

Resection Margin Width Does Not Influence the Prognosis of Solitary Hepatocellular Carcinoma After Anatomic Resection: A Real-World Study from China

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Purpose: The influence of resection margin (RM) width on the prognosis of solitary hepatocellular carcinoma (HCC) following anatomical resection (AR) has yet to be determined. Therefore, we conducted a real-world study to identify the optimal RM width and assess its impact on the outcomes of solitary HCC patients undergoing AR.

Methods: The data pertaining to patients diagnosed with solitary HCC who underwent AR between December 2012 and December 2015 were retrospectively collected. The optimal cutoff value for the width of the RM was determined using X-tile software. The Kaplan-Meier method was utilized to compare the overall survival (OS) and disease-free survival (DFS) between the narrow and wide RM groups. Additionally, propensity score matching (PSM) was performed to minimize potential bias in the data.

Results: Of the 1033 patients who met the inclusion criteria, 293 (28.4%) were categorized into the narrow RM group (≤ 4 mm) and 740 (71.6%) into the wide RM group (> 4 mm). Before and after PSM, there were no significant differences in OS and DFS between the two groups (before PSM: OS, HR=0.78, $P=0.071$; DFS, HR=0.95, $P=0.620$; after PSM: OS, HR=0.77, $P=0.150$; DFS, HR=0.90, $P=0.470$). Multivariate analysis demonstrated that RM width was not an independent risk factor for DFS and OS both before and after PSM (all $P>0.05$). However, subgroup analyses revealed that patients with ALBI grade 1, absence of cirrhosis, and AJCC stage II significantly benefited from wide RM in OS (all $P<0.05$). Similarly, patients without HBV infection and absence of cirrhosis also exhibited significant benefits from wide RM in DFS (both $P<0.05$).

Conclusion: In patients with solitary HCC undergoing AR, the width of the RM does not appear to have a significant impact on their prognosis. However, in certain selected patients, a wider RM may confer benefits.

Keywords: hepatocellular carcinoma, anatomical resection, resection margin, prognosis

Introduction

Surgical resection is considered the most cost-effective curative treatment for hepatocellular carcinoma (HCC).¹⁻³ Anatomical resection (AR) and non-anatomical resection (NAR) are the two commonly employed modalities.^{2,4} AR involves the complete removal of liver segments according to Couinaud's classification, which is typically accompanied by segmentectomy, hemihepatectomy, or trisectionectomy.⁵ Compared to NAR, AR allows for the complete removal of the tumor-bearing portal territory, decreasing the risk of tumor dissemination and metastasis in the involved liver segment

through the portal vein blood flow.^{6,7} In the concept of modern precision surgery, AR is increasingly valued. Nevertheless, the 5-year postoperative recurrence rate of HCC remains high at approximately 70%,⁸ presenting significant challenges to both surgeons and patients.

The width of the RM plays a significant role in the recurrence and metastasis of HCC after radical resection.^{9,10} Although there is no consensus on the optimal RM width, many studies have suggested that a wider RM, based on achieving R0 resection, can reduce postoperative recurrence and improve long-term survival due to the detection of more micrometastases.^{11,12} However, there is still controversy regarding the width of RM and the choice of surgical modalities. A systematic review of 12,429 samples from 43 studies revealed patients received AR were accompanied by wider RM (mean difference: +0.29cm, 95% CI: 0.15–0.44, $P < 0.001$).⁵ However, the results of a study by Su et al¹³ demonstrated that the width of RM did not influence the prognosis of patients with solitary HCC ≤ 2 cm in diameter who received AR. Conversely, for patients undergoing NAR, a wide margin (> 1 cm) may improve postoperative recurrence-free survival. Nevertheless, some studies suggest that a wider RM may improve outcomes in patients undergoing AR, particularly those with microvascular invasion (MVI).^{14,15}

This study aimed to recruit 1033 patients with solitary HCC who had undergone AR from two tertiary specialized hepatopancreatobiliary (HPB) centers to 1) determine the optimal RM width for the resection of solitary HCC, and 2) evaluate the influence of RM width on the prognosis of patients with solitary HCC.

Materials and Methods

Patient Selection

This study was in accordance with the guidance of Declaration of Helsinki and approved by Mengchao Hepatobiliary Hospital of Fujian Medical University's Ethics Committee (2021_004_01). Informed consent was obtained from all participants prior to the initiation of the study. All patients diagnosed with solitary HCC who underwent AR were considered eligible for inclusion in this study. However, patients who had undergone preoperative treatments, the presence of macrovascular or bile duct invasion or lymph node metastasis, did not undergo radical resection, experienced perioperative mortality, or had incomplete clinical or follow-up data were excluded from the study.

Data Collection

Data of HCC patients who underwent radical resection between December 2012 and December 2015 from two tertiary specialized HPB centers were collected in a predefined form, including age, gender, HBV infection (yes or no), preoperative white blood cell count, hemoglobin, platelet count, preoperative serum levels of total bilirubin (TBil), albumin, albumin-bilirubin score (ALBI, > -2.60 or ≤ -2.60), alpha-fetoprotein (AFP, > 20 or ≤ 20 ng/mL), gamma-glutamyl transferase (GGT, > 72 or ≤ 72 U/L) and alkaline phosphatase (ALP, > 104 or ≤ 104 U/L), cirrhosis (present or absent), hospital stays (> 10 or ≤ 10 days), RM width (> 4 or ≤ 4 mm), tumor diameter (> 5 or ≤ 5 cm), Edmondson-Steiner (ES) grade (I–II or III–IV), satellite (yes or no), capsule (absent or present), MVI (yes or no), adjuvant transarterial chemoembolization (TACE, yes or no) and follow-up.

