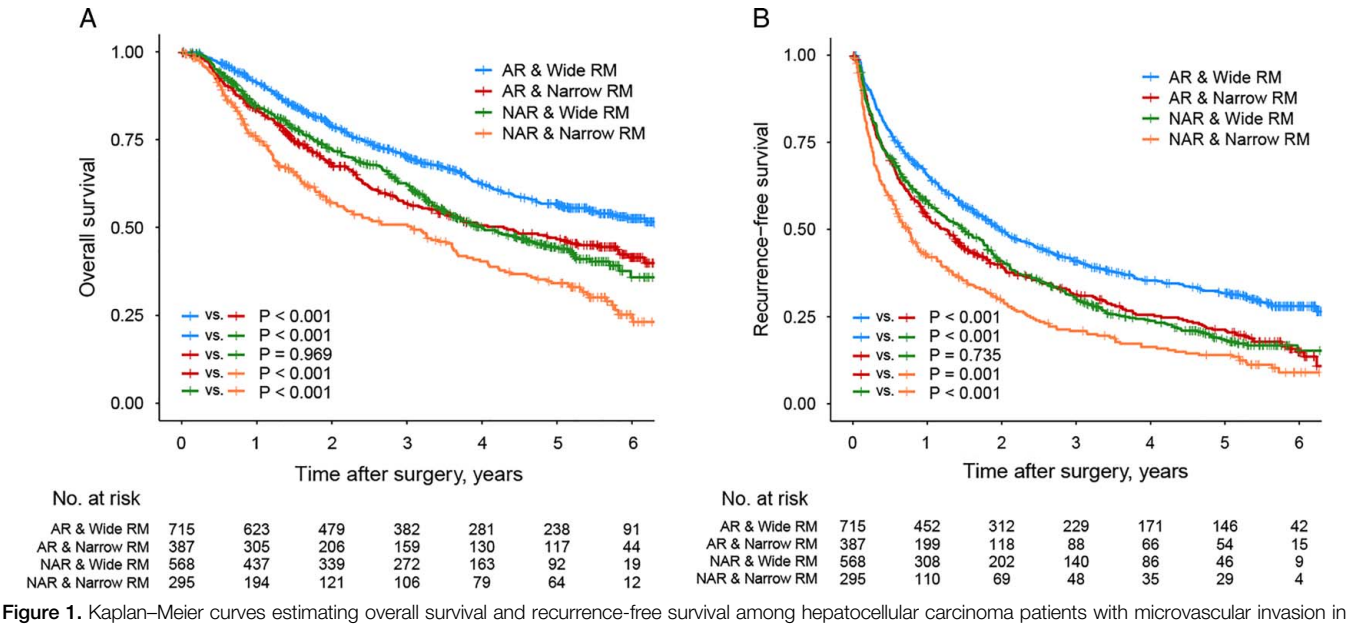

Figure 1. Kaplan–Meier curves estimating overall survival and recurrence-free survival among hepatocellular carcinoma patients with microvascular invasion in different groups before propensity score matching. (A) Overall survival of patients in anatomical resection (AR) and wide resection margin (RM) group, AR and narrow RM group, nonanatomical resection (NAR) and wide RM group, and NAR and narrow RM group. (B) Recurrence-free survival of patients in AR and wide RM group, AR and narrow RM group, NAR and wide RM group, and NAR and narrow RM group.

