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ORIGINAL SCIENTIFIC REPORT

Anatomical Resection But Not Surgical Margin Width Influence Survival Following Resection for HCC, A Propensity Score Analysis

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Abstract

Background The effects of the surgical resection margin on the clinical outcomes in hepatocellular carcinoma (HCC) cases remain controversial. The objective of this study was to further examine this issue.

Methods The details of all HCC patients who underwent hepatectomy between December 1999 and December 2009 at the Division of Hepatobiliary and Pancreas Surgery, Asan Medical Center were analyzed retrospectively. We divided 1022 HCC patients into two groups according to the most significant surgical margin length. To overcome any bias due to differences in the distribution of covariates between the two groups, the patients were in a matched 1:1 ratio by propensity score analysis.

Results A surgical margin ≤1 mm was identified as the most significant surgical margin in both disease-free survival (DFS) and overall survival (OS) ($p = 0.008$ and $p = 0.026$, respectively). However, many clinicopathological factors were different between the resection margin ≤1 mm and >1 mm groups. To reduce these different clinicopathological factors, propensity score matching was performed using 21 selected factors. After matching, no significant difference was found in DFS and OS between the two groups ($p = 0.688$, $p = 0.398$). In addition, there was no significant difference in the intrahepatic recurrence rate and pattern between the resection margin groups. Except for the preoperative patient's status and tumor stage, significant risk factors in OS were anatomical resection and postoperative morbidity ($p = 0.002$, $p = 0.001$).

Conclusion We identified that the widths of the resection margin in resectable hepatocellular carcinoma did not influence the postoperative recurrence rates, overall survival, and recurrence pattern in multivariable analysis as well as propensity score match analysis.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver tumor, being the fifth most frequently diagnosed cancer in adult men and the second leading cause of cancer-related death worldwide [1]. Surgical resection is the only potentially curative option for HCC, with a 5-year survival rate ranging from 31.8 to 59.0 % [2]. Various risk factors for HCC recurrence after surgery have been studied previously [3], particularly the influence of the resection margin status on surgical outcomes in HCC. A few studies have reported that a resection margin smaller than 1 cm

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was an adverse prognostic factor for long-term outcomes. However, other studies have found that the width of the resection margin was not correlated with long-term outcomes [2, 4–11]. Zhou et al. reported that the minimal lengths of the resection margin were required to be 5.5 and 6 mm to achieve 99 and 100 % micro-metastasis clearance, respectively, in the surrounding liver of HCC patients without macroscopic tumor thrombi or macro-satellites [11]. However, Poon et al. reported that the width of the resection margin did not influence the postoperative recurrence rates after hepatectomy for HCC [8]. These different viewpoints could be attributed to the heterogeneity of the patient series under study in terms of parameters such as tumor characteristics, activity of the underlying disease, method of surgical resection, and other host factors. Presently, there remains no consensus on the appropriate margin width for HCC. The purpose of our present study was to investigate whether the resection margin status and margin width have any influence on the posthepatectomy recurrence patterns, local recurrence rates, and disease-free survival (DFS) and overall survival (OS).

Methods

Regarding the surgical margin, the details of the HCC patients who underwent hepatectomy between December 1999 and December 2009 at the Division of Hepatobiliary and Pancreas Surgery, Asan Medical Center were analyzed retrospectively. Routine preoperative investigations of the patients, including blood biochemistry, alpha-fetoprotein measurement, chest radiography, dynamic contrast-enhanced abdominal computed tomography, and indocyanine green clearance tests were performed. The preoperative diagnosis of HCC was based on the diagnostic criteria for these lesions contained in the Practice Guidelines for Management of Hepatocellular Carcinoma 2009 [12].

Information on the clinical findings (including sex, age, hepatoviral infection status, liver function, and preoperative tumor marker level), operative results (including the type of resection, intraoperative blood loss, and presence of intraoperative red blood cell transfusion), tumor morphological characteristics, and histopathology of resected tumors, as well as complications, recurrence, and survival, were retrospectively obtained from a database.

Definition of the surgical margin

Patients were classified according to the width of the surgical margin, defined as the shortest distance from the edge of the tumor to the line of transection. The surgical margin was determined by the pathologists. An involved margin was defined as the presence of tumor cells at the line of resection. The standard form for margin measurement was established as follows: (1) the length of the resection margin was the distance from the tumor edge to the transection plane of the live parenchyma; (2) for multinodular lesions or satellite lesions, any neoplastic nodule closest to the margin was taken as the reference; (3) among the measurements of the margin length from each dimension, the smallest value was defined as the narrowest width. Based on previously reported results, we examined the statistical value of the resection margin lengths of 1, 5, and 10 mm to investigate the most significant surgical margin length.

Operative technique

Anatomical resection was defined as the complete removal of at least one Couinaud segment containing the tumor. Non-anatomical resection was defined as the removal of the tumor with a rim of non-neoplastic liver parenchyma. The 18 patients who underwent combined anatomical and non-anatomical resections were included in the anatomic resection group. Anatomical resection was performed using the Glissonean pedicle ligation technique, which allowed early delineation of the segments to remove before parenchymal transection. The hepatic parenchyma was transected at the inter-segmental plane using the crushing technique with the Kelly clamp or an ultrasonic dissector (CUSA; Tyco Health Care, Mansfield, MA) using ultrasonic energy. In the present study, anatomical resection included the following: monosegmentectomy in 223 patients, bisegmentectomy in 16 patients, left lateral sectionectomy in 89 patients, right posterior sectionectomy in 135 patients, right anterior sectionectomy in 163 patients, central bisectionectomy in 17 patients, right hemihepatectomy in 136 patients, left hemihepatectomy in 41 patients, and more extensive hepatectomy in 21 patients.

