

# Outcomes and recurrence pattern after non-anatomic liver resection for solitary hepatocellular carcinomas

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**Backgrounds/Aims:** Anatomic resection (AR) is preferred for eradicating portal tributaries in patients with hepatocellular carcinoma (HCC). However, the extent of resection is influenced by underlying liver disease and tumor location. We compared the surgical outcomes and recurrence pattern between non-anatomic resection (NR) and AR. **Methods:** From March 2009 to February 2012, 184 patients underwent surgical resection for HCC. Among these, 79 patients who were primarily treated for a single tumor without rupture or macroscopic vascular invasion were enrolled. The patients were divided into 2 groups based on the extent of resection: AR (n=31) or NR (n=48). We compared the clinical characteristics, overall survival, disease-free survival, pattern of recurrence, and biochemical liver functions during the peri-operative period between the two groups. **Results:** The extent of resection had no significant effect on overall or disease-free survival rates. The overall 1- and 3-year survival rates were 97% and 82% in the AR group, and 96% and 89% in the NR group, respectively ( $p=0.49$ ). In addition, the respective 1- and 3-year disease-free survival rates for the AR and NR groups were 84% and 63%, and 85% and 65%, respectively ( $p=0.94$ ). On the other hand, the presence of hepatic cirrhosis and a tumor size of  $>5$  cm were significant risk factors for recurrence according to multivariate analysis ( $p<0.001$  and  $p=0.003$ , respectively). The frequency of early recurrence, the first site of recurrence, and the pattern of intrahepatic recurrence were similar between the 2 groups ( $p=0.419$ ,  $p=0.210$ , and  $p=0.734$ , respectively); in addition, the frequency of marginal recurrence did not differ between the 2 groups (1 patient in the AR group and 2 in the NR group). The NR group showed better postoperative liver function than the AR group. **Conclusions:** Non-anatomic liver resection can be a safe and efficient treatment for patients with a solitary HCC without rupture or gross vascular invasion. (*Korean J Hepatobiliary Pancreat Surg* 2016;20:1-7)

**Key Words:** Hepatocellular carcinoma; Resection; Recurrence pattern; Disease-free survival

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and South Korea has one of the highest prevalence rates for this disease.<sup>1</sup> Surgical resection is accepted as the most effective intervention to cure such patients. There are several reports on the risk factors for tumor recurrence after liver resection for HCC, mostly based on patient status, pathology results, and biological factors, irrespective of the surgical precision or procedure adopted.<sup>2</sup>

When the extent and type of liver resection are considered, anatomic resection (AR) is theoretically superior to non-anatomic resection (NR) for patients with HCC be-

cause it can eradicate intrahepatic metastases that might have spread via portal tributaries.<sup>3</sup> However, the fear of further reducing the liver size causes surgeons to question the benefits of performing AR in a patient with cirrhosis. Moreover, the superiority of this procedure for oncologic safety remains controversial.<sup>4,5</sup> Therefore, we retrospectively evaluated patient survival rates and recurrence patterns, and compared the post-hepatectomy liver function with the extent of liver resection in such patients.

## MATERIALS AND METHODS

From March 2009 to February 2012, 184 patients underwent curative surgical resection for HCC at Kyungpook

**Received:** May 28, 2015; **Revised:** September 26, 2015; **Accepted:** September 30, 2015

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Korean Journal of Hepato-Biliary-Pancreatic Surgery • pISSN: 1738-6349 • eISSN: 2288-9213