In accordance with the previous formula [$0.66 \times \log_{10}(\text{bilirubin, } \mu\text{mol/L}) - 0.085 \times (\text{albumin, g/L})$], grade 1: ≤ -2.60 , grade 2: > -2.60 to ≤ -1.39 , grade 3: > -1.39], the ALBI score and grade were calculated.¹⁶ Due to the small sample size, ALBI grade 2 and ALBI grade 3 were grouped together. The RM width was defined as the shortest distance between the liver section and the tumor edge.¹⁷ The optimal cut-off value for AFP level was determined by previous reports,¹³ while those for GGT, ALP, hospital stays, and RM width were determined by X-tile software.

Follow-Up

Patients were followed up as recommended by the Chinese guideline for HCC.² Briefly, a comprehensive evaluation including AFP levels, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) at one month after surgery. Then, patients received routine examination every three months in the first 2 year after surgery, every six months from 2–5 years, and every 12 months after 5 years. Once a suspected recurrence or metastasis is confirmed by contrast enhanced CT or MRI, salvage treatment should be initiated immediately.

Study Endpoints

The primary endpoints were overall survival (OS) and disease-free survival (DFS). OS time was defined as the time between the date of the operation and either the date of death or the latest follow-up, while DFS time was defined as the time between the date of the operation and the date of recurrence or the latest follow-up.

Statistical Analysis

Data are shown as prevalence and means (standard deviation). Continuous variables were compared by the Student's *t*-test between groups, while categorical variables were by the chi-squared test. Kaplan-Meier curves of OS and DFS were compared using Log rank test with hazard ratio (HR) and 95% confidence interval (CI). Prognostic factors were identified using the forward method of the Cox regression model, and the assumption of proportional hazards was assessed using Schoenfeld residuals.¹⁸ Factors with a significance level of $P < 0.10$ in univariate analysis were subsequently included in the multivariate Cox regression analysis. Notably, RM width (wide vs narrow) were automatically incorporated in multivariate analysis, regardless of their differences in univariate analysis. Propensity score matching (PSM) was adopted to decrease the selection bias. Variables with a $P < 0.05$ between groups were used to be matched using a 1:1 nearest neighbor method with a caliber of 0.01 as depicted previously.¹⁹

The statistical analysis was conducted using Rstudio including packages of “Table 1”, “MatchIt”, “survminer”, and “survival”. For all statistical tests, statistical significance was defined as two-sided $P < 0.05$ in this study.

Table 1 Clinicopathological Characteristics Before and After PSM

Variables		Before PSM			After PSM		
		Narrow RM (n=293)	Wide RM (n=740)	P-value	Narrow RM (n=269)	Wide RM (n=269)	P-value
Age	Years	53.4±10.2	51.9±11.1	0.043	53.3±10.2	53.2±11.1	0.945
Gender	Female	41 (14.0%)	113 (15.3%)	0.673	39 (14.5%)	44 (16.4%)	0.633
	Male	252 (86.0%)	627 (84.7%)		230 (85.5%)	225 (83.6%)	
HBV infection	No	63 (21.5%)	163 (22.0%)	0.920	61 (22.7%)	62 (23.0%)	1
	Yes	230 (78.5%)	577 (78.0%)		208 (77.3%)	207 (77.0%)	
White blood cell count	×10 ⁹ /L	4.94 [4.19–5.97]	5.14 [4.21–6.21]	0.051	4.94 [4.19–5.99]	4.98 [4.17–6.07]	0.864
Hemoglobin	g/L	142±15.2	142±15.2	0.858	142±15.2	141±15.4	0.653
Platelet count	×10 ⁹ /L	146 [111–185]	154 [120–198]	0.057	151 [111–186]	148 [120–181]	0.999
ALBI grade	1	253 (86.3%)	647 (87.4%)	0.714	234 (87.0%)	232 (86.2%)	0.899
	2	40 (13.7%)	93 (12.6%)		35 (13.0%)	37 (13.8%)	
AFP	≤20 ng/mL	128 (43.7%)	347 (46.9%)	0.388	120 (44.6%)	133 (49.4%)	0.300
	>20 ng/mL	165 (56.3%)	393 (53.1%)		149 (55.4%)	136 (50.6%)	
GGT	≤72 U/L	202 (68.9%)	574 (77.6%)	0.005	198 (73.6%)	198 (73.6%)	1
	>72 U/L	91 (31.1%)	166 (22.4%)		71 (26.4%)	71 (26.4%)	
ALP	≤104 U/L	249 (85.0%)	667 (90.1%)	0.025	239 (88.8%)	240 (89.2%)	1
	>104 U/L	44 (15.0%)	73 (9.9%)		30 (11.2%)	29 (10.8%)	
Hospital stays	≤10 days	262 (89.4%)	658 (88.9%)	0.903	242 (90.0%)	235 (87.4%)	0.415
	>10 days	31 (10.6%)	82 (11.1%)		27 (10.0%)	34 (12.6%)	
Tumor diameter	≤5 cm	197 (67.2%)	535 (72.3%)	0.124	185 (68.8%)	197 (73.2%)	0.296
	>5 cm	96 (32.8%)	205 (27.7%)		84 (31.2%)	72 (26.8%)	
Cirrhosis	Absent	90 (30.7%)	238 (32.2%)	0.707	84 (31.2%)	77 (28.6%)	0.572
	Present	203 (69.3%)	502 (67.8%)		185 (68.8%)	192 (71.4%)	
ES grade	I–II	26 (8.9%)	74 (10.0%)	0.663	23 (8.6%)	27 (10.0%)	0.656
	III–IV	267 (91.1%)	666 (90.0%)		246 (91.4%)	242 (90.0%)	
Satellite	No	172 (58.7%)	415 (56.1%)	0.486	160 (59.5%)	149 (55.4%)	0.383
	Yes	121 (41.3%)	325 (43.9%)		109 (40.5%)	120 (44.6%)	

(Continued)

Table 1 (Continued).