Hepatic functional reserve estimations for individual patients were primarily calculated based on the results of the indocyanine green clearance test. A hepatectomy procedure was selected considering the primary tumor status (size, number, location, and vascular invasion), the hepatic functional reserve, and the patient's general condition. Anatomical resection with a more extensive hepatectomy procedure was performed in patients with larger tumors, more deeply located tumors, younger age, or better general conditions.

Follow-up

Patients were followed via tumor markers and dynamic computed tomography or magnetic resonance imaging

every 6 months during the 2-year follow-up after surgery. After 2 years, the follow-up period was based on the likelihood of recurrence. The site and pattern of initial recurrence was defined as either intrahepatic or extrahepatic. Intrahepatic recurrence was divided into four types: type 1, marginal recurrence; type 2, recurrence at an adjacent segment; type 3, recurrence at a distal segment; and type 4, multisegmental recurrence [8].

Statistical analysis

Data were analyzed using SPSS ver. 18 (SPSS, Chicago, IL). For continuous variables, the data were presented as the mean ± standard deviation or as medians with range. Student's *t* test or one-way analysis of variance (ANOVA) were used for continuous variables, and χ^2 or Fisher's exact test were used for categorical variables. We defined the primary and secondary endpoints as OS and DFS. The Kaplan–Meier method was used for comparisons of the OS and DFS. For univariate analysis of the risk factors for recurrence, patients with recurrence were compared with patients who did not recur. The same procedure was followed for univariate analysis of risk factors for death. For multivariate analysis, the Cox stepwise regression model was performed. A difference with a $p < 0.05$ was considered to be statistically significant.

For the comparison of survival, continuous variables were dichotomized. The indocyanine green retention rate at 15 min (ICG-R15 ≤10 vs. >10 %; normal range 0–10 %), serum albumin level (≤3.5 vs. >3.5 g/dL; normal range 3.6–5.3 g/dL), platelet level ($\leq 150 \times 10^3$/mL vs. $>150 \times 10^3$/mL; normal range 151–450 $\times 10^3$/mL), and serum total bilirubin level (≤1.2 vs. >1.2 mg/dL; normal range 0.2–1.2 mg/dL) were categorized as above or below the normal ranges. The serum aspartate aminotransferase level (AST ≤90 vs. >90 U/L; normal range 4–45 U/L) was categorized as ≤2 N versus >2 N. The serum α-fetoprotein level was categorized as ≤400 versus >400 ng/mL using the 70th percentile as the breakpoint. Tumor size was categorized as >5 versus ≤5 cm based on the AJCC 7th edition classification system.

To overcome any bias due to differences in the distribution of covariates between the RM ≤1 mm and >1 mm groups, the patients were matched in a 1:1 ratio by propensity score analysis. Twenty-one variables entered into the propensity model were 3 continuous variables (age [years], tumor size [cm], and operating time [min]) and 18 categorical variables (albumin >3.5 gm/dL, AST >90 IU/L, bilirubin >1.2 mg/dL, platelet $\leq 150 \times 10^3$/mL, Child-Pugh class B, ICG-R15 >15 %, HBsAg positive, HCV positive, multiple preoperative TACE, AFP >400 ng/mL, multiple tumors, microvascular invasion, invasion of adjacent organs, node positive, poorly differentiated, anatomical resection, intraoperative transfusion, and morbidity) [13–15]. Each patient was matched using greedy nearest neighbor matching at a ratio 1:1 within a specified caliper width.

Results

Between December 1999 and December 2009, 1179 consecutive patients underwent hepatectomy for HCC at the Division of Hepatobiliary and Pancreas Surgery, Asan Medical Center, Seoul, Korea. Among the recruited cases, 157 patients with the following characteristics were excluded: (1) those who had a histologically positive resection margin ($n = 42$); (2) those who underwent palliative resection ($n = 36$); (3) those whose surgical margin was not recorded ($n = 6$); (4) those who underwent resection of combined HCC/cholangiocarcinoma ($n = 6$); (5) those who were lost to follow-up ($n = 14$); (6) those who underwent previous liver resection for HCC ($n = 24$); and (7) those who underwent treatment with ablation during surgery ($n = 13$). A final cohort of 1022 patients was enrolled in the current investigation. The DFS rates of the 1022 HCC patients with a histologically negative resection margin at 1, 3, and 5 years were 72.8, 51.7, and 42.7 %, respectively (median DFS, 38.1 months). The OS rates at 1, 3, and 5 years were 93, 79.6, and 68.7 %, respectively (mean OS, 113.94 ± 2.28 months).

Tables 1 and 2 show the statistical value of the resection margin lengths of 1, 5, and 10 mm. Among the three resection margin lengths, only 1 mm was a significant resection margin length regarding the DFS and OS (p value = 0.008 and 0.026, respectively).