National University Hospital. Among these, 79 who underwent surgical resection as a first-line therapy for a single tumor were enrolled in this study, excluding patients with macroscopic vascular invasion or a ruptured HCC. A curative hepatic resection was defined as macroscopic removal of all tumorous tissue from the liver, and AR was defined as complete resection of the anatomical area that was identified from preceding ischemia. There were 31 cases of AR, of which, 16 involved hemihepatectomy, 4 involved extended hemihepatectomy, and 11 involved sectionectomy. All the other procedures were classified as NR and performed in 48 patients. During the NR procedures, we focused on creating a sufficient resection margin of 1 cm, regardless of the condition of the hepatic pedicle. Early recurrence was defined as a recurrence within 2 years after a curative resection, in accordance with previous studies.<sup>6,7</sup> A serial follow-up of the patients was provided to monitor for any recurrence. Contrast-enhanced abdominal computed tomography (CT) scans were repeated every 3 months during the first 2 postoperative years and alternating abdominal ultrasound and abdominal CT scans were performed every 3 months thereafter. Serum  $\alpha$ -fetoprotein (AFP) levels were measured every 3 months. Recurrence patterns after liver resection were classified according to the location of the recurring tumor and the time to recurrence, and the pattern of intrahepatic recurrence was classified according to Poon et al.<sup>8</sup> In addition, post-hepatectomy liver functions includ-

ing the circulating levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and prothrombin time were compared with the extent of liver resection during the perioperative period.

Student's independent *t* tests were used to compare the differences between continuous variables in patients with and without AR. Categorical variables were subjected to chi-squared analysis if the sample size was adequate or Fisher's exact test if the sample number was small. The cumulative overall and disease-free survival rates were calculated using the Kaplan-Meier method, and candidate variables with *p*-values < 0.2 by univariate analysis were further analyzed using the Cox proportional-hazards model. The statistical analyses were performed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA), and *p* < 0.05 was considered statistically significant. Results were presented as the hazard ratio (HR) and 95% confidence interval (CI).

## RESULTS

### Patient characteristics

The clinical features of the 79 patients were listed in Table 1. Comparing the AR group (n=31) versus the NR group (n=48), there were no significant differences in gender, age, the incidences of hepatitis B or C, AST or ALT levels, prothrombin time (PT), serum albumin, total bilir-

**Table 1.** Clinicopathological features of the anatomic and non-anatomic resection groups

	AR group (n=31)	NR group (n=48)	<i>p</i> -value
Gender (male/female) (n)	24/7	32/16	0.447
Age (years, mean±SD)	58.9±11.6	57.9±10.8	0.702
HBs Ag (positive/negative)* (n)	25/6	36/11	0.783
Anti-HCV Ab (positive/negative)* (n)	1/30	4/43	0.643
Liver cirrhosis (present/absent) (n)	6/25	24/24	0.009
AST (IU/L, mean±SD)	41.2±41.0	36.8±24.3	0.547
ALT (IU/L, mean±SD)	36.7±22.9	34.9±24.9	0.748
Platelet count ( $\times 10^3/\text{mm}^3$ , mean±SD)	211.5±76.3	170.4±59.4	0.009
Prothrombin time (% , mean±SD)	95.4±12.7	91.4±14.9	0.222
Albumin (g/dl, mean±SD)	4.1±0.5	4.2±0.5	0.348
Total bilirubin (mg/dl, mean±SD)	0.70±0.29	0.72±0.30	0.787
AFP > 200 ng/ml (present/absent)* (n)	9/21	17/31	0.800
ICG R15 (% , mean±SD)	9.0±4.3	10.3±13.8	0.605
Tumor size > 5 cm (present/absent) (n)	13/18	8/40	0.019
Resection margin $\leq 10$ mm (present/absent) (n)	20/11	29/19	0.814

