

The Impact of Resection Margin and Microscopic Vascular Invasion for Patients with HBV-related Intrahepatic Cholangiocarcinoma

Wen-Feng Lu

Eastern Hepatobiliary Surgery Hospital

Pei-Qin Chen

Eastern Hepatobiliary Surgery Hospital

Kai Yan

Eastern Hepatobiliary Surgery Hospital

Ye-Chen Wu

Eastern Hepatobiliary Surgery Hospital

Lei Liang

Zhejiang Provincial People's Hospital

Jian-Yong Yuan

Eastern Hepatobiliary Surgery Hospital

Yong Fu

Eastern Hepatobiliary Surgery Hospital

Hai-Bin Zhang (✉ zhanghbehbh@126.com)

Eastern Hepatobiliary Surgery Hospital <https://orcid.org/0000-0002-9076-9563>

Research

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Abstract

Background and Aim: The resection margin (RM) status and microscopic vascular invasion (MVI) are known prognostic factors for intrahepatic cholangiocarcinoma (ICC). An enhanced understanding of their impact on long-term prognosis is required to improve oncological outcomes.

Methods: We reviewed data on 711 consecutive patients who underwent curative liver resection for hepatitis B virus-related ICC. The different impact of the RM status (narrow, <1 cm, or wide, ≥ 1 cm) and MVI (positive, +, or negative, -) on overall survival (OS) and recurrence-free survival (RFS) were analyzed.

Results: The 1-, 3-, and 5-year OS rates were 67.6%, 42.5% and 33.2% in wide RM & MVI (-), 58.0%, 36.1% and 26.5% in narrow RM & MVI (-), 51.0%, 27.0% and 24.3% in wide RM & MVI (+), and 39.0%, 20.4% and 14.3% in narrow RM & MVI (+) ($p < 0.001$). The 1-, 3-, and 5-year RFS rates were 60.0%, 40.2% and 28.7% in wide RM & MVI (-), 45.2%, 34.3% and 24.2% in narrow RM & MVI (-), 40.0%, 18.5% and 12.3% in wide RM & MVI (+), and 28.2%, 11.5% and 9.8% in narrow RM & MVI (+) ($p < 0.001$). Multivariate analysis showed that RM & MVI were independent risk factors for the OS and RFS.

Conclusions: Combined analysis of RM and MVI can better stratify the risks of postoperative death and recurrence in patients with HBV-related ICC, which may help subsequent adjuvant therapy and follow-up.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a primary liver cancer with incidence only second to the hepatocellular carcinoma that arising from the epithelial cells of the intrahepatic bile ducts, either small intrahepatic ductules or large intrahepatic ducts proximal to the bifurcation of the hepatic ducts¹. The incidence of ICC has been rising in the global scale over the last twenty years, which may reflect both a true increase and the trend of earlier detection of the disease^{2,3}. Other than some well recognized causative risk factors, the association between hepatitis B virus and ICC pathogenesis has been increasingly identified recently⁴. Previous studies reported a 5-year survival only ranging from 30 to 35%⁵.

Liver resection remains as the first-line curative treatment. Recent improvements in operative techniques and perioperative care have significantly decreased the operative mortality rate, and to some degree, improved the long-term survival outcomes of ICC patients. However, the long-term prognosis after curative liver resection remains unsatisfactory due to a very high tumor recurrence rate and a lack of effective adjuvant therapy. A better understanding of the risk factors associated with tumor recurrence and their impact on survival helps to tailor adjuvant therapy against recurrence with improved long-term oncological outcomes.

Several clinicopathologic parameters, including microscopic vascular invasion (MVI), resection margin (RM) status, lymph node metastasis, tumor diameter and tumor number, have been raised as the potential prognostic factors determining the clinical outcomes^{6,7}. MVI, which is defined as microscopic

tumor invasion as identified in the portal or hepatic veins in the surrounding liver tissues contiguous to the tumor, has always been regarded as a definite risk factor associated with long-term prognosis after ICC resection, and was getting more and more attention by pathologists, surgeons and researchers worldwide⁷⁻⁹. Meanwhile, another risk factor which has been increasingly recognized to affect ICC recurrence is the RM status¹⁰⁻¹³. The RM status is a surgical technology-related factor. It is therefore highly valued in the past decades. Whether patients with wide RM (≥ 1 cm) gain the survival advantage over the ones with narrow RM (< 1 cm) is an ongoing debate. Spolverato et al. also demonstrated that there was an incremental worsening overall survival (OS) and recurrence-free survival (RFS) as margin width decreased¹¹. Given that both the RM status and MVI involve the chance of residual tumor left in the liver remnant after liver resection, they are likely to have a common effect on ICC recurrence after curative resection, although there are some differences of mechanisms for recurrence between both of them.

A single center retrospective study was conducted to evaluate the prognostic impact of both the RM status and MVI on long-term oncologic survival outcomes after curative liver resection for HBV-related ICC. This study aimed to identify high risk groups of patients, who might benefit from adjuvant therapy in decreasing postoperative ICC recurrence.