Tables 1 and 2 summarize the results of both univariate and multivariate analyses of the factors affecting DFS and OS. On Multivariable analysis, albumin >3.5 gm/dL (HR 0.79, $p = 0.008$), AST > 90 IU/L (HR 2.11, $p < 0.001$), platelet $\leq 150 \times 10^3$/mL (HR 1.41, $p < 0.001$), tumor size >5 cm (HR 1.40, $p < 0.001$), multiple tumors (HR 1.71, $p < 0.001$), microvascular invasion (HR 1.68, $p < 0.001$), macrovascular invasion (HR 1.50, $p = 0.008$), positive node (HR 3.13, $p = 0.003$), and anatomical resection (HR 0.73, $p = 0.002$) significantly affected DFS. In addition, age >65 years (HR 1.56, $p = 0.003$), albumin >3.5 gm/dL (HR 0.65, $p < 0.001$), AST >90 IU/L (HR 1.60, $p = 0.015$), AFP >400 ng/mL (HR 1.28, $p = 0.028$), HCV positive status (HR 1.62, $p = 0.011$), multiple preoperative TACE procedures (HR 1.56, $p = 0.004$), tumor size >5 cm (HR 1.61, $p < 0.001$), multiple tumors (HR 2.00, $p < 0.001$), macrovascular invasion (HR 2.31, $p < 0.001$), microvascular invasion (HR 2.31, $p < 0.001$), anatomical resection (HR 0.67, $p = 0.002$), and postoperative

Table 1 Clinicopathologic factors associated with disease-free survival in 1022 consecutive HCC patients

	No. of patients	Univariable analysis		Multivariable analysis	
		HR[a]	*p*	HR[a]	*p*
Age (years)					
≤65	900 (88.1)	1.14 (0.90, 1.14)	0.271		
>65	122 (11.9)	1.00 (reference)			
Albumin (gm/dL)					
>3.5	717 (70.2)	0.65 (0.55, 0.76)	<0.001	0.79 (0.66, 0.94)	0.008
≤3.5	305 (29.8)	1.00 (reference)		1.00 (reference)	
AST (IU/L)					
>90	54 (5.3)	2.44 (1.80, 3.30)	<0.001	2.11 (1.54, 2.89)	<0.001
≤90	968 (94.7)	1.00 (reference)		1.00 (reference)	
Bilirubin (mg/dL)					
>1.2	141 (13.8)	1.10 (0.88, 1.38)	0.413		
≤1.2	881 (86.2)	1.00 (reference)			
Platelet (10^3/mL)					
≤150	516 (50.5)	1.28 (1.09, 1.49)	0.002	1.41 (1.19, 1.67)	<0.001
>150	506 (49.5)	1.00 (reference)		1.00 (reference)	
AFP (ng/mL)					
>400	302 (29.5)	1.28 (1.09, 1.52)	0.004	1.12 (0.93, 1.34)	0.226
≤400	720 (70.5)	1.00 (reference)		1.00 (reference)	
Child score					
C	0				
B	4 (0.4)	1.40 (0.35, 5.60)	0.637		
A	1018 (99.6)	1.00 (reference)			
ICG-R15 mean (%)					
>10	565 (55.3)	1.21 (1.04, 1.42)	0.017	1.03 (0.85, 1.24)	0.791
≤10	457 (44.7)	1.00 (reference)		1.00 (reference)	
HBV					
Positive	806 (78.9)	1.23 (1.01, 1.51)	0.041	1.16 (0.94, 1.44)	0.166
Negative	216 (21.1)	1.00 (reference)		1.00 (reference)	
HCV					
Positive	71 (6.9)	1.28 (0.95, 1.71)	0.106		
Negative	951 (93.1)	1.00 (reference)			
Preoperative TACE					
Multiple	96 (9.4)	1.44 (1.11, 1.85)	0.005	1.26 (0.97, 1.64)	0.084
Single	128 (12.5)	1.08 (0.86, 1.37)	0.496	1.09 (0.86, 1.39)	0.468
None	798 (78.1)	1.00 (reference)		1.00 (reference)	
Tumor size (cm)					
>5	410 (40.1)	1.52 (1.30, 1.78)	<0.001	1.40 (1.17, 1.67)	<0.001
≤5	612 (59.9)	1.00 (reference)		1.00 (reference)	
Tumor number					
Multiple	144 (14.1)	1.95 (1.59, 2.39)	<0.001	1.71 (1.39, 2.11)	<0.001
Single	878 (85.9)	1.00 (reference)		1.00 (reference)	
Macrovascular invasion					
Yes	75 (7.3)	1.98 (1.51, 2.60)	<0.001	1.50 (1.11, 2.02)	0.008
No	947 (92.7)	1.00 (reference)		1.00 (reference)	