Variables		Before PSM			After PSM		
		Narrow RM (n=293)	Wide RM (n=740)	P-value	Narrow RM (n=269)	Wide RM (n=269)	P-value
Capsule	Present	231 (78.8%)	565 (76.4%)	0.438	216 (80.3%)	211 (78.4%)	0.670
	Absent	62 (21.2%)	175 (23.6%)		53 (19.7%)	58 (21.6%)	
MVI	No	189 (64.5%)	498 (67.3%)	0.433	179 (66.5%)	177 (65.8%)	0.927
	Yes	104 (35.5%)	242 (32.7%)		90 (33.5%)	92 (34.2%)	
AJCC stage	Ia	23 (7.8%)	87 (11.8%)	0.172	23 (8.6%)	30 (11.2%)	0.568
	Ib	173 (59.0%)	427 (57.7%)		163 (60.6%)	155 (57.6%)	
	II	97 (33.1%)	226 (30.5%)		83 (30.9%)	84 (31.2%)	
Adjuvant TACE	No	209 (71.3%)	540 (73.0%)	0.649	193 (71.7%)	193 (71.7%)	1
	Yes	84 (28.7%)	200 (27.0%)		76 (28.3%)	76 (28.3%)	

Abbreviations: PSM, propensity score matching; HBV, hepatitis B virus; ALBI, albumin bilirubin score; AFP, alpha-fetoprotein; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; ES, Edmondson-Steiner; MVI, microvascular invasion; AJCC, the American Joint of Cancer Committee system; TACE, transarterial chemoembolization.

Results

Patient's Characteristics

Initially, a total of 1552 patients with solitary HCC who received AR were enrolled for this study. Based on the pre-defined inclusion and exclusion criteria, 1033 patients were eligible for the analysis. The patient's selection process is depicted in Figure 1. The optimal cut-off value for the RM was determined using the X-tile software. [Supplementary Figure 1](#) shows that the RM was skewed distribution, and a cut-off value of 4mm was chosen, which corresponded to the maximum X^2 value for both OS and DFS analyses (Figure 1A: OS, $P=0.071$, $X^2=3.54$; Figure 1B: DFS, $P=0.620$, $X^2=0.245$).

Using the current cut-off value, 293 patients (28.4%) were classified into the narrow RM group ($RM \leq 4mm$), while 740 patients (71.6%) were categorized into the wide RM group ($RM > 4mm$). As shown in Table 1, the narrow RM group had a significantly higher age and percentages of GGT $>72U/L$ and ALP $>104U/L$ than the wide RM group (all $P < 0.05$, Table 1). However, after conducting 1:1 PSM, the baseline characteristics between the two groups were comparable (all $P > 0.05$, Table 1).

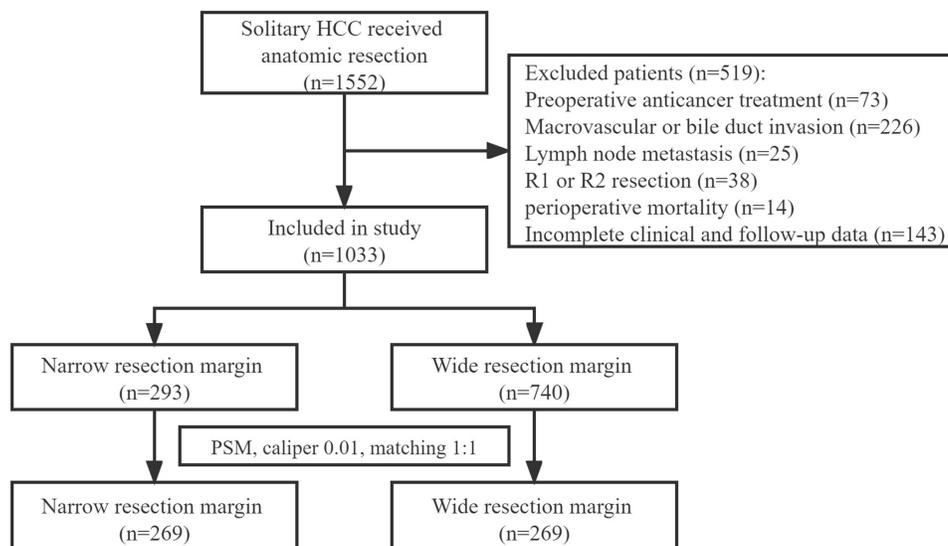


Figure 1 The flow chart in patient's selection.

Survival Analysis Between Wide and Narrow RM

Before PSM, the 1-, 3-, and 5-year OS rates for the wide RM group were 94.1%, 76.8%, and 59.1%, respectively. In contrast, the corresponding OS rates for the narrow RM group were 91.3%, 71.9%, and 49.6%, respectively (Figure 2A). Regarding DFS, the 1-, 3-, and 5-year rates for the wide RM group were 81.4%, 58.9%, and 43.4%, respectively, while for the narrow RM group, they were 78.2%, 59.2%, and 39.1%, respectively (Figure 2B). There was no significant survival advantage observed for the wide RM group compared to the narrow RM group in terms of both OS and DFS (OS: HR=0.78, 95% CI: 0.60–1.02, $P=0.071$; DFS: HR=0.95, 95% CI: 0.76–1.17, $P=0.620$, Figure 2A and B).