Patients And Methods

Patient selection

A retrospective study was conducted on consecutive patients with HBV-related ICC, who underwent curative liver resection from Jan 2005 to Dec 2016 in the Eastern Hepatobiliary Surgery Hospital (EHBH) in Shanghai, China. Curative liver resection was defined as removal of all microscopic and macroscopic tumors with a microscopically clear margin of surgical specimen (R0 resection). All these patients were HBV surface antigen-positive (HBsAg), or they had detectable HBV DNA, or were both e-antibody- and c-antibody-positive, did not have a history of preoperative anticancer treatment or of other malignancy, did not have macroscopic tumor thrombus in major portal/hepatic veins, and did not have distant metastasis. Informed consent was obtained from all the enrolled patients for their data to be utilized in clinical researches. The present study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies by the Institutional Ethics Committee of the EHBH.

Baseline characteristics and operative variables

All patients underwent liver resection, 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. Liver resection based on systematic removal of one or more adjacent Couinaud's 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 resections¹⁴. The resected tumors with surrounding liver tissues

were examined histopathology¹⁵. 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.

The patient- and liver-related variables included the age, sex, comorbid illnesses (consists of diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and renal dysfunction history), preoperative serum total bilirubin (TBIL); albumin (ALB); alanine aminotransferase (ALT); aspartate transaminase (AST), glutamyltranspeptidase (GGT), prothrombin time (PT), platelet count (PLT) levels and cirrhosis. The tumor-related variables included preoperative AFP level, CEA level, CA19-9 level, maximum tumor size, tumor number, microscopic vascular invasion (negative or positive), lymph node metastasis (negative or positive) and tumor differentiation (well, moderately or poorly). The presence of MVI was defined as tumors within a vascular space lined by endothelium that was visible only on microscopy. The operative variables included extent of hepatectomy (minor or major), type of resection (anatomical or non-anatomical), blood transfusion and RM status. Major hepatectomy was defined as resection of three or more Couinaud's segments, while minor hepatectomy was resection of fewer than three segments.

Postoperative follow-up

Patients were observed once every 2 months in the first 2 years after surgery and then every 3 to 6 months thereafter. At each of the follow-up visits, a detailed history and a complete physical examination were carried out. Blood was taken for serum CA 19 – 9, CEA, AFP, and liver function tests, and an abdominal ultrasound was carried out. Contrast-enhanced CT or magnetic resonance imaging was performed once every 6 months or earlier when tumor recurrence or metastasis was suspected. Further investigation was carried out when clinically indicated. ICC recurrence/metastasis was defined as the appearance of a newly detected tumor confirmed on two radiologic images, with or without elevation of serum tumor markers. OS and RFS were used as primary end points. OS was defined as the interval between partial hepatectomy and death or the last date of follow-up. RFS was calculated from the date of liver resection to the date of first ICC recurrence or the date of the last follow-up.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 25.0 (SPSS, Chicago, IL, USA) and R 3.5.3 (<http://www.r-project.org/>). Continuous variables with a normal distribution were expressed as mean \pm standard deviation or median (range). Categorical variables were expressed as number (n) or proportion (%). The Student's t test was used for comparison of continuous variables when applicable, otherwise, the Mann–Whitney U test was applied. Categorical variables were compared using the χ^2 test or the Fisher's exact test, as appropriate. The OS and RFS were calculated by the Kaplan–Meier method, which was generated by the log-rank test. Univariate and multivariable Cox Regression analyses were used to identify the independent risk factors of OS and RFS. Variables with $p < 0.1$ on univariable analysis were subjected to the multivariable Cox regression model using a forward stepwise variable selection. The statistical significance level was set at $p < 0.05$ in all the analyses.

Results

Baseline characteristics and operative variables

A total of 711 patients undergoing curative liver resection for newly-diagnosed ICC met the inclusion criteria and were included. Among them, 492 (68.9%) were male and 279 (31.1%) were female, and the median age was 54 years (range, 20–85 years). 333 (46.8%) patients were in wide RM & MVI (-) group, 242 (34.0%) patients were in narrow RM & MVI (-) group, 66 (9.3%) patients were in wide RM & MVI (+) group and 70 (9.9%) patients were in narrow RM & MVI (+) group. Baseline characteristics among each group are listed in Table 1. The results showed that patients in wide RM & MVI (+) or narrow RM & MVI (+) group had a higher proportion of major hepatectomy, tumor size and lymph node metastasis. There were no significant differences in all other variables among each group (all $p > 0.05$). There were also no significant differences among these 4 groups in the perioperative mortality and morbidity rates, and in the postoperative hospital stay (all $p > 0.05$).

