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ORIGINAL ARTICLE

Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma

Masaki Kaibori · Masanori Kon · Tomoki Kitawaki · Takayuki Kawaura · Kiyoshi Hasegawa · Norihiro Kokudo · Shunichi Ariizumi · Toru Beppu · Hiroyuki Ishizu · Shoji Kubo · Toshiya Kamiyama · Hiroyuki Takamura · Tsuyoshi Kobayashi · Dong-Sik Kim · Hee Jung Wang · Jong Man Kim · Dai Hoon Han · Sang-Jae Park · Koo Jeong Kang · Shin Hwang · Younghoon Roh · Young Kyung You · Jae-Won Joh · Masakazu Yamamoto

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The author's affiliations are listed in the Appendix.

Correspondence to: Masakazu Yamamoto, Department of Surgery, Tokyo Women's Medical University, 8-1 Kawata-cho, Shinjyuku-ku, Tokyo 162-8666, Japan
e-mail: yamamoto.ige@twmu.ac.jp

Jae-Won Joh, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Kangnam-Ku, Seoul 135-710, Korea
e-mail: jw.joh@samsung.com

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Abstract

Background The aim of the present study was to compare the prognostic impact of anatomic resection (AR) versus non-anatomic resection (NAR) on patient survival after resection of a single hepatocellular carcinoma (HCC).

Methods To control for confounding variable distributions, a 1-to-1 propensity score match was applied to compare the outcomes of AR and NAR. Among 710 patients with a primary, solitary HCC of <5.0 cm in diameter that was resectable by either AR or NAR from 2003 to 2007 in Japan and Korea, 355 patients underwent NAR and 355 underwent AR of at least one section with complete removal of the portal territory containing the tumor.

Results Overall survival (OS) was better in the AR than NAR group (hazard ratio 1.67, 95% confidence interval 1.28–2.19, $P < 0.001$) while disease-free survival showed no significant difference. Significantly fewer patients in the AR than NAR group developed intrahepatic HCC recurrence and multiple intrahepatic recurrences. Patients with poorly differentiated HCC who underwent AR had improved disease-free survival and OS.

Conclusions Anatomic resection decreases the risk of tumor recurrence and improves OS in patients with a primary, solitary HCC of <5.0 cm in diameter.

Keywords Anatomic resection · Hepatocellular carcinoma · Non-anatomic resection · Overall survival

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently encountered malignancies in clinical practice worldwide. It is more prevalent in Asia and Africa, but rates are increasing in Western countries [1]. Advances in surgical techniques and perioperative management have transformed the resection of HCC into a relatively safe operation with a low mortality rate [2]. Liver resection is now accepted as the first-line treatment for HCC in patients with preserved hepatic resection [3, 4]. A recent retrospective study revealed that surgical resection may have a prognostic advantage over radiofrequency ablation, especially in patients with a solitary HCC [5]. However, long-term survival is still unsatisfactory because of the high recurrence rate of HCC after curative hepatectomy [6–8]. Because HCC has a high propensity to invade the

intrahepatic vascular structures and spreads mainly via the closest portal veins [9, 10], anatomic resection (AR) including systematic removal of the tumor-bearing portal territories was proposed in the 1980s as a theoretically curative surgical procedure for HCC to eradicate potential micrometastases surrounding tumors [11]. Some studies [5, 12–15] have demonstrated the superiority of AR over non-anatomic resection (NAR) for HCC. However, the optimum liver resection technique in patients with liver dysfunction remains controversial, and there is no clear evidence that AR results in better long-term survival than does NAR [16–19]. Most of these reported studies had limited statistical power, and no case-matched or randomized clinical trials have compared the outcomes of AR and NAR for treatment of HCC.

In 2013, a multicenter-based collaboration study in the field of liver disease was proposed by the Korean Association of Hepato-Biliary-Pancreatic Surgery (KAHBPS) and the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS). In the present study, the outcomes of AR and NAR for treatment of HCC with curative intent were investigated using propensity score matching (PSM) to select patients for each group from both Japan and Korea to minimize bias arising from patient backgrounds.

Methods

We conducted a retrospective cohort study as a project of the multicenter-based collaboration study by the JSHBPS and KAHBPS. We collected the perioperative data of 1,126 and 721 patients who underwent hepatic resection from 2003 to 2007 at 63 and eight institutions that participated in the JSHBPS and KAHBPS, respectively. The inclusion criteria were curative resection of HCC, a solitary tumor with a diameter of ≤5 cm in the preoperative examination, an indocyanine green retention rate at 15 min (ICGR15) of ≤15%, and surgical resection as first-line therapy. Surgical procedures were classified according to the Brisbane 2000 nomenclature of liver resection [20]. AR was defined as complete resection of the anatomic area as identified by preceding ischemia or dye staining. Right hemihepatectomy, left hemihepatectomy, central bisectionectomy, right trisectionectomy, and left trisectionectomy were included as AR involving more than two sections. Left lateral, left medial, right anterior, and right posterior sectionectomy were included as AR involving one section. In NAR, a surgical margin of 5–10 mm from the tumor was secured unless the tumor was attached to the hepatic vein or Glissonian pedicle. The indication for surgery was based on an algorithm that included the presence/absence of ascites, serum total bilirubin concentration, and ICG test result as previously described [21, 22]. Liver surgeons in Japan and Korea performed either AR or NAR depending on the hepatic functional reserve, tumor location, and tumor size. Peripheral tumors and those with extrahepatic growth were treated by partial hepatectomy because this achieved a sufficient surgical margin. Conversely, central tumors located near the hepatic hilum or major vessels were treated by enucleation because it was too difficult to obtain an adequate margin. Therefore, NAR was not only performed for tumors at favorable locations but also for those at unfavorable locations in patients with preoperative hepatic impairment. Ultimately, the operation technique was selected by each institute in Japan and Korea. The indication criteria for AR and NAR were determined by each individual institute; therefore, a clear description of the indication criteria cannot be provided in the present report. The diagnosis of HCC was confirmed by histologic examination of resected specimens in all patients. The tumor stage was classified according to the American Joint Committee on Cancer (AJCC) International Union Against Cancer (UICC) TNM staging system [23]. This study was approved by the ethics committee of the JSHBPS as well as the Institutional Review Board of Kansai Medical University (No. H131267). This study protocol was also approved by each participating institution from Japan and Korea. All data were collected and analyzed at the Department of Surgery and Department of Mathematics of Kansai Medical University.