After PSM, the 1-, 3-, and 5-year OS rates in the wide RM group were 93.6%, 86.3%, and 57.6%, respectively, whereas in the narrow RM group, the corresponding rates were 93.3%, 72.9%, and 53.7%, respectively (Figure 2C). Similarly, the 1-, 3-, and 5-year DFS rates in the wide RM group were 83.0%, 61.2%, and 45.6%, respectively, whereas

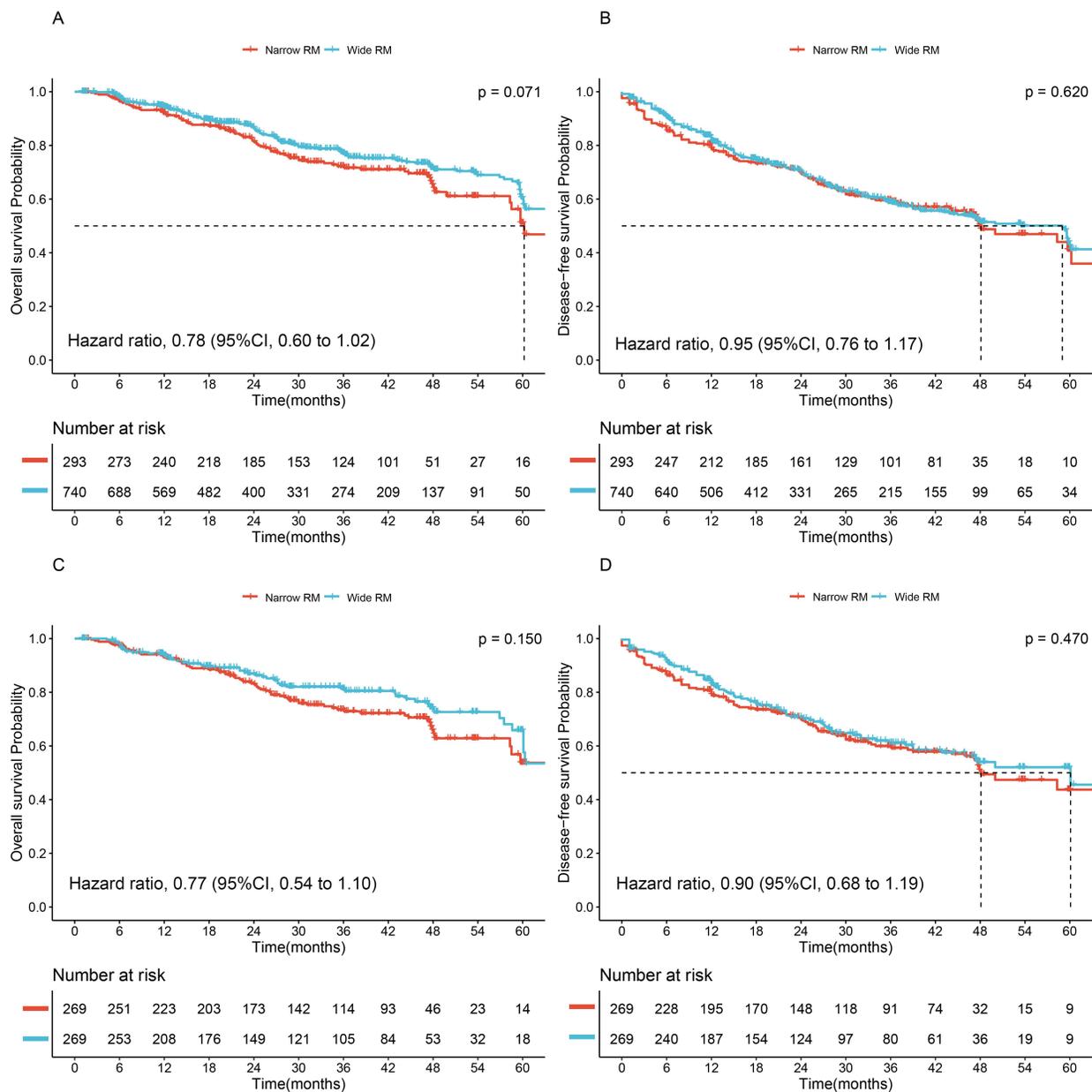


Figure 2 Survival analysis of wide RM and narrow SM groups before and after PSM (before PSM: (A), overall survival; (B), disease-free survival; after PSM: (C), overall survival; (D), disease-free survival).

in the narrow RM group, the corresponding rates were 79.1%, 59.3%, and 43.7%, respectively (Figure 2D). Statistical analysis revealed no significant survival advantage for the wide RM group compared to the narrow RM group in terms of both OS and DFS (OS: HR=0.77, 95% CI: 0.54–1.10, $P=0.150$; DFS: HR=0.90, $P=0.470$, Figure 2C and D).

Independent Factors Associated with OS and DFS

The assessment of the assumption of proportional hazards was conducted in both the pre- and post-PSM cohorts, with the results presented in [Supplementary Table 1](#). Upon careful examination of the test outcomes, it is apparent that none of the covariates exhibit statistical significance ($P > 0.05$), and the global test also fails to achieve statistical significance. As a consequence, we can infer that the Cox model employed in this study satisfies the assumption of proportional hazards.

Prior to PSM, the results presented in [Table 2](#) indicated that several variables were independent risk factors for OS, including ALP >104U/L (HR=1.55, 95% CI=1.07–2.26), hospital stays >10 days (HR=1.77, 95% CI=1.27–2.47), tumor diameter >5cm (HR=1.65, 95% CI=1.26–2.17), presence of cirrhosis (HR=1.47, 95% CI=1.12–1.96), and MVI (HR=1.94, 95% CI=1.46–2.57). Additionally, HBV infection (HR=1.32, 95% CI=1.02–1.72), GGT>72U/L (HR=1.30, 95% CI=1.03–1.63), ALP >104U/L (HR=1.42, 95% CI=1.05–1.92), hospital stays >10 days (HR=1.54, 95% CI=1.16–2.04), tumor diameter >5cm (HR=1.46, 95% CI=1.17–1.82), and presence of MVI (HR=1.47, 95% CI=1.15–1.87) were identified as independent risk factors for DFS.