Table 1

Demographics and clinicopathologic characteristics of patients with intrahepatic cholangiocarcinoma, stratified by resection margin and microvascular invasion

N, %	Group I (N = 333)	Group II (N = 242)	Group III (N = 66)	Group IV (N = 70)	<i>p</i>
Age, years	55.0 ± 10.5	53.9 ± 10.9	54.0 ± 11.7	54.6 ± 10.4	0.406
Sex, Male	225 (67.6)	163 (67.4)	49 (74.2)	55 (78.6)	0.215
Co-morbid illness	81 (24.3)	59 (24.4)	18 (27.3)	16 (22.9)	0.944
TBIL, ≤ 23 μmol/L	253 (76.0)	193 (79.8)	44 (66.7)	48 (68.6)	0.071
ALB, ≤ 35 g/L	25 (7.5)	21 (8.7)	9 (13.6)	11 (15.7)	0.099
ALT, ≤ 40 IU/L	231 (69.4)	168 (69.4)	35 (53.0)	45 (64.3)	0.056
AST, ≤ 40 U/L	246 (73.9)	189 (78.1)	46 (69.7)	46 (74.1)	0.154
GGT, ≤ 60 U/L	151 (45.3)	123 (50.8)	24 (36.4)	28 (40.0)	0.121
PT, ≤ 13 S	294 (88.3)	216 (89.3)	55 (83.3)	55 (78.6)	0.078
Platelet count, ≤ 100 × 10 ⁹ /L	30 (9.0)	19 (7.9)	4 (6.1)	9 (12.9)	0.502
Preoperative AFP level, ≤ 20 ug/L	254 (76.3)	201 (83.1)	54 (81.8)	49 (70.0)	0.061
Preoperative CA19-9 level, ≤ 39 U/mL	150 (45.0)	109 (45.0)	22 (33.3)	27 (38.6)	0.259
Preoperative CEA level, ≤ 10 ug/L	288 (86.5)	203 (83.9)	56 (84.8)	56 (80.0)	0.543
Major hepatectomy	110 (33.0)	53 (21.9)	30 (45.5)	34 (48.6)	< 0.001
Anatomical resection	72 (21.6)	62 (25.6)	17 (25.8)	20 (28.6)	0.514
Blood transfusion	68 (20.4)	34 (14.0)	17 (25.8)	16 (22.9)	0.074
Maximum tumor size, > 5 cm	216 (64.9)	130 (53.7)	50 (75.8)	51 (72.9)	0.001
Tumor number, ≥ 2	28 (8.4)	21 (8.7)	9 (13.6)	12 (17.1)	0.093
Lymph node metastasis (+)	59 (17.7)	43 (17.8)	20 (30.3)	22 (31.4)	0.008
Cirrhosis	102 (30.6)	70 (28.9)	18 (27.3)	24 (34.3)	0.792
Tumor differentiation, Poorly	24 (7.2)	14 (5.8)	5 (7.6)	2 (2.9)	0.542

TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; Group I: wide resection margin and negative MVI; Group II: narrow resection margin and negative MVI; Group III: wide resection margin and positive MVI; Group IV: narrow resection margin and positive MVI; MVI: microscopic vascular invasion.

N, %	Group I (N = 333)	Group II (N = 242)	Group III (N = 66)	Group IV (N = 70)	<i>p</i>
Perioperative mortality	2 (0.6)	1 (0.4)	2 (3.0)	2 (2.9)	0.083
Perioperative morbidity	54 (16.2)	45 (18.6)	15 (22.7)	18 (25.7)	0.227
Postoperative hospital stays, days	10.2 ± 3.1	10.3 ± 3.2	9.9 ± 2.9	10.7 ± 3.3	0.131
TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; Group I: wide resection margin and negative MVI; Group II: narrow resection margin and negative MVI; Group III: wide resection margin and positive MVI; Group IV: narrow resection margin and positive MVI; MVI: microscopic vascular invasion.					

Comparisons of long-term OS and RFS

The median follow-up time was 19.9 (14.2–25.6) months. Death and ICC recurrence were observed in 458 (64.4%) and 419 (58.9%) patients, respectively. There were significant differences in the mortality rate and the recurrence rates among these 4 groups (all $p < 0.001$). Figure 1A shows the comparison of the OS and DFS curves among the 4 groups stratified by RM and MVI. Compared with patients in wide RM & MVI (-) group, other 3 groups were all significantly associated with decreased OS rates after curative liver resection for HBV-related ICC (HR 1.212, 95% CI 1.003–1.459, $p = 0.042$, HR 1.559, 95% CI 1.125–2.161, $p = 0.008$, and HR 2.108, 95% CI 1.564–2.841, $p < 0.001$, respectively). Figure 1B shows that, compared with patients in wide RM & MVI (-) group, other 3 groups were all significantly associated with decreased RFS rates after curative liver resection for HBV-related ICC (HR 1.274, 95% CI 1.023–1.586, $p = 0.031$, HR 1.571, 95% CI 1.119–2.207, $p = 0.009$, and HR 2.360, 95% CI 1.728–3.224, $p < 0.001$, respectively).

