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ORIGINAL ARTICLE

Effectiveness of Anatomical Resection for Small Hepatocellular Carcinoma: a Propensity Score–Matched Analysis of a Multi-institutional Database

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Abstract

Background The superiority of outcomes associated with anatomical resection (AR) versus those associated with non-anatomical resection (NAR) remains controversial in patients with hepatocellular carcinoma (HCC). The aim of this study was to evaluate the significance of AR on therapeutic outcomes of patients with small HCCs (≤ 5 cm), using propensity score–matched (PSM) analysis.

Methods A total of 195 patients who had undergone elective hepatic resection for small HCCs (≤ 5 cm) were included in this study. We conducted PSM analysis for baseline characteristics (age, sex, hepatitis virus status, retention rate of indocyanine green at 15 min, and Child-Pugh grade), preoperative serum α-fetoprotein, and tumor characteristics (tumor size, tumor number, portal vein invasion, and surgical margin status) to eliminate potential selection bias. The prognostic significance of AR on the disease-free and overall survival was analyzed in patients selected by PSM analysis.

Results Applying PSM analysis, the patients were divided into PSM-AR ($N = 66$) and PSM-NAR ($N = 66$) groups. Disease-free survival was significantly better in the PSM-AR group than that of the PSM-NAR group ($P = 0.018$), while there was no significant difference in the overall survival between the PSM-AR and PSM-NAR groups ($P = 0.292$). The univariate HRs of the PSM-AR group were 0.55 (95% CI, 0.33–0.90) for disease-free survival and 0.61 (95% CI, 0.24–1.53) for overall survival, respectively. Remnant liver recurrence was significantly lower in the AR group ($P = 0.014$).

Conclusions AR may improve the disease-free survival in HCC patients with tumors of ≤5 cm diameter.

Keywords Hepatocellular carcinoma · Anatomical resection · Propensity score matching

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common malignancy, but it is the second most common cause of cancer deaths worldwide.[1] Advances in surgical techniques and perioperative management have made liver resection a potentially curative treatment for HCC. Among the several options for treatment, surgical resection may have a prognostic advantage over radiofrequency ablation, especially for solitary HCCs.[2] However, the recurrence rate of HCC after curative hepatic resection remains high. Previous reports showed that even in patients with small HCCs, approximately 50–60% of those who underwent resection recurred within the first 3 years, and more than 70% recurred within the first 5 years.[3,4]

Anatomical resection (AR) is considered likely to improve outcome after liver resection since it may suppress tumor

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spread and micrometastasis through the portal vein by accomplishing systematic removal of the tumor-bearing portal region.[5–9] On the other hand, several studies have suggested that AR provides no prognostic benefit over limited partial non-anatomical resection (NAR).[10–12] The efficacy of AR remains controversial and may vary according to clinicopathological factors such as tumor size, portal vein invasion, and functional liver reserve.[13,14] Therefore, in this study, we examined the prognostic significance of AR in patients with small HCCs (≤ 5 cm) by using a multi-institutional database. To minimize potential selection bias, we conducted propensity score–matched (PSM) analysis for baseline and tumor characteristics.

Patients and Methods

Patient Selection

Between April 2003 and December 2015, 306 patients with HCC underwent primary hepatic resection at the five institutions affiliated with the Jikei University (Department of Surgery, The Jikei University Hospital; The Jikei University Kashiwa Hospital; The Jikei University Daisan Hospital; The Jikei University Katsushika Medical Center; and Department of Digestive Surgery, Kawaguchi Municipal Medical Center). Of the original 306 patients, 29 were excluded: 16 patients for concomitant resection of other malignancies, 5 patients for lack of data, and 8 patients for postoperative mortality. Of the remaining 277 patients, 195 with available data and HCCs ≤5 cm in diameter were enrolled in the study. We performed a retrospective review of a prospectively maintained patient database. This study was approved by the Ethics Committee of the Jikei University School of Medicine.