Table 1 continued

	No. of patients	Univariable analysis		Multivariable analysis	
		HR[a]	*p*	HR[a]	*p*
Microvascular invasion					
Yes	185 (18.1)	1.94 (1.61, 2.34)	<0.001	1.68 (1.38, 2.06)	<0.001
No	837 (81.9)	1.00 (reference)		1.00 (reference)	
Invasion of adjacent organ					
Yes	16 (1.6)	1.51 (0.83, 2.75)	0.174		
No	1006 (98.4)	1.00 (reference)			
Node status					
Positive	7 (0.7)	4.2 (2.00, 8.93)	<0.001	3.13 (1.46, 6.72)	0.003
Negative	1015 (99.3)	1.00 (reference)		1.00 (reference)	
ES grade (worst)					
1	15 (1.5)	1.00 (reference)			
2	310 (30.3)	1.07 (0.55, 2.10)	0.841		
3	484 (47.4)	1.26 (0.65, 2.45)	0.492		
4	155 (15.2)	1.37 (0.69, 2.70)	0.370		
Anatomical resection					
Yes	843 (82.5)	0.74 (0.61, 0.90)	0.002	0.73 (0.60, 0.89)	0.002
No	179 (17.5)	1.00 (reference)		1.00 (reference)	
Surgical resection margin (RM)					
≤1 mm	195 (19.1)	1.29 (1.07, 1.57)	0.008	1.11 (0.91, 1.36)	0.296
>1 mm	827 (80.9)	1.00 (reference)		1.00 (reference)	
≤5 mm	453 (44.3)	1.18 (1.01, 1.37)	0.044		
>5 mm	569 (55.7)	1.00 (reference)			
≤10 mm	673 (65.9)	1.15 (0.97, 1.36)	0.111		
>10 mm	349 (34.1)	1.00 (reference)			
Intraoperative transfusion					
Yes	98 (9.6)	1.36 (1.05, 1.76)	0.022	1.05 (0.80, 1.39)	0.732
No	924 (90.4)	1.00 (reference)		1.00 (reference)	
Postop complication					
Yes	126 (12.3)	1.11 (0.88, 1.41)	0.393		
No	896 (87.7)	1.00 (reference)			

Values in parentheses are percentages unless indicated otherwise

HBV hepatitis B, *HCV* hepatitis C, *AFP* α-fetoprotein, *TACE* transcatheter arterial chemoembolization, *AST* aspartate aminotransferase, *ES* Edmondson–Steiner

complications (HR 1.58, $p = 0.001$) significantly affected OS. Although the surgical margin length was not a significant prognostic value in both DFS and OS, multivariable analyses were difficult to eliminate the bias in the factors overall. The fundamental difference between multivariable and propensity score analyses is that multivariable analysis focuses on the relationship between baseline characteristics and outcomes, whereas propensity score analysis focuses on the relationship between baseline characteristics and primary predictor variable. Hence, propensity score analysis was attempted to reconstruct a situation similar to randomization.

Propensity score matching between RM ≤1 mm and RM >1 mm group

Propensity score matching was performed using 21 selected patient characteristics, tumor-related factors, and surgical factors. Following propensity score matching, there were no significant between-group differences in the factors overall (Table 3).

In unmatched patients, Fig. 1 shows the Kaplan–Meier survival curve of DFS and OS of HCC patients between the RM >1 mm and RM ≤1 mm groups. The 1-, 3-, and 5-year DFS rates were 74.4, 53.7, and 44.8 %, respectively, in the

Table 2 Clinicopathologic factors associated with an overall survival in 1022 consecutive HCC patients

	No. of patients	Univariable analysis		Multivariable analysis	
		HR[a]	*p*	HR[a]	*p*
Age (years)					
>65	122 (11.9)	1.55 (1.18, 2.04)	0.002	1.56 (1.18, 2.07)	0.003
≤65	900 (88.1)	1.00 (reference)		1.00 (reference)	
Albumin (gm/dL)					
>3.5	717 (70.2)	0.51 (0.42, 0.62)	<0.001	0.65 (0.52, 0.81)	<0.001
≤3.5	305 (29.8)	1.00 (reference)		1.00 (reference)	
AST (IU/L)					
>90	54 (5.3)	2.58 (1.81, 3.67)	<0.001	1.60 (1.09, 2.33)	0.015
≤90	968 (94.7)	1.00 (reference)		1.00 (reference)	
Bilirubin (mg/dL)					
>1.2	141 (13.8)	1.17 (0.88, 1.56)	0.272		
≤1.2	881 (86.2)	1.00 (reference)			
Platelet (10^3/mL)					
≤150	516 (50.5)	1.18 (0.97, 1.44)	0.104		
>150	506 (49.5)	1.00 (reference)			
AFP (ng/mL)					
>400	302 (29.5)	1.62 (1.32, 1.98)	<0.001	1.28 (1.03, 1.59)	0.028
≤400	720 (70.5)	1.00 (reference)		1.00 (reference)	
Child score					
C	0				
B	4 (0.4)	2.39 (0.60, 9.59)	0.220		
A	1018 (99.6)	1.00 (reference)			
ICG-R15 mean (%)					
>10	565 (55.3)	1.19 (0.98, 1.46)	0.087		
≤10	457 (44.7)	1.00 (reference)			
HBV					
Positive	806 (78.9)	0.93 (0.73, 1.18)	0.558		
Negative	216 (21.1)	1.00 (reference)			
HCV					
Positive	71 (6.9)	1.44 (1.02, 2.04)	0.039	1.62 (1.12, 2.33)	0.011
Negative	951 (93.1)	1.00 (reference)		1.00 (reference)	
Preoperative TACE					
Multiple	96 (9.4)	1.67 (1.24, 2.23)	0.001	1.56 (1.15, 2.11)	0.004
Single	128 (12.5)	0.97 (0.72, 1.32)	0.852	1.04 (0.76, 1.42)	0.816
None	798 (78.1)	1.00 (reference)		1.00 (reference)	
Tumor size (cm)					
>5	410 (40.1)	2.16 (1.77, 2.63)	<0.001	1.61 (1.29, 2.00)	<0.001
≤5	612 (59.9)	1.00 (reference)		1.00 (reference)	