Subgroup analysis for patients with negative or positive lymph node metastasis

Figure 2A and 2B shows the comparison of the OS and DFS curves among the 4 groups stratified by RM and MVI for patients with negative lymph node metastasis. Compared with patients in wide RM & MVI (-) group, other 3 groups were all significantly associated with decreased OS and RFS rates after curative liver resection for HBV-related ICC. Figure 3A and 3B shows the comparison of the OS and DFS curves among the 4 groups stratified by RM and MVI for patients with positive lymph node metastasis. Compared with patients in wide RM & MVI (-) group, other 3 groups were also significantly associated with decreased OS and RFS rates after curative liver resection for HBV-related ICC.

Univariable and multivariable analyses of OS and RFS

The results of univariable and multivariable Cox-regression analyses of OS and RFS are showed in Table 2 and Table 3. Significant variables ($p < 0.1$) on univariable analysis were entered into multivariable analysis. In the Cox-regression multivariable analysis, a narrow RM & MVI (-) (HR 1.288, 95% CI 1.040–

1.594, $p = 0.020$), wide RM & positive MVI (HR 1.524, 95% CI 1.093–2.126, $p = 0.013$) and a narrow RM & positive MVI (HR 2.219, 95% CI 1.632–3.017, $p < 0.001$) were independent risk factors of decreased OS after curative resection for HBV-related ICC. Meanwhile, the Cox-regression multivariable analysis also showed that a narrow RM & MVI (-) (HR 1.356, 95% CI 1.086–1.693, $p = 0.007$), wide RM & positive MVI (HR 1.523, 95% CI 1.087–1.958, $p = 0.019$) and a narrow RM & positive MVI (HR 2.299, 95% CI 1.678–3.149, $p < 0.001$) were also independent risk factors of decreased RFS after curative resection for HBV-related ICC. Notably, a narrow RM & positive MVI had the highest hazard ratio among all the independent risk factors associated with reduced OS (HR 2.219) and RFS (HR 2.299), respectively. In addition, the results also indicated preoperative CA19-9 (> 39 U/mL), CEA (> 10 ug/L), tumor size (> 5 cm), tumor number (≥ 2) and lymph node metastasis (+) were the independent risk factors associated with worse OS and RFS.

Table 2
Univariable and multivariable Cox-regression analyses on risk factors of overall survival

Variables	HR comparison	UV HR (95%CI)	UV P	MV HR (95CI)	MV P
Age	Continuous	1.009 (1.001–1.008)	0.032	1.009 (1.000-1.018)	0.051
Sex	Male vs. Female	1.005 (0.824–1.226)	0.959		
Co-morbid illness	Yes vs. No	1.033 (0.835–1.278)	0.763		
TBIL	> 23 vs. ≤23 μmol/L	0.908 (0.730–1.129)	0.908		
ALB	≤ 35 vs. >35 g/L	1.189 (0.874–1.618)	0.271		
ALT level	> 40 vs. ≤40 IU/L	0.960 (0.789–1.169)	0.687		
AST level	> 40 vs. ≤40 IU/L	1.030 (0.835–1.271)	0.782		
GGT level	> 60 vs. ≤60U/L	1.230 (1.023–1.480)	0.028	0.970 (0.797–1.180)	0.761
PT	> 13 vs. ≤13 S	0.956 (0.720–1.270)	0.757		
Platelet count	> 100 vs. ≤100 × 10 ⁹ /L	0.752 (0.532–1.061)	0.105		
AFP level	> 20 vs. ≤20 ug/L	1.009 (0.808–1.260)	0.936		
CA19-9 level	> 39 vs. ≤39 U/mL	1.806 (1.492–2.185)	< 0.001	1.462 (1.188-1.800)	< 0.001
CEA level	> 10 vs. ≤10ug/L	2.779 (2.190–3.526)	< 0.001	1.812 (1.392–2.360)	< 0.001
Extent of hepatectomy	Major vs. Minor	1.242 (1.023–1.508)	0.029	0.920 (0.747–1.133)	0.431
Type of resection	Anatomical vs. Non-anatomical	1.169 (0.939–1.455)	0.161		
Blood transfusion	Yes vs. No	1.103 (0.878–1.385)	0.401		

TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; WRM: wide resection margin; NRM: narrow resection; MVI: microscopic vascular invasion. * Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable analyses. HR, hazard ratio; UV, univariable; MV, multivariable; CI, Confidence interval.

Variables	HR comparison	UV HR (95%CI)	UV P	MV HR (95CI)	MV P
Resection margin & MVI	WRM & MVI (-)	Reference		Reference	
	NRM & MVI (-)	1.212 (1.003–1.459)	0.042	1.288 (1.040–1.594)	0.020
	WRM & MVI (+)	1.559 (1.125–2.161)	0.008	1.524 (1.093–2.126)	0.013
	NRM & MVI (+)	2.108 (1.564–2.841)	< 0.001	2.219 (1.632–3.017)	< 0.001
Maximum tumor size	> 5 vs. ≤5 cm	1.696 (1.392–2.066)	< 0.001	1.486 (1.208–1.827)	< 0.001
Tumor number	≥ 2 vs. 1	1.591 (1.187–2.132)	0.002	1.416 (1.051–1.908)	0.022
Lymph node metastasis	Yes vs. No	2.503 (2.020–3.102)	< 0.001	2.098 (1.671–2.634)	< 0.001
Cirrhosis	Yes vs. No	0.807 (0.658–0.991)	0.040	1.002 (0.808–1.242)	0.989
Tumor differentiation	Poorly vs. Well or moderately	1.034 (0.705–1.515)	0.865		
<p>TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; WRM: wide resection margin; NRM: narrow resection; MVI: microscopic vascular invasion. * Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable analyses. HR, hazard ratio; UV, univariable; MV, multivariable; CI, Confidence interval.</p>					