After PSM, the results presented in [Table 3](#) showed that ALBI grade 2 (HR=1.97, 95% CI=1.25–3.11), hospital stays >10 days (HR=1.79, 95% CI=1.13–2.85), presence of cirrhosis (HR=1.56, 95% CI=1.05–2.33), and MVI (HR=2.30, 95% CI=1.57–3.37) were identified as independent risk factors for OS. Hospital stays >10 days (HR=1.65, 95% CI=1.11–2.44), tumor diameter >5cm (HR=1.38, 95% CI=1.01–1.89), and presence of MVI (HR=1.63, 95% CI=1.21–2.18) were identified as independent risk factors for DFS.

Of note, as presented in both [Table 2](#) and [3](#), wide RM was not found to be independent factor for either OS or DFS.

Subgroup Analysis

Subgroup analyses were conducted on the PSM cohort, stratified by different factors, and the findings are presented in [Figures 3](#) and [4](#). It was observed that patients with ALBI grade 1, the absence of cirrhosis, and AJCC stage II benefited from wide RM in terms of OS (all $P<0.05$, [Figure 3](#)). Furthermore, patients without HBV infection and absence of cirrhosis exhibited a significant benefit from wide RM in terms of DFS (all $P<0.05$, [Figure 4](#)).

Discussion

Despite being a subject of controversy, the prevailing view maintains that AR surpasses NAR in terms of reducing postoperative recurrence.^{6,20} Moreover, the necessity of achieving extensive RM in patients undergoing AR remains underreported. In this study, a total of 1033 patients who were diagnosed with solitary HCC and underwent AR at two specialized HPB centers were analyzed. The X-tile software was utilized to determine the optimal cut-off value for RM, which was found to be 4mm. Subsequent analysis demonstrated that there was no statistically significant difference in OS and DFS between the wide RM group (RM >4mm) and narrow RM group (RM ≤4mm) in both the unmatched and matched cohorts. Furthermore, the width of RM was not identified as an independent risk factor for either OS or DFS (both $P>0.05$).

The objective of HPB surgeons is to minimize potential lesions as much as possible. Previous studies have demonstrated that wide RM can reduce the risk of postoperative recurrence.^{12,21} Therefore, wide RM has been recommended for patients with good liver function and sufficient residual liver volume.² However, the optimal cut-off value for wide RM remains controversial. Several commonly used cut-off values for RM width include 1cm, 2cm, 5mm, and 2mm, but these values are not often supported by high-level evidence-based medicine.^{10,12,13,22} Nitta et al²³ proposed a cut-off value of 7mm for RM width based on the minimum P value. Other studies suggested that the optimal RM width is determined by the pretreatment AFP levels.^{24,25} In the current study, X-tile software was utilized to identify the optimal cut-off value for RM width, and a width of 4mm was chosen as the optimal RM width.

However, the efficacy of a wide RM in improving the prognosis of patients receiving AR for HCC remains a controversial topic. To explore the impact of RM width on patient outcomes, Aoki et al²⁶ conducted a multicenter

Table 2 Univariate and Multivariate Analysis of Overall Survival and Disease-Free Survival Before PSM

Characteristics	OS				DFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95CI)	P-value						
Age (years)	1.00 (0.99–1.01)	0.644			1.00 (0.99–1.01)	0.598		
Gender (Male vs Female)	0.99 (0.69–1.43)	0.963			1.17 (0.87–1.57)	0.289		
HBV infection (Yes vs No)	0.92 (0.67–1.25)	0.582			1.31 (1.01–1.69)	0.043	1.32 (1.02–1.72)	0.036
White blood cell count ($\times 10^9/L$)	1.05 (0.99–1.12)	0.106			1.03 (0.98–1.08)	0.278		
Hemoglobin (g/L)	0.99 (0.98–1.01)	0.170			1.00 (0.99–1.01)	0.727		
Platelet count ($\times 10^9/L$)	1.01 (0.99–1.02)	0.257			1.00 (0.99–1.01)	0.994		
ALBI grade (2 vs 1)	1.59 (1.14–2.23)	0.007	1.41 (0.99–2.01)	0.053	1.42 (1.08–1.87)	0.013	1.25 (0.94–1.65)	0.126
AFP (>20 vs ≤ 20 ng/mL)	1.40 (1.07–1.82)	0.012	1.17 (0.89–1.53)	0.267	1.30 (1.06–1.59)	0.012	1.11 (0.90–1.37)	0.308
GGT(>72 vs ≤ 72 U/L)	1.61 (1.23–2.11)	0.001	1.29 (0.97–1.73)	0.081	1.53 (1.24–1.90)	<0.001	1.30 (1.03–1.63)	0.026
ALP (>104 vs ≤ 104 U/L)	2.03 (1.44–2.88)	<0.001	1.55 (1.07–2.26)	0.022	1.75 (1.32–2.32)	<0.001	1.42 (1.05–1.92)	0.021
RM (wide vs narrow)	0.78 (0.60–1.02)	0.072	0.88 (0.67–1.16)	0.369	0.95 (0.76–1.17)	0.616	0.94 (0.86–1.33)	0.555
Hospital stays (>10 vs ≤ 10 days)	2.06 (1.49–2.83)	<0.001	1.77 (1.27–2.47)	0.001	1.67 (1.27–2.20)	<0.001	1.54 (1.16–2.04)	0.003
Tumor diameter (>5 vs ≤ 5 cm)	2.06 (1.59–2.67)	<0.001	1.65 (1.26–2.17)	<0.001	1.65 (1.34–2.03)	<0.001	1.46 (1.17–1.82)	0.001
Cirrhosis (Present vs Absent)	1.29 (1.01–1.69)	0.048	1.47 (1.12–1.96)	0.006	1.02 (0.83–1.27)	0.867		
ES grade (III/IV vs I/II)	1.43 (0.90–2.26)	0.129			1.29 (0.91–1.82)	0.155		
Satellite (Yes vs No)	1.18 (0.90–1.54)	0.223			1.26 (1.02–1.54)	0.028	1.07 (0.84–1.35)	0.555
Capsule (Absent vs Present)	1.46 (1.11–1.94)	0.007	1.20 (0.89–1.61)	0.226	1.27 (1.02–1.59)	0.036	1.15 (0.91–1.45)	0.250
MVI (Yes vs No)	2.13 (1.64–2.76)	<0.001	1.94 (1.46–2.57)	<0.001	1.72 (1.41–2.11)	<0.001	1.47 (1.15–1.87)	0.002
Adjuvant TACE (Yes vs No)	0.90 (0.67–1.20)	0.465			0.96 (0.78–1.17)	0.682		

Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; ALBI, albumin bilirubin score; AFP, alpha-fetoprotein; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; ES, Edmondson-Steiner; MVI, microvascular invasion; TACE, transarterial chemoembolization.

Table 3 Univariate and Multivariate Analysis of Overall Survival and Disease-Free Survival After PSM

Characteristics	OS				DFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95CI)	P-value						
Age (years)	1.00 (0.99–1.02)	0.808			1.00 (0.99–1.02)	0.595		
Gender (Male vs Female)	0.90 (0.54–1.48)	0.666			1.46 (0.94–2.27)	0.095	1.34 (0.86–2.11)	0.200
HBV infection (Yes vs No)	0.87 (0.57–1.31)	0.492			1.35 (0.94–1.92)	0.104		
White blood cell count($\times 10^9/L$)	1.03 (0.93–1.14)	0.583			1.05 (0.98–1.13)	0.172		
Hemoglobin (g/L)	0.99 (0.98–1.02)	0.321			1.00 (0.99–1.01)	0.645		
Platelet count ($\times 10^9/L$)	1.01 (1.01–1.02)	0.024	1.01 (0.99–1.02)	0.180	1.01 (1.00–1.02)	0.033	1.01 (0.99–1.01)	0.118
ALBI grade (2 vs 1)	1.85 (1.19–2.87)	0.006	1.97 (1.25–3.11)	0.003	1.44 (0.99–2.09)	0.056	1.40 (0.95–2.06)	0.085
AFP (>20 vs ≤ 20 ng/mL)	1.35 (0.94–1.93)	0.106			1.14 (0.86–1.51)	0.354		
GGT (>72 vs ≤ 72 U/L)	1.64 (1.12–2.39)	0.011	1.39 (0.93–2.07)	0.105	1.42 (1.05–1.92)	0.024	1.15 (0.83–1.59)	0.395
ALP (>104 vs ≤ 104 U/L)	1.83 (1.09–3.05)	0.022	1.63 (0.95–2.77)	0.074	1.51 (0.98–2.31)	0.061	1.39 (0.89–2.17)	0.146
RM (wide vs narrow)	0.77 (0.54–1.10)	0.153	0.76 (0.53–1.09)	0.139	0.90 (0.68–1.19)	0.466	0.89 (0.68–1.19)	0.461
Hospital stays (>10 vs ≤ 10 days)	1.86 (1.18–2.92)	0.007	1.79 (1.13–2.85)	0.013	1.67 (1.13–2.46)	0.010	1.65 (1.11–2.44)	0.013
Tumor diameter (>5 vs ≤ 5 cm)	2.09 (1.46–3.00)	<0.001	1.46 (0.99–2.16)	0.056	1.75 (1.31–2.35)	<0.001	1.38 (1.01–1.89)	0.043
Cirrhosis (Present vs Absent)	1.39 (0.96–2.00)	0.081	1.56 (1.05–2.33)	0.026	1.15 (0.85–1.56)	0.342		
ES grade (III/IV vs I/II)	2.65 (1.17–6.03)	0.020	1.96 (0.85–4.49)	0.114	1.53 (0.90–2.59)	0.115		
Satellite (Yes vs No)	1.19 (0.82–1.72)	0.369			1.12 (0.84–1.49)	0.452		
Capsule (Absent vs Present)	1.27 (0.85–1.91)	0.243			1.27 (0.92–1.76)	0.143		
MVI (Yes vs No)	2.20 (1.53–3.16)	<0.001	2.30 (1.57–3.37)	<0.001	1.73 (1.30–2.31)	<0.001	1.63 (1.21–2.18)	0.001
Adjuvant TACE (Yes vs No)	0.88 (0.59–1.32)	0.542			0.75 (0.55–0.99)	0.054	0.80 (0.59–1.09)	0.161

Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; ALBI, albumin bilirubin score; AFP, alpha-fetoprotein; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; ES, Edmondson-Steiner; MVI, microvascular invasion; TACE, transarterial chemoembolization.