Treatment and Follow-up

Generally, the extent and type of hepatic resection was determined by preoperative tumor staging, retention rate of indocyanine green at 15 min (ICG_{R15}) before surgery, and hepatic reserve, as described by Miyagawa et al..[15] Nomenclature of the segment and types of operations followed the Brisbane 2000 terminology.[16] Resection types were classified into two groups: AR (extended lobectomy, lobectomy, segmentectomy, or subsegmentectomy) and limited partial NAR. AR was defined as complete resection of the anatomical lesion identified by prior ischemia or dye staining. Liver parenchymal transection was performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA™; Integra LifeSciences Corporation, Princeton, NJ, USA) with a few exceptions, and the method was standardized between institutions. Tumor-Node-Metastasis (TNM) classification was based on tumor pathology and the General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan.[17] No adjuvant and/or neoadjuvant therapy was administered during this period.

The recurrence of HCC was defined as hypervascular hepatic or extrahepatic tumors newly detected by ultrasonography, computed tomography, magnetic resonance imaging, or angiography with or without an increase in serum α-fetoprotein, or protein induced by vitamin K absence or antagonist-II. Recurrent liver HCC was treated by repeated hepatic resection, local ablation therapy, or transarterial chemoembolization based on hepatic functional reserve assessed mainly by ICG_{R15} results. Extrahepatic recurrence was treated conservatively in most cases.

Statistical Analyses

All statistical analyses were conducted using IBM® SPSS statistics version 20.0 (IBM Japan, Tokyo, Japan), and all *P*-values were two-sided with α level of 0.05. To eliminate potential selection bias, we conducted PSM analysis. Our primary analyses assessed the association of AR with disease-free and overall survival. Secondary analyses consisted of all other tests, including assessment of risk estimates.

Data are expressed as median, range, or ratio. Continuous and categorical variables were compared using the Mann-Whitney *U* or chi-square tests, as appropriate.

We evaluated the prognostic significance of AR in patients with HCCs ≤5 cm. Univariate and multivariate Cox proportional-hazards regression models were used to estimate the hazard ratios (HR) for disease-free and overall survival. The multivariable Cox regression model initially included age (continuous), sex (female vs. male), hepatitis virus status (HBC vs. HCV vs. non-B non-C), ICG_{R15} (continuous), Child-Pugh grade (A vs. B), serum AFP level (continuous), tumor size (continuous), tumor number (single vs. multiple), portal vein invasion (yes vs. no), and surgical margin status (negative vs. positive). A backward elimination was conducted with a *P* threshold of 0.05 to select variables for the final models.

The propensity score was calculated using baseline characteristics in the logistic regression model. Baseline characteristics included age, sex, hepatitis virus status, ICG_{R15}, Child-Pugh score, serum AFP level, tumor size, tumor number, portal vein invasion, and surgical margin status. The AR and NAR resection groups were matched in a 1:1 ratio by PSM using a caliper of 0.0335. The Kaplan-Meier method was used to estimate cumulative survival probabilities, and the differences between groups were compared using the log-rank test. Cox proportional-hazards regression models were used to calculate HR and 95% confidence interval (CI) for disease-free and overall survival.

Table 1 Baseline characteristics of HCC ≤ 5 cm according to type of resection

Factor	Type of resection		*P*-value†
	Anatomical (*n* = 93)	Non-anatomical (*n* = 102)	
Age (years)	66 (29–85)	66 (45–86)	0.739
Sex (male : female)	77 : 16	81 : 21	0.587
Hepatitis virus (HBV : HCV : No)	23 : 35 : 35	19 : 47 : 36	0.419
ICG_{R15} (%)	13 (3 - 37)	15 (3 - 53)	0.012
Child-Pugh grade (A : B)	88 : 5	92 : 10	0.291
Serum AFP (ng/ml)	7.5 (2–13,987)	9.9 (2–15,918)	0.664
Tumor size (cm)	3.0 (1.0–5.0)	2.5 (0.9–5.0)	0.015
Tumor number (single : multiple)	77 : 16	90 : 12	0.311
Portal vein invasion (yes : no)	12 : 80	9 : 93	0.268
Surgical margin (negative : positive)	91 : 2	94 : 8	0.104