Table 3

Univariable and multivariable Cox-regression analyses on risk factors of recurrence-free survival

Variables	HR comparison	UV HR (95%CI)	UV P	MV HR (95CI)	MV P
Age	Continuous	0.999 (0.991–1.009)	0.910		
Sex	Male vs. Female	1.024 (0.832–1.260)	0.826		
Co-morbid illness	Yes vs. No	1.023 (0.819–1.279)	0.840		
TBIL	> 23 vs. ≤23 μmol/L	0.872 (0.694–1.097)	0.242		
ALB	≤ 35 vs. >35 g/L	0.806 (0.558–1.162)	0.247		
ALT level	> 40 vs. ≤40 IU/L	1.045 (0.853–1.281)	0.670		
AST level	> 40 vs. ≤40 IU/L	1.055 (0.847–1.314)	0.635		
GGT level	> 60 vs. ≤60U/L	1.115 (0.920–1.351)	0.268		
PT	> 13 vs. ≤13 S	0.889 (0.653–1.212)	0.458		
Platelet count	> 100 vs. ≤100 × 10 ⁹ /L	0.675 (0.465–0.978)	0.038	0.774 (0.531–1.128)	0.182
AFP level	> 20 vs. ≤20 ug/L	1.056 (0.837–1.331)	0.645		
CA19-9 level	> 39 vs. ≤39 U/mL	1.409 (1.158–1.714)	0.001	1.249 (1.013–1.541)	0.038
CEA level	> 10 vs. ≤10ug/L	1.856 (1.415–2.434)	< 0.001	1.347 (1.007–1.802)	0.045
Extent of hepatectomy	Major vs. Minor	1.141 (0.929–1.400)	0.208		
Type of resection	Anatomical vs. Non-anatomical	0.981 (0.766–1.257)	0.881		
Blood transfusion	Yes vs. No	0.927 (0.722–1.191)	0.556		

TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; WRM: wide resection margin; NRM: narrow resection; MVI: microscopic vascular invasion. * Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable analyses. HR, hazard ratio; UV, univariable; MV, multivariable; CI, Confidence interval.

Variables	HR comparison	UV HR (95%CI)	UV P	MV HR (95CI)	MV P
Resection margin & MVI	WRM & MVI (-)	Reference		Reference	
	NRM & MVI (-)	1.274 (1.023–1.586)	0.031	1.356 (1.086–1.693)	0.007
	WRM & MVI (+)	1.571 (1.119–2.207)	0.009	1.523 (1.087–1.958)	0.019
	NRM & MVI (+)	2.360 (1.728–3.224)	< 0.001	2.299 (1.678–3.149)	< 0.001
Maximum tumor size	> 5 vs. ≤5 cm	1.532 (1.253–1.874)	< 0.001	1.423 (1.155–1.754)	0.001
Tumor number	≥ 2 vs. 1	1.643 (1.201–2.249)	0.002	1.506 (1.098–2.065)	0.011
Lymph node metastasis	Yes vs. No	1.757 (1.387–2.226)	< 0.001	1.492 (1.169–1.905)	0.001
Cirrhosis	Yes vs. No	0.840 (0.680–1.039)	0.108		
Tumor differentiation	Poorly vs. Well or moderately	1.023 (0.688–1.522)	0.910		
TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; WRM: wide resection margin; NRM: narrow resection; MVI: microscopic vascular invasion. * Those variables found significant at P < 0.1 in univariable analyses were entered into multivariable analyses. HR, hazard ratio; UV, univariable; MV, multivariable; CI, Confidence interval.					

Discussion

This retrospective study of 711 patients with HBV-related ICC aimed to explore the patient population who had the highest risk of long-term recurrence and mortality after curative liver resection, whom are worthwhile to carry out adjuvant therapy or clinical trials against recurrence. Therefore, RM status and MVI were combined for analysis in this study, as these two important risk factors have the correlative and common impact on ICC recurrence. In the present study, MVI was histologically present in 17.2% patients. The width of the resection margin did not show a significant impact on operative complication rates (including severity of complication) or operative mortality. On the multivariable Cox-regression analyses, a narrow RM & positive MVI had the highest hazard ratio for OS (HR 2.219, 95% CI 1.632–3.017) and RFS (HR 2.299, 95% CI 1.678–3.149) among all the independent risk factors associated with decreased OS and RFS. In other words, concomitant having a narrow RM and positive MVI increases the risks of postoperative death and recurrence by about 2-fold in patients who underwent curative resection of ICC.