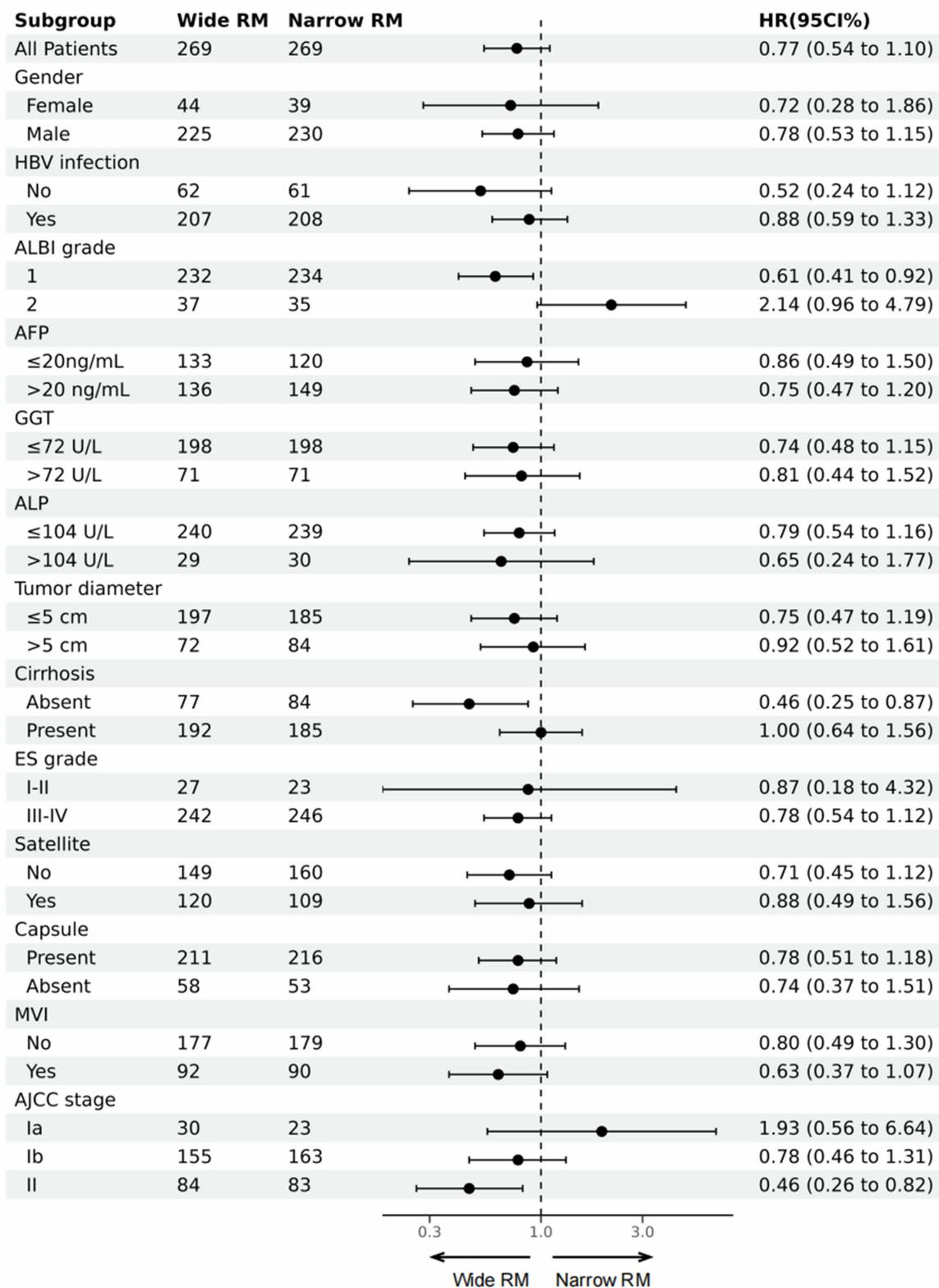


Figure 3 Overall survival of wide RM and narrow RM groups stratified by different potential confounders in PSM cohort.

study utilizing a nationwide survey database in Japan. The study revealed that OS and DFS were comparable for patients with negative-0mm RM and those with negative>0mm RM, as long as AR was performed. Conversely, two studies by Shi et al¹⁴ and Zhang et al¹⁵ in China concluded that for patients undergoing AR, a wide RM led to better prognosis than