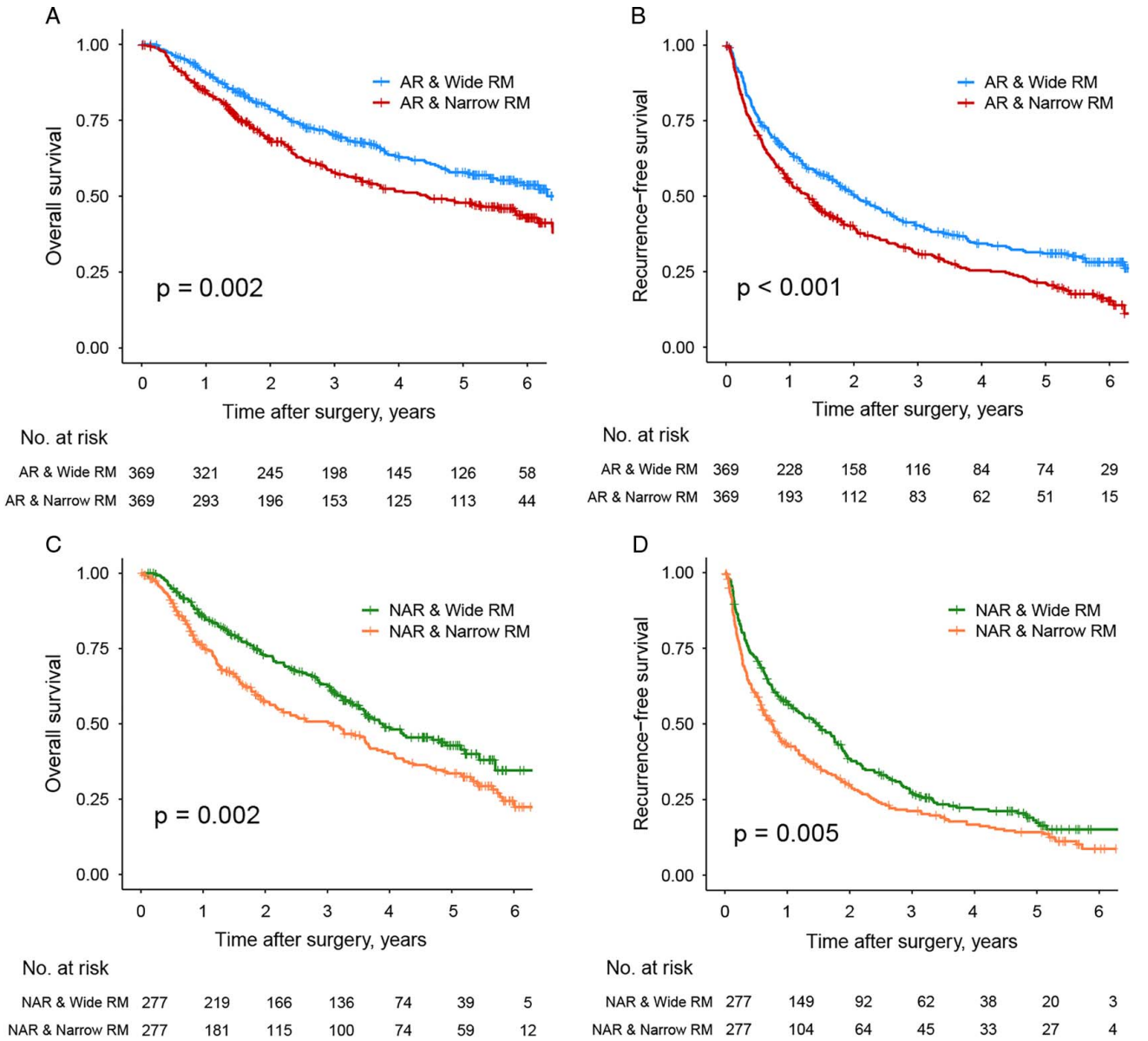

Figure 2. Kaplan–Meier curves estimating overall survival (OS) and recurrence-free survival (RFS) between hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI) in different hepatectomy method groups after propensity score matching (PSM) for resection margin (RM) status. (A, B) OS and RFS of patients with different RMs in anatomical resection (AR) group. (C, D) OS and RFS of patients with different RMs in nonanatomical resection (NAR) group.

the data, however, there are still no studies focusing on the impact of AR and RM status on HCC recurrence in patients with HCC and MVI following curative LR. This multicenter study on 1965 HBV-related HCC patients with MVI is the first to demonstrate the correlations between AR/NAR and RM status (narrow/wide margin) with long-term survival outcomes of patients with HCC and MVI.