For achieving a curative resection, liver resection with a wide operative margin is usually considered for ICCs that show locally aggressive features, such as large tumors size or multiple tumors^{10–13}. 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 phenomenon⁷⁻⁹. If an operative margin is narrow, intrahepatic metastases caused by residual MVI can result in recurrence. Our results demonstrated that, compared to narrow margin liver resection, a wide-margin liver resection could decrease the recurrence in patients with MVI.

Cirrhosis is a limiting factor for the more extensive liver resection for ICC. Liver with HBV infection is often accompanied with cirrhosis¹⁶⁻¹⁹. In this study, there was no significant difference in the proportion of cirrhosis among each group, and no significant difference in the incidence of postoperative complications. However, the use of a wide resection margin in these patients with cirrhosis still should be assessed carefully to obtain adequate liver functional reserve after liver resection.

Lymph node status was another important predictor of long-term survival as patients with ICC^{20,21}. Patients with ICC and positive lymph node metastasis had a significantly worse prognosis compared to those with negative lymph node metastasis. In the present study, we demonstrated combined analysis of RM status and MVI can also well stratified the patients with or without lymph node metastasis.

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. 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 possible²². For patients who are estimated to have a high risk of MVI according to preoperative prediction, a wide resection margin should be obtained if technically feasible and safe. Moreover, the patient population who had the highest risk of long-term recurrence and mortality after curative liver resection, whom are worthwhile to carry out adjuvant therapy or clinical trials against recurrence.

This study had several limitations. First, this study used 1 cm as the cut-off value for a narrow or a wide RM. However, the optimal width of a RM is still controversial. Second, this study focused on patients with HBV infection, and whether the results can be applied to patients with other etiologies of ICC remains to be determined. Though, we know that the presence of MVI is a troubling prognostic indicator in HBV-related and other etiologies of ICC²³. Third, as the defect of previous pathological data, we cannot count the number and range of lymph node resection in all patients. Finally, this study is not a randomized controlled trail and therefore biases in patient's selection may exist.

Conclusion

In conclusion, the present study demonstrated that using both RM status and MVI could well stratify patients into four different risk groups on recurrence and survival outcomes after curative resection of HBV-related ICC. The results of this study suggested that further studies on adjuvant therapy should be carried out for this subgroup of patients who have the highest risk of developing HBV-related ICC recurrence after liver resection.

Abbreviations

ICC, intrahepatic cholangiocarcinoma; HBV, hepatitis B virus; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; GGT, gamma-glutamyltranspeptidase; PT, prothrombin time; AFP, Alpha-fetoprotein; WRM: wide resection margin; NRM: narrow resection; MVI: microscopic vascular invasion; CI, confidence interval; HR, hazard ratio.

Declarations

Availability of data and materials

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

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Authors' Contribution

Affiliations: ¹Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), Shanghai, China; ²Department of Hepatobiliary, Pancreatic and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou, Zhejiang, China

Contributions Wen-Feng Lu, Pei-Qin Chen and Kai Yan are co-first authors. Hai-Bin Zhang had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hai-Bin Zhang and Yong Fu. Acquisition, analysis, or interpretation of data: Wen-Feng Lu, Pei-Qin Chen and Kai Yan. Drafting of the manuscript: Wen-Feng Lu and Pei-Qin Chen. Critical revision of the manuscript for important intellectual content: Ye-Chen Wu. Statistical analysis: Lei Liang. Administrative, technical, or material support: Jian-Yong Yuan. All authors read and approved the final manuscript.

Correspondence: Dr. Hai-Bin Zhang, MD or Dr. Yong Fu, MD, Department of Hepatobiliary Surgery, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University (Navy Medical University), No. 225, Changhai Road, Shanghai 200438, China; E-mail: zhanghbehbh@126.com or fuyg1982@163.com.

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Ethics declarations

Complete follow-up data were retrospectively reviewed after approval from the Institutional Review Board. This study was performed in accordance with the principles of the Declaration of Helsinki. The Human Investigation Committee of the Second Military Medical University (Navy Medical University), Eastern Hepatobiliary Surgery Hospital, approved this study (Protocol No.20200506309).

Consent for publication

Written informed consent for publication was obtained from all patients.

Competing interests

All authors have no potential competing interests.