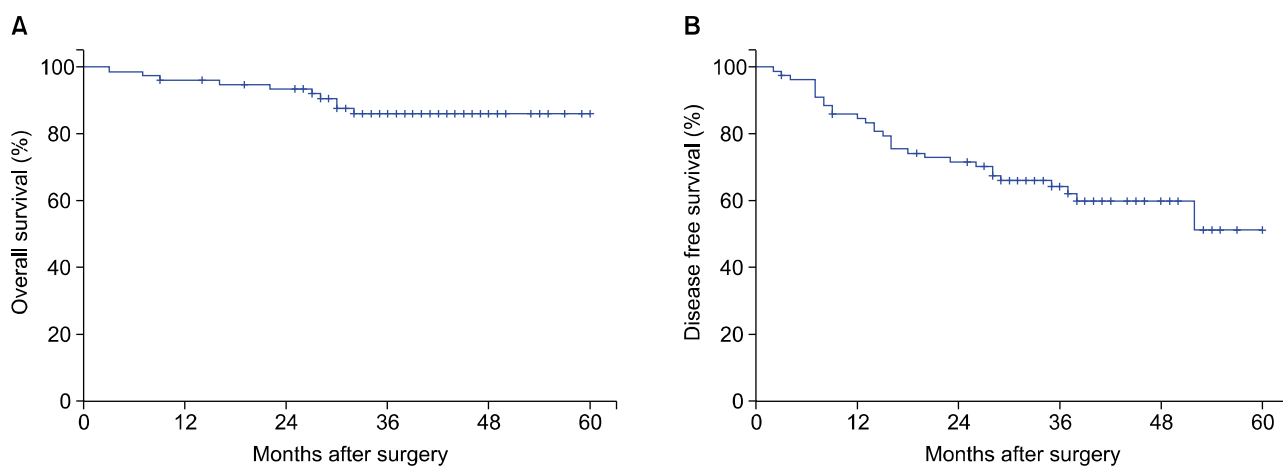
\*Data available for 79 patients. AR, anatomic resection; NR, non-anatomic resection; HBs Ag, hepatitis B surface antigen; anti-HCV Ab, anti-Hepatitis C virus antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP,  $\alpha$ -fetoprotein; ICG R15, indocyanine green dye retention rate at 15 minutes

ubin, AFP levels, indocyanine green dye retention rate at 15 min, or tumor-free resection margin. However, tumors were significantly larger in the AR group, as compared with the NR group ( $p=0.019$ ); in addition, patients in the NR group had a significantly lower platelet count ( $p=0.009$ ) and higher rates of hepatic cirrhosis ( $p=0.009$ ), as compared with those in the AR group. There were no patients with Child-Pugh class B or C tumors in either group.

### Recurrence and survival outcomes

After a median follow-up of 37.0 months (range 3-60) post-resection, the 1- and 3-year overall and disease-free survival rates for all patients were 97% and 86%, and 85% and 64%, respectively (Fig. 1).

Thirty patients (38%) had recurrence and 10 patients died during the follow-up period. In the NR group, 4 patients died of recurrent HCC, 1 died of hepatic failure, 14 patients remain alive with recurrent HCC, and 29 are alive and disease free. Among the patients in the AR group, 5 died of recurrent HCC, 7 remain alive with re-



**Fig. 1.** Cumulative survival curves of all 79 patients. The overall survival rates (A) and disease-free survival rates (B) were 97%, 86% at 1 year and 85%, 64% at 3 years, respectively.

**Table 2.** Univariate and multivariate analysis of variables related to overall survival after hepatic resection for HCC

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Gender (male) (n)	0.976	0.252-3.777	0.972			
Age (years)	0.993	0.938-1.051	0.807			
HBs Ag (positive)* (n)	0.965	0.205-4.553	0.964			
Anti HCV Ab (positive)* (n)	1.666	0.211-13.164	0.629			
Liver cirrhosis (present) (n)	2.559	0.722-9.072	0.146	6.293	1.414-28.001	0.016
AST, IU/L	1.006	0.993-1.018	0.366			
ALT, IU/L	1.012	0.989-1.035	0.310			
Platelet count, $\times 10^3/\text{mm}^3$	0.999	0.990-1.009	0.880			
Prothrombin time, %	0.995	0.950-1.043	0.833			
Albumin, g/dl	0.482	0.124-1.874	0.292			
Total bilirubin, mg/dl	2.294	0.305-17.272	0.420			
AFP > 200 ng/ml (present)*	2.919	0.843-10.103	0.091	3.428	0.965-12.170	0.057
ICG R15, %	1.004	0.956-1.055	0.862			
Tumor size > 5 cm (present) (n)	3.039	0.879-10.509	0.079	6.951	1.628-29.684	0.009
Resection margin $\leq 10$ mm (present) (n)	1.420	0.367-5.493	0.611			
Anatomic resection (n)	0.651	0.188-2.250	0.498			