† To compare categorical data between type of resection, the chi-square test was performed. To compare continuous variables, Mann-Whitney *U*-test was performed

Abbreviations: *HCC*, hepatocellular carcinoma; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; ICG_{R15}, retention rate of indocyanine green at 15 min; *AFP*, alpha-fetoprotein

Results

Baseline Characteristics of HCCs ≤5 cm According to Type of Resection

Baseline patient characteristics are specified in Table 1 as median, range, or ratio. Of 195 patients with HCCs ≤5 cm in diameter, 93 patients underwent AR, whereas 102 patients underwent limited partial NAR. AR included more than 2 segmentectomies in 11 patients, segmentectomy in 37 patients, and subsegmentectomy in 45 patients. Patients who underwent AR had lower ICG_{R15} values and larger tumor diameters. Among 195 patients, none exhibited lymph node metastases. In total; the 5-year disease-free survival and overall survival rates after hepatic resection for HCC were 39.5% and 80.4%, respectively.

Type of Resection in Relation to Disease-Free and Overall Survival for HCCs ≤5 cm

We examined the association of AR with disease-free and overall survival in patients with HCCs ≤5 cm (Table 2). In multivariate Cox regression analyses, AR was associated with lower recurrence (P = 0.001), but not with overall mortality (P = 0.426). The multivariate-adjusted HRs for recurrence and overall mortality were 0.46 (95% CI, 0.29–0.88) and 0.73 (95% CI, 0.34–1.58), respectively.

Baseline Characteristics of HCCs ≤5 cm Matched by Propensity Score According to Type of Resection

Based on a 1:1 PSM analysis, 132 patients were classified into propensity-matched AR (PSM-AR) (N = 66) and

Table 2 Type of resection in relation to disease-free and overall survival for HCC ≤ 5 cm

	N	Disease-free survival		Overall survival	
		Univariate HR (95% CI)	Multivariate* HR (95% CI)	Univariate HR (95% CI)	Multivariate* HR (95% CI)
Type of resection					
Anatomical	93	0.69 (0.46–1.04)	0.46 (0.29–0.88)	0.78 (0.39–1.56)	0.73 (0.34–1.58)
Non-anatomical	102	1 (reference)	1 (reference)	1 (reference)	1 (reference)
P-value		0.079	0.001	0.476	0.426

*The multivariable Cox regression model initially included age, sex, hepatitis virus status, ICG_{R15}, Child-Pugh grade, serum AFP level, tumor size, tumor number, portal vein invasion, and surgical margin status. A backward elimination was conducted with a threshold *P* of 0.05 to select variables for the final models

Abbreviations: *HCC*, hepatocellular carcinoma; *HR*, hazard ratio; *CI*, confidence interval

Table 3 Baseline characteristics of HCC ≤ 5 cm matched by propensity score according to type of resection

Factor	Type of resection		*P*-value†
	Anatomical (*n* = 66)	Non-anatomical (*n* = 66)	
Age (years)	67 (37–85)	66 (45–83)	0.797
Sex (male : female)	54 : 12	54 : 12	1.000
Hepatitis virus (HBV : HCV : No)	15 : 25 : 26	15 : 25 : 26	1.000
ICG_{R15} (%)	13 (3–37)	13 (3–37)	0.788
Child-Pugh grade (A : B)	62 : 4	63 : 3	1.000
Serum AFP (ng/ml)	8 (2–13,987)	8 (2–15,918)	0.882
Tumor size (cm)	2.7 (1.0–5.0)	2.8 (1.1–5.0)	0.793
Tumor number (single : multiple)	56 : 10	56 : 10	1.000
Portal vein invasion (yes : no)	4 : 62	7 : 59	0.531
Surgical margin (negative : positive)	64 : 2	63 : 3	1.000