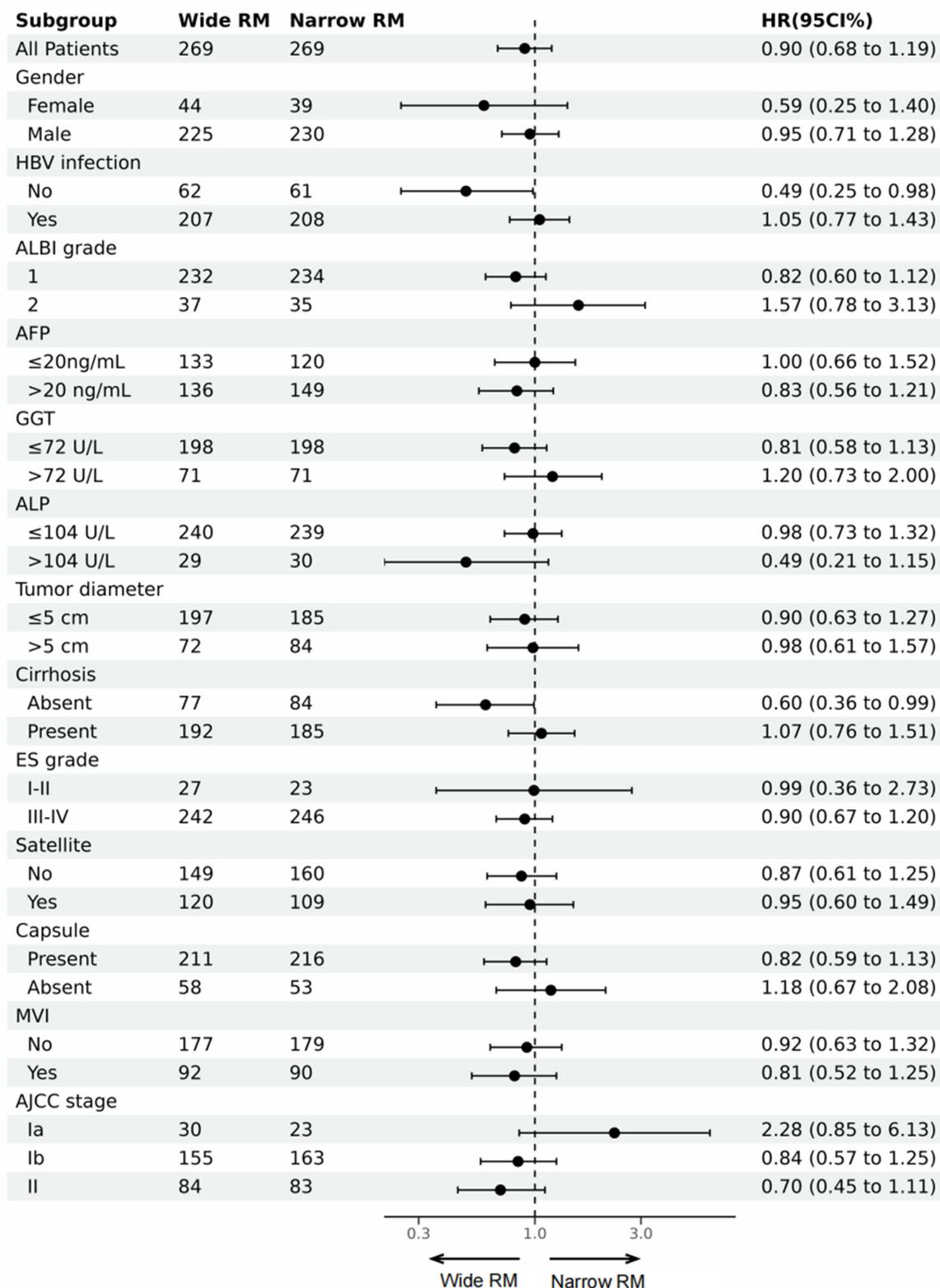


Figure 4 Disease-free survival of wide RM and narrow RM groups stratified by different potential confounders in PSM cohort.

a narrow RM. However, in the present study, which included patients with solitary HCC who underwent AR, there was no significant improvement in OS and DFS when comparing wide RM to narrow RM, both before and after PSM, consistent with Aoki et al’s findings.²⁶ Previous research has established that portal vein invasion and/or intrahepatic

metastases tend to spread through the portal territories, as opposed to radially in all directions.²⁷ This finding may help to shed light on the present study results, which indicate that the width of the RM does not have a significant impact on the prognosis of patients undergoing AR for solitary HCC.

Since liver function or cirrhosis is crucial in determining whether AR or wide RM can be performed, excessive resection of liver tissue may lead to complications, such as postoperative liver failure.²² Additionally, cirrhosis is an independent prognostic factor in patients with solitary HCC.²⁸ Our study found that none of the patients with solitary HCC who underwent AR developed postoperative liver failure. Based on the results of subgroup analysis, we observed that wide RM improved the prognosis of patients with ALBI grade I, the absence of cirrhosis, or hepatitis B infection. Therefore, selected patients may benefit from wide RM among solitary HCC patients undergoing AR.

MVI is a well-known invasive characteristic of HCC and an independent risk factor for intrahepatic and distant metastasis.²⁹ The prevalence of MVI in HCC patients varies from 15–57% and can be detected at different stages of the disease.³⁰ Previous studies have indicated that portal vein invasion and intrahepatic micrometastasis occur predominantly within 1 cm of the main tumor and seldom extend beyond 2 cm.^{11,31} Therefore, a wide RM (≥ 1 cm) may be more effective in eradicating MVI from adjacent tumors following surgical resection. Evidence suggests that wide RM can improve the prognosis of HCC patients with MVI.^{10,32} In current study, the benefits of wide RM were evaluated in HCC patients with MVI who underwent AR. The findings suggested that wide RM may not benefit these patients since the included studies were solitary HCC cases with a relatively favorable prognosis. Furthermore, AR involves the complete removal of the tumor-bearing portal territory, including the MVI along the distribution of portal vein branches within the peritumoral liver tissue. Therefore, the width of the RM may have little impact on the prognosis of these patients.

Furthermore, postoperative management is crucial in reducing the risk of recurrence and improving the long-term prognosis of HCC, which includes rigorous follow-up and efficient adjuvant treatment. TACE and targeted therapy represent viable and effective options for the comprehensive management of HCC.³³ These therapeutic modalities are suitable for both first-line treatment in intermediate to advanced stages of HCC and as adjuvant treatment following radical hepatectomy, yielding promising outcomes.^{34–36} Furthermore, the utilization of radiotherapy and immune checkpoint inhibitors has also been reported in the postoperative management of HCC.^{37,38} In this study, we observed that narrow RM patients were more likely to receive adjuvant TACE, as previously reported.²¹ This finding suggests that a wide RM may not be the sole optimal approach, as subsequent adjuvant treatment can be utilized to complement the potential risks associated with a narrow RM.

The strength of this study lies in its large multicenter design, utilizing data from two specialized HPB centers located in China. Additionally, PSM and subgroup analysis were conducted to minimize potential biases. However, certain limitations of the study should be acknowledged. Firstly, selection and recall biases are challenging to avoid in retrospective studies, even with the implementation of PSM and multivariate Cox models. Secondly, operator-related factors, such as the use of open versus laparoscopic approaches, Pringle maneuver, and intraoperative navigation, may impact the width of the RM and subsequently affect the outcomes of hepatectomy. Lastly, there exist evident differences between the epidemiology, tumor characteristics, and management of HCC in the East and West, indicating the need for further validation of the study's conclusions in Western series.

Conclusion

In patients with solitary HCC undergoing AR, the width of the RM does not appear to have a significant impact on their prognosis. However, in certain selected patients, a wider RM may confer benefits. However, further prospective, randomized controlled studies are necessary to validate this conclusion.

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Disclosure

The authors report no conflicts of interest in this work.

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