\*Data available for 79 patients. HR, Hazard ratio; CI, confidence interval; HBs Ag, hepatitis B surface antigen; anti-HCV Ab, anti-Hepatitis C virus antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP,  $\alpha$ -fetoprotein; ICG R15, indocyanine green dye retention rate at 15 minutes

current HCC, and 19 are alive and disease free.

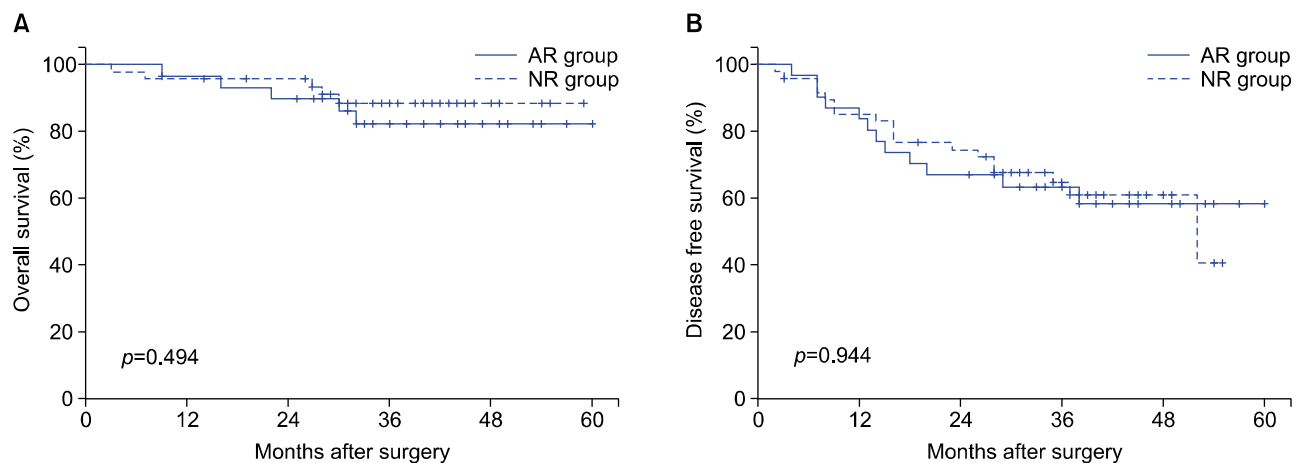
Table 2 listed the prognostic factors associated with overall survival of these patients identified from univariate and multivariate analyses. In univariate analysis, the presence of liver cirrhosis, an AFP level >200 ng/ml, and a tumor size of >5 cm showed *p*-values of <0.2 and were further included in multivariate Cox proportional-hazard regression analysis; the presence of liver cirrhosis (HR 6.293; 95% CI 1.414-28.001; *p*=0.016) and tumor size >5 cm (HR 6.951; 95% CI 1.628-29.684; *p*=0.009) were independent prognostic factors for overall

survival. On univariate analysis of the risk factors for tumor recurrence, the presence of liver cirrhosis and tumor size >5 cm showed *p*-values <0.2 and the presence of liver cirrhosis (HR 5.465; 95% CI 2.339-12.770; *p*<0.001) and tumor size >5 cm (HR 3.646; 95% CI 1.537-8.650; *p*=0.003) were significant independent predictors of tumor recurrence after liver resection (Table 3). On the other hand, the extent of liver resection was not a significant risk factor for recurrence with the 1- and 3-year overall survival rates for the AR and NR groups of 97% and 82%, and 96% and 89%, respectively

**Table 3.** Univariate and multivariate analysis of variables related to disease free-survival after hepatic resection for HCC