In the present study, there were significant differences in long-term prognosis among the four groups stratified by RM status and hepatectomy methods: AR with wide RM, AR with narrow RM, NAR with wide RM, and NAR with narrow RM. Patients with HCC and MVI who were in the AR with wide RM group had the best oncologic outcomes, while those in the NAR with narrow RM group had the worst long-term prognosis. After PSM, multivariate Cox regression analysis of survival outcomes demonstrated that both the NAR procedure and the narrow RM status were independent risk factors for OS or RFS. For the impact of these two factors on the timings and patterns of tumor recurrence, this study revealed that patients in both AR and NAR groups who underwent wide RM resulted in significantly lower operative margin recurrence rates than those who underwent narrow RM. Thus, AR combined with wide RM was the most favorable approach in patients with HCC and MVI.

Surgical procedure for patients with HCC aims to completely extirpate the tumor to achieve a pathologically negative RM, to clear all possible vascular and adjacent organ invasion and/to prevent potential intrahepatic or extrahepatic metastases beyond the tumor[20,25]. AR is better suited to prevent the spread of HCC

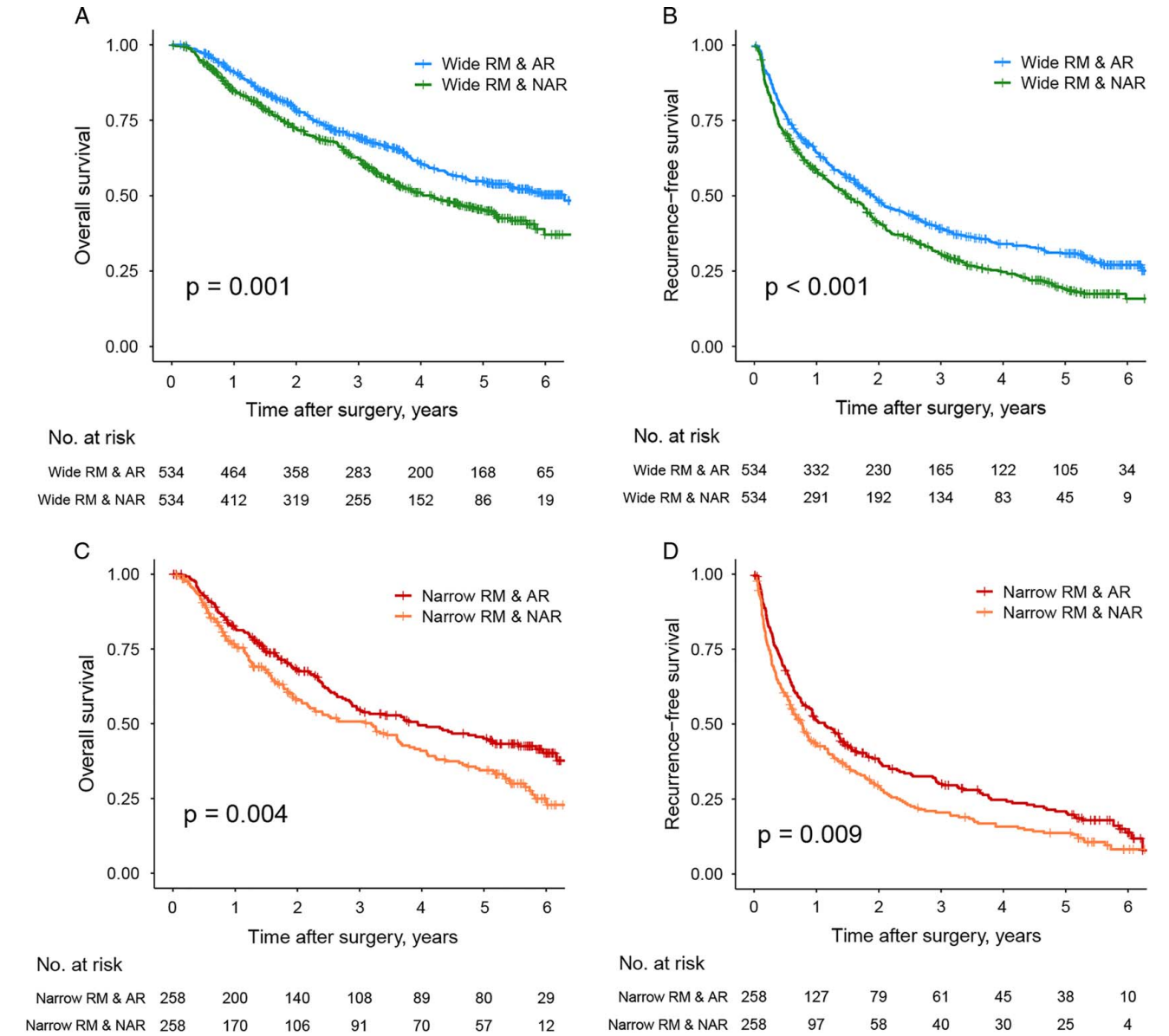

Figure 3. Kaplan–Meier curves estimating overall survival (OS) and recurrence-free survival (RFS) between hepatocellular carcinoma (HCC) patients with microvascular invasion (MVI) in different resection margin (RM) status groups after propensity score matching (PSM) for hepatectomy method. (A, B) OS and RFS of patients with different hepatectomy methods in wide RM group; (C, D) OS and RFS of patients with different hepatectomy methods in narrow RM group.

through the portal vein when pathological progression of HCC is considered. Previous studies reported that AR improved the OS and RFS rates after LR, and was an independent factor for long-term prognosis of HCC with similar survival outcomes as in patients with absence of MVI[15,26]. A meta-analysis demonstrated that AR provided significantly better long-term prognosis than NAR in HCC patients without MVI or macrovascular invasion[27]. Another multicenter study from our team on the actual long-term survival in patients with HCC and MVI indicated that AR resulted in significantly better long-term survival outcomes[14]. Interestingly, a Japanese multi-institutional