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Figures

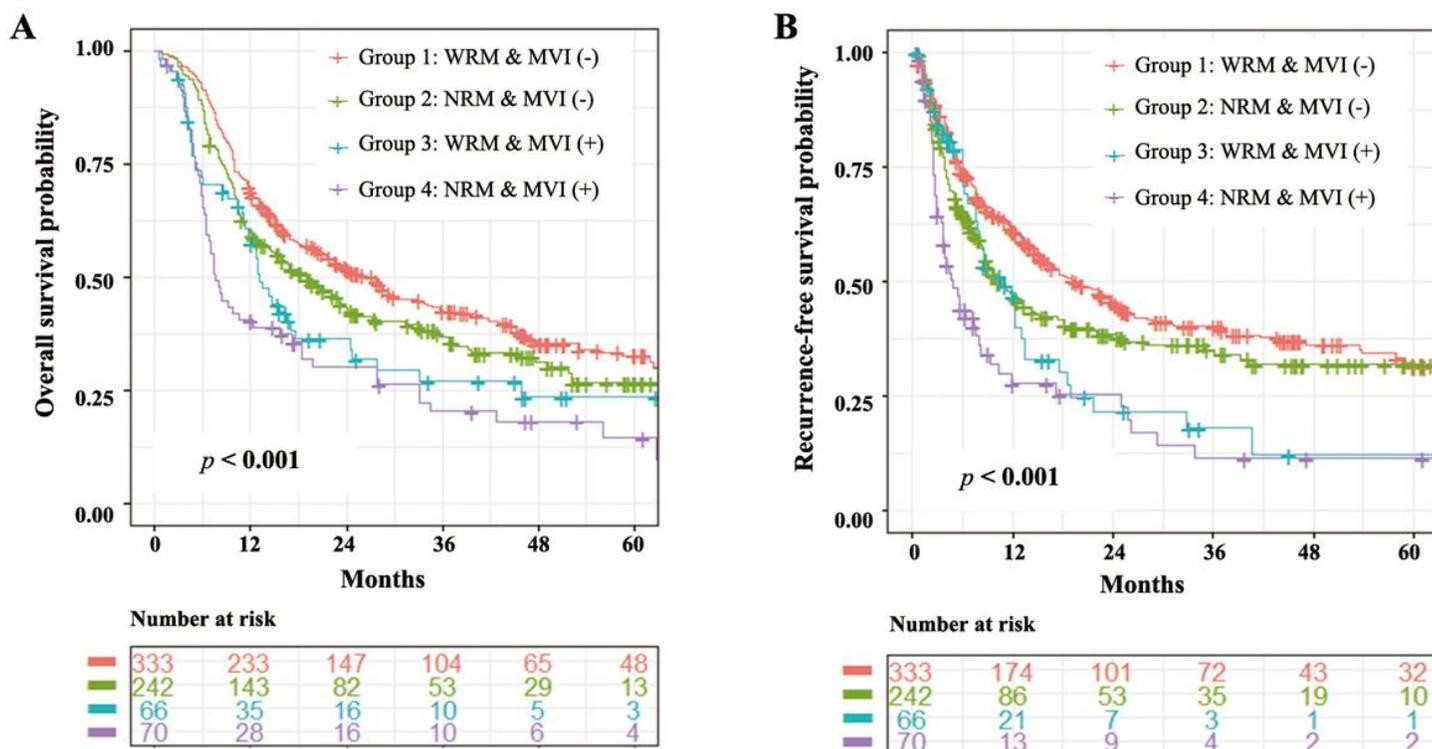


Figure 1

Comparisons of overall survival (A) and recurrence-free survival (B) curves among the 4 groups stratified by resection margin and microvascular invasion.

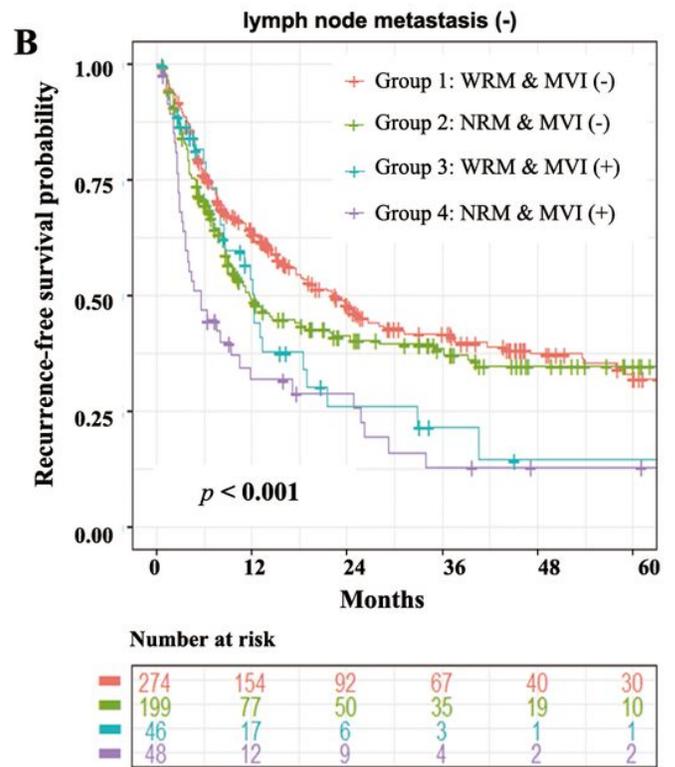
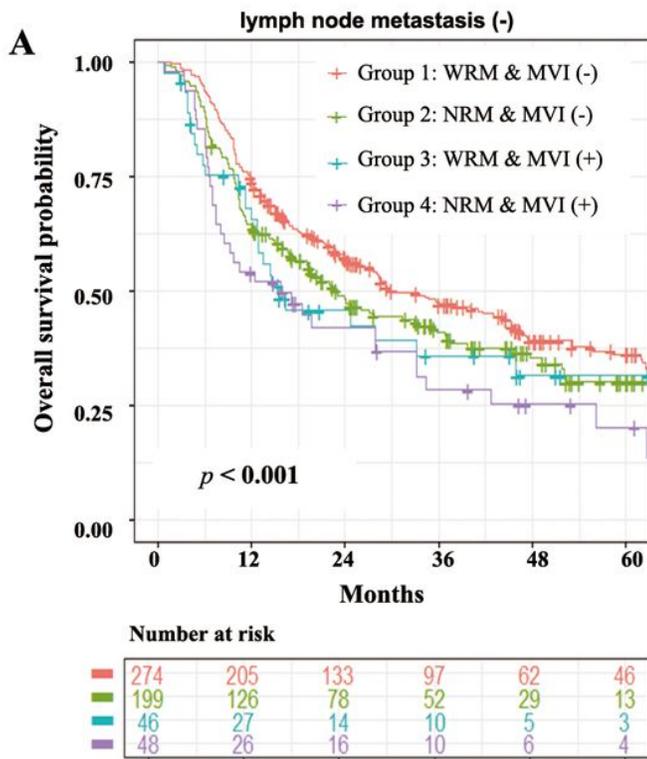