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>p</i> -value	HR	95% CI	<i>p</i> -value
Gender (male) (n)	1.370	0.584-3.212	0.469			
Age (years)	1.017	0.983-1.052	0.338			
HBs Ag (positive)* (n)	0.837	0.359-1.952	0.680			
Anti HCV Ab (positive)* (n)	1.243	0.295-5.230	0.767			
Liver cirrhosis (present) (n)	3.389	1.605-7.156	0.001	5.465	2.339-12.770	<0.001
AST, IU/L	1.000	0.989-1.010	0.945			
ALT, IU/L	0.993	0.975-1.010	0.400			
Platelet count, ×10 <sup>3</sup> /mm <sup>3</sup>	0.998	0.993-1.004	0.541			
Prothrombin time, %	1.000	0.974-1.026	0.973			
Albumin, g/dl	0.778	0.362-1.715	0.548			
Total bilirubin, mg/dl	0.683	0.210-2.218	0.526			
AFP >200 ng/ml (present)* (n)	1.071	0.474-2.419	0.869			
ICG R15, %	0.971	0.915-1.030	0.328			
Tumor size >5 cm (present) (n)	1.728	0.808-3.697	0.158	3.646	1.537-8.650	0.003
Resection margin ≤10 mm (present) (n)	1.031	0.490-2.168	0.937			
Anatomic resection (n)	0.974	0.468-2.027	0.944			

\*Data available for 79 patients. HR, Hazard ratio; CI, confidence interval; HBs Ag, hepatitis B surface antigen; anti-HCV Ab, anti-Hepatitis C virus antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AFP, α-fetoprotein; ICG R15, indocyanine green dye retention rate at 15 minutes



**Fig. 2.** Survival curves showing the overall survival (A) and disease-free survival (B) after curative surgery for HCC in the anatomic resection (AR) group (solid line) and non-anatomic resection (NR) group (dotted line).

( $p=0.494$ ), and the 1- and 3-year disease-free survival rates of 84% and 63% in the AR group, and 85% and 65% in the NR group ( $p=0.944$ ; Fig. 2).