Table 2 continued

	No. of patients	Univariable analysis		Multivariable analysis	
		HR[a]	*p*	HR[a]	*p*
Tumor number					
Multiple	144 (14.1)	2.27 (1.78, 2.89)	<0.001	2.00 (1.56, 2.54)	<0.001
Single	878 (85.9)	1.00 (reference)		1.00 (reference)	
Macrovascular invasion					
Yes	75 (7.3)	2.58 (1.90, 3.51)	<0.001	1.99 (1.42, 2.77)	<0.001
No	947 (92.7)	1.00 (reference)		1.00 (reference)	
Microvascular invasion					
Yes	185 (18.1)	2.67 (2.14, 3.32)	<0.001	2.31 (1.81, 2.93)	<0.001
No	837 (81.9)	1.00 (reference)		1.00 (reference)	
Invasion of adjacent organ					
Yes	16 (1.6)	2.27 (1.21, 4.25)	0.011	1.16 (0.60, 2.23)	0.665
No	1006 (98.4)	1.00 (reference)		1.00 (reference)	
Node status					
Positive	7 (0.7)	4.23 (1.88, 9.49)	<0.001	1.49 (0.62, 3.58)	0.373
Negative	1015 (99.3)	1.00 (reference)		1.00 (reference)	
ES grade (worst)					
1	15 (1.5)	1.00 (reference)			
2	310 (30.3)	0.75 (0.35, 1.62)	0.464		
3	484 (47.4)	0.92 (0.43, 1.95)	0.817		
4	155 (15.2)	1.08 (0.50, 2.35)	0.848		
Anatomical resection					
Yes	843 (82.5)	0.71 (0.56, 0.91)	0.006	0.67 (0.53, 0.86)	0.002
No	179 (17.5)	1.00 (reference)		1.00 (reference)	
Surgical resection margin (RM)					
≤1 mm	195 (19.1)	1.31 (1.03, 1.66)	0.026	1.03 (0.80, 1.33)	0.796
>1 mm	827 (80.9)	1.00 (reference)		1.00 (reference)	
≤5 mm	453 (44.3)	1.12 (0.92, 1.37)	0.264		
>5 mm	569 (55.7)	1.00 (reference)			
≤10 mm	673 (65.9)	1.11 (0.90, 1.37)	0.334		
>10 mm	349 (34.1)	1.00 (reference)			
Intraoperative transfusion					
Yes	98 (9.6)	1.77 (1.32, 2.39)	<0.001	1.05 (0.76, 1.45)	0.766
No	924 (90.4)	1.00 (reference)		1.00 (reference)	
Postop complication					
Yes	126 (12.3)	1.61 (1.23, 2.11)	0.001	1.58 (1.20, 2.08)	0.001
No	896 (87.7)	1.00 (reference)		1.00 (reference)	

Values in parentheses are percentages unless indicated otherwise

[a] values in parentheses are 95 % confidence intervals

HBV hepatitis B, *HCV* hepatitis C, *AFP* α-fetoprotein, *TACE* transcatheter arterial chemoembolization, *AST* aspartate aminotransferase, *ES* Edmondson–Steiner

RM >1 mm group, and 65.9, 43.4, and 33.8 %, respectively, in the RM ≤1 mm group ($p = 0.008$). The 1-, 3, and 5-year OS rates were 93.5, 80.6, and 70.9 %, respectively, in the RM >1 mm group, and 90.8, 75.9, and 60.8 %, respectively, in the RM ≤1 mm group ($p = 0.025$). However, a comparison of the survival outcomes in the propensity score-matched groups showed that the 1-,3-, and 5-year DFS rates were 63.1, 43.1, and 36.0 %, respectively, in the RM >1 mm group, and 65.9, 43.4, and 33.8 %, respectively, in the RM ≤1 mm group ($p = 0.688$, Fig. 2a). The 1-, 3-, and 5-year OS rates were 86.7, 68.7, and 60.8 %, respectively, in the RM >1 mm group, and 90.8, 75.9, and 60.8 %, respectively, in the RM ≤1 mm group ($p = 0.398$, Fig. 2b).

Table 3 Clinicopathological factors in patients with HCC after propensity score matching of RM ≤1 mm and RM >1 mm groups