† To compare categorical data between type of resection, the chi-square test was performed. To compare continuous variables, Mann-Whitney *U*-test was performed

Abbreviations: *HCC*, hepatocellular carcinoma; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; ICG_{R15}, retention rate of indocyanine green at 15 min; *AFP*, alpha-fetoprotein

propensity-matched NAR groups (PSM-NAR) (*N* = 66). Baseline patient characteristics are outlined in Table 3. After PSM analysis, there were no significant differences in the baseline characteristics between the PSM-AR and PSM-NAR groups.

Type of Resection in Relation to Disease-Free and Overall Survival for HCCs ≤5 cm with PSM Analysis

Table 4 shows the association of AR with disease-free and overall survival by PSM analysis (Table 4). AR was associated with lower recurrence (*P* = 0.018, Fig. 1a), but not with overall mortality (*P* = 0.292, Fig. 1b). The HRs for recurrence and overall mortality were 0.55 (95% CI 0.33–0.90) and 0.61 (95% CI, 0.24–1.53), respectively.

Short- and Long-term Outcomes for HCCs ≤5 cm According to Type of Resection

Table 5 shows the relationship between type of resection and short- and long-term outcomes. In univariate analyses, the duration of operation was significantly longer in the AR group (*P* = 0.013). Moreover, remnant liver recurrence was significantly lower in the AR group (*P* = 0.014).

Discussion

In the current study, utilizing the PSM method, we found that anatomical resection was associated with lower recurrence in patients with HCCs ≤5 cm. Furthermore, remnant liver recurrence was significantly lower in the AR group. These findings

Table 4 Type of resection in relation to disease-free and overall survival for HCC ≤ 5 cm with propensity score matching

	*N**	Disease-free survival		Overall survival	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Type of resection					
Anatomical	66	0.55 (0.33–0.90)	0.018	0.61 (0.24–1.53)	0.292
Non-anatomical	66	1 (reference)		1 (reference)	

*Anatomical resection group and non-anatomical resection group were matched in a 1:1 ratio by propensity score matching using the baseline characteristics (age, sex, hepatitis virus status, ICG_{R15}, Child-Pugh score, serum AFP level, tumor size, tumor number, portal vein invasion, and surgical margin status)

Abbreviations: *HCC*, hepatocellular carcinoma; *HR*, hazard ratio; *CI*, confidence interval; ICG_{R15}, retention rate of indocyanine green at 15 min; *AFP*, alpha-fetoprotein

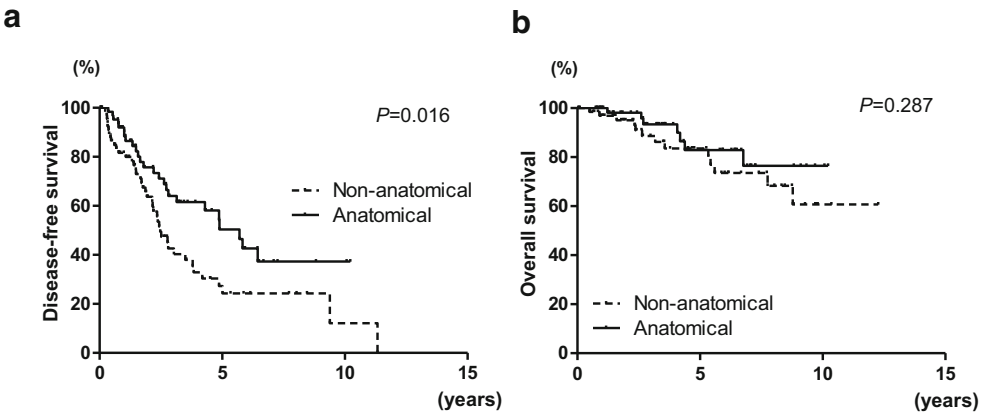

Fig. 1 Kaplan-Meier curves of disease-free (**a**) and overall survival (**b**) after hepatic resection for HCC. Anatomical resection was significantly associated with better disease-free survival (P = 0.016), but was not associated with overall survival (P = 0.287)

support the significance of AR for the therapeutic outcome of small hepatocellular carcinoma (≤ 5 cm), and reinforce its role in preventing spread through the portal vein.