### Patterns of tumor recurrence

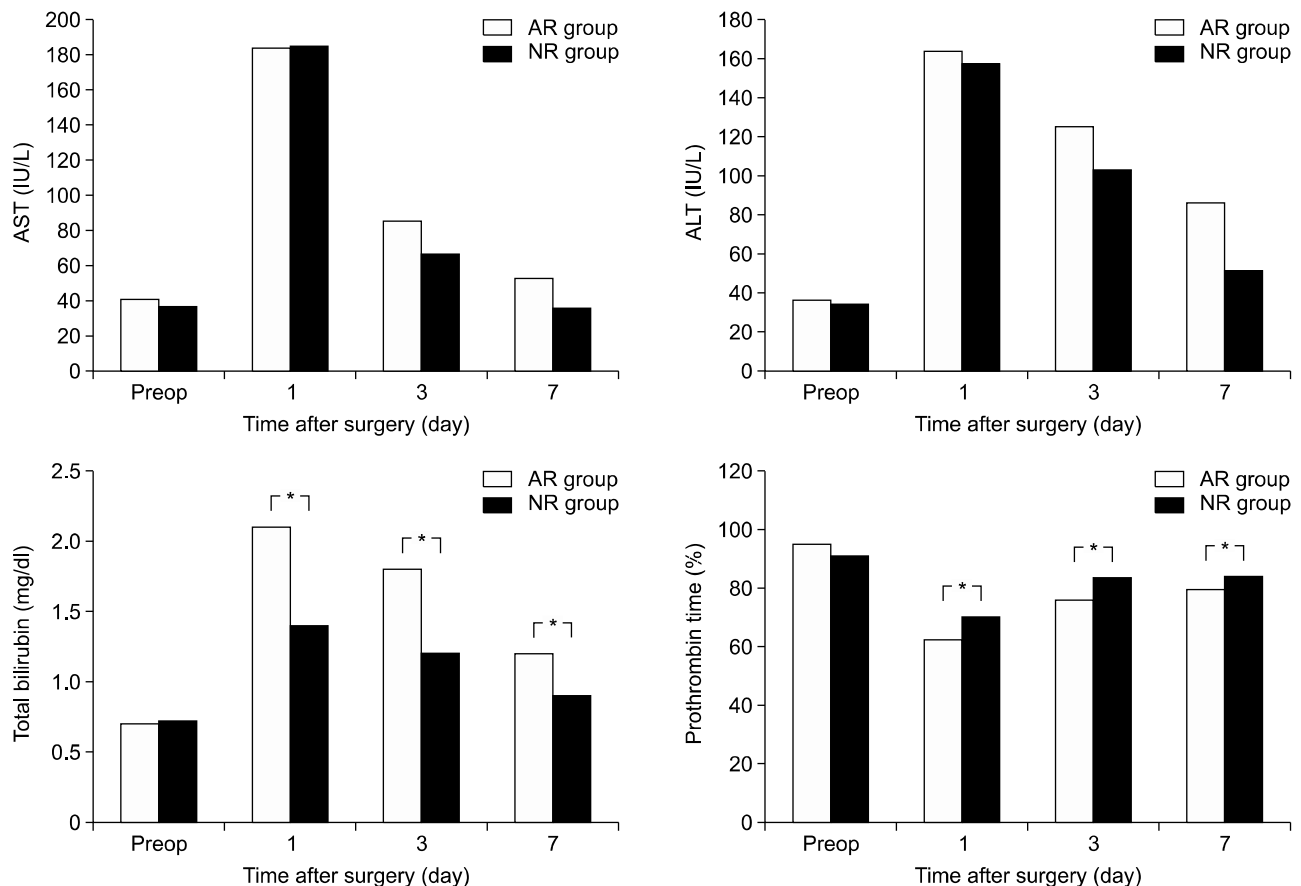
Twenty-two patients (28%) had tumors that recurred within 2 years after liver resection (10 patients after AR and 12 after NR) and the frequency of early recurrences was similar between the 2 groups ( $p=0.419$ ). Regarding the pattern of recurrence, in the NR group, 2 patients had a recurrence at the liver transection margin (1 of these showed a marginal recurrence at 36 months after liver resection), 5 had a recurrence in an adjacent section, 3 in a distal section, 5 had a multi-sectional recurrence, and 3 developed extrahepatic recurrences. In the AR group, a marginal recurrence occurred in 1 patient. The other intrahepatic recurrences consisted of 2 at an adjacent section, 3 at a distal section, and 1 in multiple sections. Five patients had a recurrence at an extrahepatic site. There were

no significant differences between the 2 groups with respect to the first site of recurrence or the pattern of intrahepatic recurrence ( $p=0.210$  and  $p=0.734$ , respectively; Table 4).

**Table 4.** Patterns of tumor recurrence following hepatic resection for HCC

	Extent of resection		<i>p</i> -value
	AR group	NR group	
Time until recurrence			0.419
≤2 years	10	12	
>2 years	2	6	
First site of recurrence			0.210
Intrahepatic	7	15	
Extrahepatic	5	3	
Pattern of intrahepatic recurrence			0.734
Marginal	1	2	
Adjacent section	2	5	
Distal section	3	3	
Multisectional	1	5	

AR, anatomic resection; NR, non-anatomic resection



**Fig. 3.** Biochemical liver function parameters of the anatomic resection (AR) group (solid line) and non-anatomic resection (NR) group during the perioperative period. Asterisks indicated  $p$ -value  $< 0.05$ .

### Perioperative liver function

Biochemical liver function parameters were similar between the 2 groups during the preoperative period. However, the serum bilirubin level and PT value of the AR group were worse than those of the NR group during the postoperative period (Fig. 3).