Factors	Prepropensity score matching, $n = 1022$			Postpropensity score matching, $n = 390$		
	RM ≤1 mm, $n = 195$	RM >1 mm, $n = 827$	p	RM ≤1 mm, $n = 185$	RM >1 mm, $n = 185$	p
Patients characteristics						
Age, years	54.46 (±0.72)	53.38 (±0.33)	0.424	54.55 (±0.72)	53.60 (±0.74)	0.357
Albumin (gm/dL) >3.5	124 (63.6)	593 (71.3)	0.026	124 (64.2)	129 (66.8)	0.592
AST (IU/L) >90	14 (7.2)	40 (4.8)	0.188	13 (6.7)	12 (6.2)	0.836
Bilirubin (mg/dL) >1.2	28 (14.4)	113 (13.7)	0.800	28 (14.5)	31 (16.1)	0.671
Platelet (10^3/mL) ≤150	99 (50.8)	417 (50.4)	0.931	99 (51.3)	103 (53.4)	0.684
Child-Pugh class B or C	0	4 (0.5)	1.000	0	0	1.000
ICG-R15 (%) >10	108 (55.4 %)	457 (55.3)	0.975	107 (55.4)	97 (50.3)	0.308
HBsAg	153 (78.5)	653 (79.0)	0.878	151 (78.2)	157 (81.3)	0.447
HCV	17 (8.7)	54 (6.5)	0.280	16 (8.3)	12 (6.2)	0.432
Preoperative TACE, multiple	19 (9.7)	77 (9.3)	0.852	19 (9.8)	18 (9.3)	0.863
Tumor-related factors						
AFP (ng/mL) >400	60 (30.8)	242 (29.3)	0.678	59 (30.6)	56 (29.0)	0.738
Tumor size (cm)	6.10 (±0.31)	5.04 (±0.12)	0.002	6.00 (±0.31)	5.92 (±0.29)	0.859
Tumor number, single/multiple	156 (80.0)/39 (20.0)	722 (87.3)/105 (12.7)	0.008	156 (80.8)/37 (19.2)	153 (79.3)/40 (20.7)	0.702
Microvascular invasion	46 (23.6)	139 (16.8)	0.027	45 (23.3)	43 (22.3)	0.808
Invasion of adjacent organ	2 (1.0)	14 (1.7)	0.750	2 (1.0)	2 (1.0)	1.000
Node status	0	7 (0.8)	0.358	0	0	1.000
Poor differentiated	34 (17.4)	121 (14.6)	0.326	34 (17.6)	33 (17.1)	0.893
Surgical factors						
Operative time (min)	205.35 (±5.07)	193.16 (±2.49)	0.033	204.67 (±5.07)	204.67 (±5.51)	0.999
Anatomical resection	165 (84.6)	678 (82.0)	0.384	163 (84.5)	164 (85.0)	0.888
Intraoperative transfusion	28 (14.4)	70 (8.5)	0.012	26 (13.5)	27 (14.0)	0.882
Morbidity	30 (15.4)	96 (11.6)	0.149	29 (15.0)	27 (14.0)	0.773
Recurrence	136 (69.7)	492 (59.5)	0.008	134 (69.4)	130 (67.4)	0.661
Multiplicity of recurrence, single/multiple	80 (41.0)/56 (28.7)	296 (35.8)/196 (23.7)	0.029	80 (41.5)/54 (28.0)	71 (36.8)/59 (30.6)	0.641
Extrahepatic recurrence (EHC)	32 (16.4)	85 (10.3)	0.016	31 (16.1)	23 (11.9)	0.240
Intrahepatic recurrence (IHC)	111 (56.9)	428 (51.8)	0.193	110 (57.0)	111 (57.5)	0.918
Type of IHC			0.066			0.367
I	7 (3.6)	40 (4.8)		7 (3.6)	8 (4.1)	
II	50 (25.6)	173 (20.9)		50 (25.9)	39 (20.2)	
III	22 (11.3)	122 (14.8)		22 (11.4)	34 (17.6)	
IV	32 (16.4)	89 (10.8)		31 (16.1)	27 (14.0)	

Values in parentheses are percentages unless indicated otherwise

HBV hepatitis B, *HCV* hepatitis C, *AFP* α-fetoprotein, *TACE* transcatheter arterial chemoembolization, *AST* aspartate aminotransferase, *ES* Edmondson–Steiner