Figure 2

Comparisons of overall survival (A) and recurrence-free survival (B) curves among the 4 groups stratified by resection margin and microvascular invasion for patients with negative lymph node metastasis.

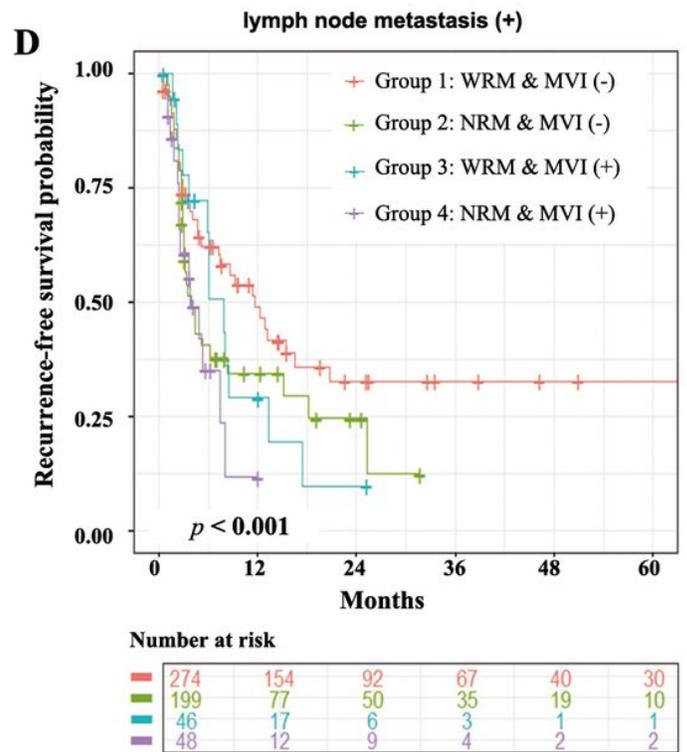
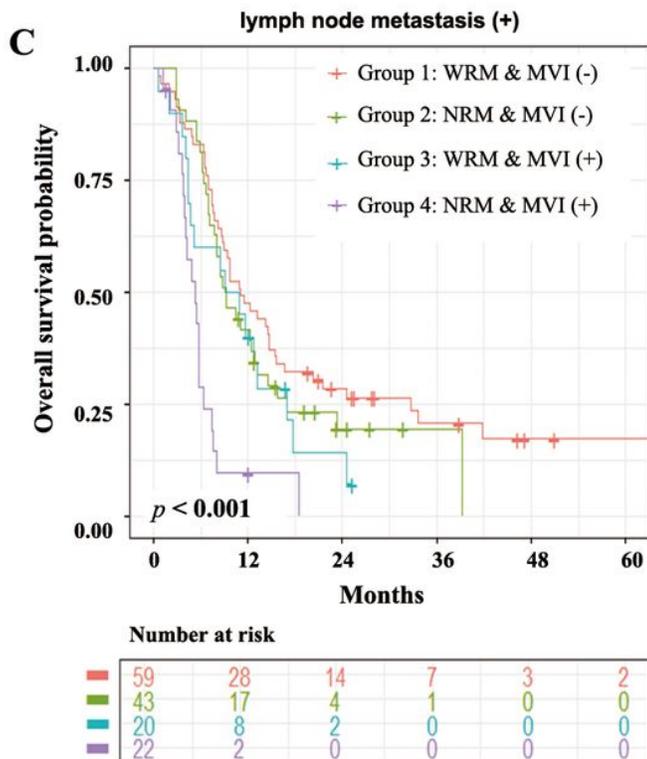


Figure 3

Comparisons of overall survival (A) and recurrence-free survival (B) curves among the 4 groups stratified by resection margin and microvascular invasion for patients with positive lymph node metastasis.