The effectiveness of AR varies across studies and decades.[8] A Japanese nationwide survey showed that AR was an independent factor influencing disease-free survival for patients with HCCs of 2–5 cm in diameter.[18] Two recent PSM analyses from Japan[19] and China[20] investigated HCCs with microvascular invasion. One study demonstrated that local recurrence around the resection site was suppressed by AR,[20] whereas the other study revealed that AR did not significantly improve disease-free or overall survival in patients with HCCs exhibiting micro-portal invasion.[19] This evidence suggests that the beneficial effect of AR may vary depending on a number of tumor factors such as size, portal vein invasion, and location.[13,14] In addition, selection of a surgical approach could be influenced by liver functional reserve and volume. Thus, a PSM analysis minimizing potential selection bias enables a more accurate evaluation of the AR effect. In this study, we showed that AR improved disease-free survival, but did not improve overall survival in patients with small HCCs (≤ 5 cm). A possible reason for the discrepancy between disease-free and overall survival is that the prognosis for HCC strongly depends on the types and quality of repeated treatments for recurrent tumors.[21] In addition, the balance between the extent of surgical excision and preservation of remnant liver function might affect overall survival because underlying liver function has previously been associated with prognosis.[22,23]

With recent developments in preoperative liver simulation using three-dimensional imaging, the concept of cone-unit liver resection has been described.[6,24,25] Cone-unit resection is an AR procedure that attempts to remove tumor-bearing portal territory branches, enabling a parenchymal-sparing resection. Evidence suggests that cone-unit resection may confer oncological benefits.[24] In addition, this approach can be performed using a laparoscopic approach.[25] Given that the survival of patients with HCC depends on underlying liver function,[22,23] a liver parenchymal-preserving approach might allow repeated liver resections for recurrent HCC, ultimately improving outcomes.

We acknowledge the potential limitations of this study. Although we attempted to minimize selection bias and the effect of baseline characteristics by applying PSM analysis, the possibility of other unconsidered biases still remains.

Table 5 Short- and long-term outcome for HCC ≤ 5 cm according to type of resection

Factor	Type of resection		P-value[†]
	Anatomical (n = 66)	Non-anatomical (n = 66)	
Duration of operation (min)	382 (128–886)	323 (100–614)	0.013
Intraoperative blood loss (g)	672 (0–5230)	428 (0–5040)	0.158
Blood transfusion (yes : no)	17 : 49	12 : 54	0.401
Postoperative complication (yes : no)	8 : 58	7 : 59	1.000
Postoperative hospital stay (days)	12 (4–51)	12 (7–67)	0.583
Remnant liver recurrence (yes : no)	23 : 43	38 : 28	0.014

[†] To compare categorical data between type of resection, the chi-square test was performed. To compare continuous variables, Mann-Whitney U-test was performed

Abbreviations: *HCC*, hepatocellular carcinoma

A core strength of our study was the access to a multi-institutional database. The study population was derived from five hospitals, increasing the generalizability of our findings. Nonetheless, our results will require validation in independent, randomized controlled studies in the new era of laparoscopic surgery, molecular targeted therapy, and immunotherapy.[25,26]

Conclusion

We demonstrated that AR was associated with lower recurrence in patients with HCCs ≤5 cm, suggesting it may be beneficial for preventing the spread of small tumors through the portal vein. Our results, obtained using data from multiple institutions, may inform future research regarding the influence of tumor characteristics, size, and pathological features on AR and patient outcomes.

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Declarations

Conflict of Interest The authors declare no competing interests.

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