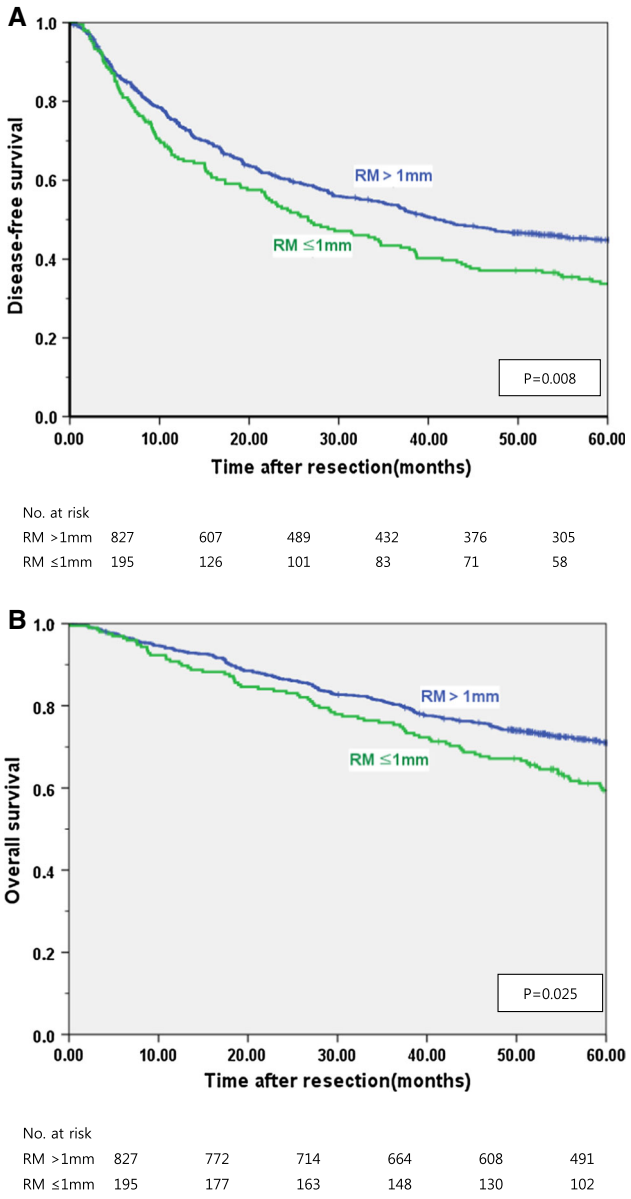


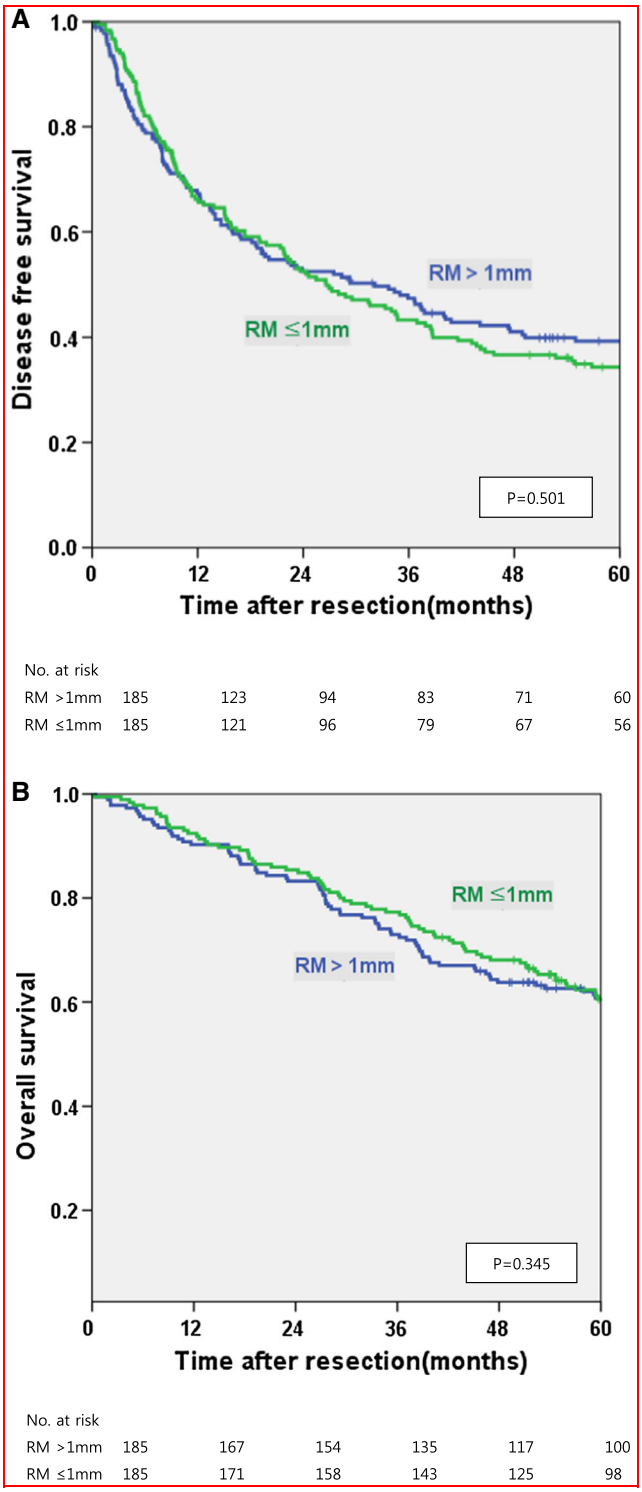
Fig. 1 In unmatched patients, Kaplan–Meier survival curve of DFS (**a**) and OS (**b**) of HCC patients between RM >1 mm and RM ≤1 mm group. Data for RM >1 mm group ($n = 827$) are shown by *thick blue lines*, and data for RM >1 mm group ($n = 195$) are shown by red dotted lines. **a** the 1-,3-, and 5-year DFS rates were 74.4, 53.7, and 44.8 %, respectively, in the RM >1 mm group, and 65.9, 43.4, and 33.8 %, respectively, in RM ≤1 mm group ($p = 0.008$). **b** The 1-,3-, and 5-year OS rates were 93.5, 80.5, and 70.9 %, respectively, in the RM >1 mm group, and 90.8, 75.9, and 60.8 %, respectively, in RM ≤1 mm group ($p = 0.025$)

Additionally, Table 3 shows the differences in the tumor recurrent rate, site (extrahepatic or intrahepatic), and type of intrahepatic recurrence (I–IV) among the two groups. Before propensity score matching, the RM ≤1 mm group showed a significantly higher recurrent rate and extrahepatic recurrent rate than the RM >1 mm group ($p = 0.029$, $p = 0.016$). However, after propensity score matching, there were no significant differences between the two groups in both the overall recurrent rate and extrahepatic recurrent rate ($p = 0.641$ and $p = 0.240$, respectively). In addition, there were no significant differences in the intrahepatic recurrent rate and type of intrahepatic recurrence ($p = 0.193$ and $p = 0.066$, respectively). In matched patients, there were no significant differences in the tumor recurrence rate, site, and type of intrahepatic recurrence.