## DISCUSSION

AR is theoretically ideal for a patient with HCC from functional and oncological aspects, because the related portal vein and corresponding hepatic territory are removed. This reduces the ischemic area, minimizes any bile leakage, and lessens the possibility of any local recurrence of the tumor. However, the removal of a larger liver volume in the AR vs. NR procedure raises the possibility that the remaining liver mass might not meet the patient's metabolic requirements.<sup>9,10</sup> Therefore, several studies have aimed to evaluate the effects of the extent of surgery for HCC.<sup>4,5,11-13</sup> In 2014, 3 studies used propensity-matching score analysis with the aim of identifying any benefit in patient survival after AR. However, none of these found conclusive results despite efforts to minimize confounding factors; in fact, they reported three different results. Okamura et al.<sup>14</sup> showed that the overall and recurrence-free survival in patients with HCC infected with hepatitis C virus were not superior in AR than NR procedure. In contrast, Cucchetti et al.<sup>15</sup> showed a lower early recurrence rate for patients with unfavorable tumor features after AR; while Ishii et al.<sup>16</sup> showed a statistically significant difference in overall patient survival, but not in disease-free survival, after AR.

In this study, there were no significant disease-free or overall survival differences between the 2 groups. A tumor >5 cm and the presence of cirrhosis were statistically significant risk factors for a recurrence, irrespective of the extent of resection. Considering the tumor size, we concur with Eguchi et al.<sup>13</sup> who recommended AR for patients with HCCs sized 2-5 cm to improve survival. In general, HCCs sized <2 cm show a low prevalence of micrometastases and more favorable tumor differentiation. Conversely, tumors >5 cm have more aggressive biology. Both situations might diminish the oncologic benefits of AR. Unfortunately, we could not stratify our patients according to the size of the HCC because of the small-sized

cohort.

Intrahepatic metastases or multicentric occurrence are 2 common explanations for intrahepatic recurrence of HCC after liver resection. Intrahepatic metastasis can occur in 2 ways involving either locoregional direct spread of tumor cells or systemic intrahepatic metastases by circulating tumor cells.<sup>17</sup> When tumors recur in multiple centers or by systemic intrahepatic metastases, they cannot be cured surgically by increasing the extent of liver resection. Accordingly, this should be attempted if locoregional direct dissemination of tumor cells is the cause of intrahepatic recurrence, and if performing AR could prevent it. However, in the present study only 1 patient showed an early marginal recurrence after NR, implying that a locoregional direct spread is not the main route of intrahepatic recurrence in patients with a solitary HCC without macroscopic vascular invasion. Marubashi et al.<sup>18</sup> reported very similar results to our study, and further indicated that NR performed with a surgical margin of 5-10 mm leads to negligible recurrence by local dissemination for both AR and NR.

NR has a benefit in managing patients with HCC. First, by preserving the liver parenchyma as much as possible, postoperative liver function is better than AR, as indicated by our results. Second, the chance of performing multimodality treatment is higher on tumor recurrence, and repeat resections can be performed. Third, when salvage liver transplantation is considered, a prior AR might lead to difficulties in dissecting the hilum and severe adhesions, resulting in massive bleeding.<sup>19</sup>

The present study had some limitations that must be taken into consideration. The small-scale, retrospective, observational nature of the study might have influenced the results, and some selection bias was inevitable. Another limitation is that we did not analyze the gross classification of the tumors, which is a potential risk factor for recurrence.<sup>20</sup> Therefore, a large-scale prospective randomized trial would be ideal for investigating surgical outcomes according to the extent of hepatic resection.

In conclusion, the operative outcomes and the patterns of recurrence were similar between the AR and NR groups for treatment of a solitary HCC without macroscopic vascular invasion. In particular, marginal recurrences were negligible in both groups. Therefore, we suggested that NR could be a good alternative treatment op-

tion for patients with a solitary HCC by balancing the need to maintain an adequate hepatic reservoir with oncologic clearance. However, further studies are required to confirm the effects of the extent of hepatic resection in such cases.

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