study proved that AR for HCC with MVI in microportal vein did not influence the long-term survival outcomes after hepatectomy[17], although local recurrence around the resection site was significantly decreased by AR. The conflicting findings in these studies are probably related to the differences in the background of vital status, the proportion of patients with liver cirrhosis, the RM status and the severity of MVI between groups. This multicenter, large sample size study demonstrated that AR improved long-term survival outcomes in patients with HCC and MVI when compared to NAR, regardless of wide or narrow RM. Patients who underwent AR with wide RM had the best survival outcomes. Since MVI is a known risk factor for tumor recurrence in patients with HCC following hepatectomy, it is expected that AR with wide RM results in significantly lower marginal recurrence rates, lower early recurrence rates, and better long-term outcomes in patients with HCC and MVI.

Previous studies have demonstrated that portal vein invasion and intrahepatic micrometastasis mainly occur within 1 cm of the

main tumor, and rarely extend to more than 2 cm of the tumor[28,29], which suggested that surgical resection with a wide RM (≥ 1 cm) may better eradicate MVI adjacent to tumors[30]. Yang *et al.*[19] indicated that a wide-margin hepatectomy prevented tumor recurrence only in patients with MVI, but not in patients without MVI. However, the decision to use a wide margin hepatectomy in patients with cirrhosis should be made carefully based on adequate liver functional reserve of the remnant liver before LR. Another study found HCC patients with MVI had a significantly higher incidence of intrahepatic recurrence (with or without extrahepatic recurrence) after narrow RM hepatectomy than those without MVI who underwent wide RM hepatectomy[18]. However, Aoki *et al.*[20] reported that a negative but 0 mm surgical margin to be associated with worse long-term survival outcomes when compared with a wide margin only in the NAR group. In the AR group, the width of surgical margin was not associated with long-term survival outcomes. Our previous study indicated that AR had the advantages of decreasing intraoperative blood loss and achieving wider RM[14]. The present study confirmed that patients in the AR with wide RM group had a significantly better long-term prognosis than patients in the other three groups.