Discussion

The significance of the resection margin following hepatectomy for HCC is an important clinical issue. Previously, many surgeons and pathologists have reported that wide resection of a malignant tumor with an adequate margin was important to prevent marginal recurrence [7, 8, 10]. However, such an approach may not be applicable to HCC, which is characterized by two unique pathologic features. First, intrahepatic spread occurs mainly by means of portal venous invasion and entirely different from how other tumors invade the surrounding tissue. Second, multicentric recurrence is common and could occur anywhere in the remnant liver. Thus, some authors have suggested that anatomic resection is preferable to non-anatomic resection for liver cancers when it is being performed with curative intent [16–18]. However, the preservation of non-tumorous liver parenchyma is also an important consideration, particularly for cirrhotic liver resections. The advantages of preserving as much of the liver parenchyma as possible include not only decreasing the incidence of postoperative liver failure but also improving the chance of performing multimodal treatments and repeating resections in cases of tumor recurrence. For the above reasons, Matsue et al. [19]. reported that limited resection with no margin seems to the best procedure for patients with tumors close to the major hepatic vessels and with hepatic functions that do not permit wide margin resections.

In unmatched patients, there was a significant difference in DFS and OS of the 1,022 R0 resected HCC patients between the RM ≤1 mm and >1 mm groups ($p = 0.008$ and $p = 0.025$, respectively). However, 6 clinicopathological factors were different between the 2 groups of patients (preoperative albumin level [$p = 0.026$], tumor size [$p = 0.002$], tumor multiplicity [$p = 0.008$], positive microvascular invasion [$p = 0.027$], operative time [$p = 0.033$], and intraoperative transfusion [$p = 0.012$]). Probably, in marginal liver function patients, large size, multiple tumors, and vascular invasive HCC lesions could not provide a sufficient RM. To reduce these different



◀**Fig. 2** In matched patients, Kaplan–Meier survival curve of DFS (**a**) and OS (**b**) of HCC patients between RM >1 mm and RM ≤1 mm group. Data for RM >1 mm group ($n = 185$) are shown by *thick blue lines*, and data for RM >1 mm group ($n = 185$) are shown by *thick green lines*. **a** the 1-,3-, and 5-year DFS rates were 66.5, 44.9, and 32.4 %, respectively, in the RM >1 mm group, and 65.4, 44.9, and 32.4 %, respectively, in RM ≤1 mm group ($p = 0.501$). **b** The 1-,3-, and 5-year OS rates were 90.3, 73.0, and 54.1 %, respectively, in the RM >1 mm group, and 92.4, 77.3, and 53.0 %, respectively, in RM ≤1 mm group ($p = 0.345$)

clinicopathological factors, propensity score matching was performed using 21 selected patient characteristics, tumor-related, and surgical factors. After propensity score matching, there were no significant differences between the 2 RM groups in both DFS ($p = 0.688$) and OS ($p = 0.398$).

Also, in unmatched patients, there was a significant difference in extrahepatic recurrence ($p = 0.016$). However, there was not a significant difference in the intrahepatic recurrent rate and type of intrahepatic recurrence ($p = 0.193$ and $p = 0.066$, respectively). After propensity score matching, there was no significant difference in the tumor recurrence rate, site, and type of intrahepatic recurrence. A few different factors produce these unexpectedly results. First, in this study, hepatic resection was performed with the Glissonean pedicle transection method (as described by Takasaki) [20] and transected at the intersegmental plane, as described by Couinaud, by Kelly clamp crushing technique [21, 22]. RM 1 mm notwithstanding, crushing hepatic parenchyma by kelly clamp and electrocoagulated parenchyma give more safe margin. Second, clinicopathological characteristics in this study (such as HCV infection ratio, races, vascular invasion ratio, and tumor number) is somehow different from previous reports.

The prognostic factors for DFS or OS after HCC resection have been widely studied. To date, most authors have emphasized the important role of vascular invasion in HCC recurrence after surgery, although many factors (such as preoperative liver function [including elevated ALT, elevated AST, lower serum albumin, and Child-Pugh status], tumor characteristics [including tumor characteristics in HCC recurrence after surgery and differentiation], and perioperative features [including the extent of surgery, surgical margin, and blood transfusion) are regarded as independent risk factors for DFS and OS in multivariate analysis [2, 6, 16–18, 23–27]. Similar results were obtained in the current study. In multivariable analysis, albumin >3.5 gm/dL, AST >90 IU/L, Platelet $\leq 150 \times 10^3$/mL, tumor size >5 cm, and multiple tumors, microvascular invasion, macrovascular invasion, positive node status, and anatomical resection were significantly associated with DFS. In addition, age >65 years, albumin >3.5 gm/dL, AST >90 IU/L, AFP >400 ng/mL, HCV positive status, multiple preoperative TACE procedures, tumor size >5 cm, multiple tumors, macrovascular invasion, microvascular invasion, anatomical resection, and postoperative complication significantly affected OS. Except for the preoperative patient's status and tumor stage, the

factors affected by the operator were anatomical resection and postoperative complication.

However, this study was retrospectively collected, and the surgeon tried to perform anatomical resection if the patient's liver function was sufficient—i.e., this result might have been intentional. Also, the patients in insufficient liver function and invasive tumor characteristic status could have more complication rate. Thus, these factors were required for the prospective study or propensity score-matched analysis. A propensity score analysis attempted to evaluate the effect of randomization demonstrated that a wide resection margin for HCC was not an effective strategy to reduce the risk of postoperative recurrence. Therefore, the present study identified that the widths of the resection margin in resectable hepatocellular carcinoma did not influence the postoperative recurrence rates, overall survival, and recurrence pattern in multivariable analysis as well as propensity score match analysis.

Compliance with ethical standards

Conflict of interest None of the authors have a conflict of interest in this study.

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