Since the presence of MVI before hepatectomy is the key to determining the method of hepatectomy and the status of RM, it is particularly vital to accurately predict the presence or absence of MVI before surgery. Recently, a number of nomograms have been reported, which can help surgeons predict MVI in HCC patients before operation[7,31,32]. For example, Lei *et al.*[7] demonstrated that the preoperative factors associated with MVI were large tumor diameter, multiple nodules, incomplete capsule, α-fetoprotein level greater than 20 ng/mL, platelet count less than 100×10^3/μl, HBV DNA load greater than 10^4 IU/ml, and a typical dynamic pattern of tumors on contrast-enhanced magnetic resonance imaging. Incorporating these seven factors, the nomogram achieved good concordance indexes in predicting MVI in the training and validation cohorts, respectively, and had well-fitted calibration curves. Although a highly specific tool is still lacking, there is growing evidence that it is becoming increasingly possible to identify patients at high risk of MVI before surgery. For patients who are predicted to be at high risk of MVI based on preoperative assessment, AR with wide RM should be recommended if technically feasible and safe. The results of this study also suggested that narrow RM hepatectomy increased the risk of postoperative recurrence. The worse prognosis in HCC patients with MVI who underwent NAR and narrow RM indicated that further studies of adjuvant therapy should be performed in this group of patients.

This study also had several limitations. First, this is a retrospective study, with its inherent shortcomings. Better designed prospective studies should be conducted to further evaluate the impact of AR and RM status on these patients. Second, this study focused on patients with HBV infection, and it is uncertain whether the results obtained in this study can be extrapolated to HCV-related or alcohol-related HCC. Third, due to the limitations of the pathology techniques used during the study, a more detailed stratification of the MVI could not be performed. Fourth, the heterogeneity in preoperative and postoperative imaging assessment methods is also a non-negligible bias. Finally, as a retrospective study, the information on postoperative adjuvant therapy was not collected, it was very difficult to compare the prognostic effects between whether adjuvant therapy was used or not, and on the different adjuvant strategies when they were used.

In conclusion, this study revealed that AR with wide RM was associated with the best survival outcomes in patients with HCC and MVI after hepatectomy. Wide RM resulted in a significantly lower RM recurrence rate than narrow RM, regardless of whether the patient was in the AR or NAR group. If technically feasible and safe, AR with wide RM is the best therapeutic strategy for HCC patients who are estimated to have a high risk of MVI using the currently available preoperative predictive models.

Ethical approval

This study was approved by the Institutional Ethics Committees of all the seven participating hospitals.

Consent to publishing

Consent for publication was obtained from all authors.

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Authors contributions

R.L., S.-Q.C., W.Y.L., X.-P.Z., S.X., M.-G.H.: conception and design. R.L., S.-Q.C., M.-G.H.: financial support. K.W., Z.-L.C., M.-L.Y., F.Z., Y.-F.T., Z.-M.Z., C.-G.L.: provision of study materials or patients. X.-P.Z., S.X., Q.-L.G.: collection and assembly of data. X.-P.Z., S.X., Z.-Y.L.: data analysis and interpretation. X.-P.Z. and W.Y.L.: manuscript writing. Final approval of manuscript done by all authors.

Conflicts of interest disclosure

The authors who participate in this study have no conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: Significance of Anatomical Resection and Resection Margin Status in Patients with HBV-related Hepatocellular Carcinoma and Microvascular Invasion: A Multicenter Propensity Score-Matched Study.
2. Unique Identifying number or registration ID: The Unique Identification Number is researchregistry8069.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): The study was registered with https://www.researchregistry.com/registernow#home/registrationdetails/62bfc20fe158f5001e4703d0/

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Data availability

The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Animal research

Not applicable.

Plant reproducibility

Not applicable.

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