Follow-up

Perioperative/postoperative complications or death (i.e. those occurring within 1 month of surgery or during the same hospital admission) were recorded to assess the morbidity and mortality of the procedures.

After discharge, all patients were followed up with ultrasonography, computed tomography, or magnetic resonance imaging at least every 3 to 6 months. Various laboratory parameters were also monitored, including the serum concentrations of α-fetoprotein (AFP) and protein induced by vitamin K antagonist-II (PIVKA-II).

When recurrence of HCC was suspected based on tumor marker levels or imaging findings, tumor recurrence limited to the remnant liver was treated by transcatheter arterial chemoembolization, lipiodolization, repeat hepatectomy, or ablation therapy such as percutaneous radiofrequency therapy. Disease-free survival (DFS) was defined as the time interval between the date of the operation and the date of diagnosis of the first recurrence or last follow-up.

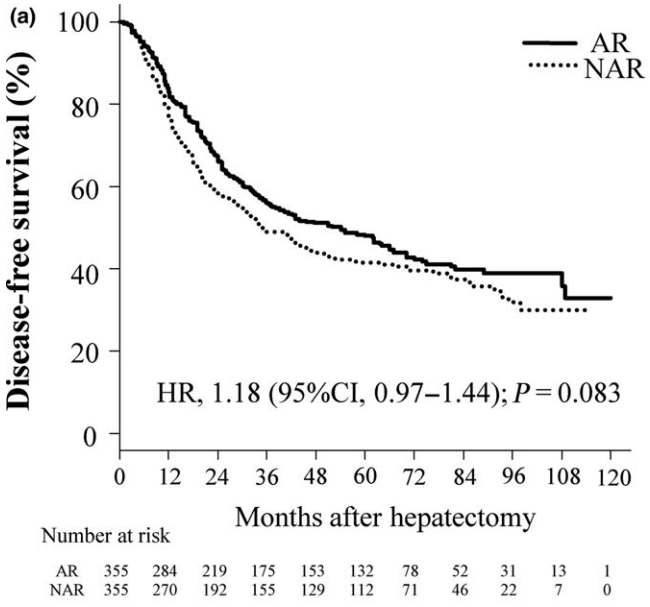
Table 1 Perioperative characteristics of AR and NAR groups before and after PSM

Factors	Before PSM (n = 1,265)			After PSM (n = 710)		
	AR group (n = 643; J, 492; K, 151)	NAR group (n = 622; J, 527; K, 95)	P value	AR group (n = 355; J, 279; K, 76)	NAR group (n = 355; J, 299; K, 56)	P value
Background characteristics						
Sex (male/female)	505/138	469/153	0.204	274/81	272/83	0.929
Age (years)	65 (24–86)	64 (27–86)	0.284	65 (28–85)	64 (27–86)	0.766
HBsAg (+/−)	236/407	241/381	0.486	124/231	132/223	0.584
HCV Ab (+/−)	253/390	256/366	0.528	149/206	141/214	0.593
Total bilirubin (mg/dl)	0.7 (0.1–2.8)	0.7 (0.2–2.1)	0.511	0.7 (0.1–2.8)	0.7 (0.2–2.1)	0.296
Platelet count ($\times 10^4$/ml)	15.7 (3.7–48.2)	14.3 (2.2–46.2)	<0.001	14.7 (3.7–48.2)	14.9 (2.9–44.1)	0.832
ALT (U/l)	34 (4–231)	36 (1.5–220)	0.622	37 (4–190)	34 (1.5–220)	0.298
Albumin (g/dl)	4.1 (2.2–4.9)	4.1 (2.6–4.9)	0.470	4.1 (2.9–4.9)	4.0 (2.6–4.9)	0.880
Child–Pugh class (A/B)	638/5	606/16	0.015	353/2	350/5	0.451
ICGR15 (%)	9.3 (0.5–15)	9.6 (0–15)	0.170	9.2 (0.9–15)	9.6 (0–15)	0.276
AFP (ng/ml)	15 (0–61,010)	11 (0–35,490)	0.011	12 (0–15,940)	11 (1–35,490)	0.565
PIVKA-II (mAU/ml)	59 (0–45,660)	36 (2–36,900)	<0.001	46 (4–45,660)	50 (2–36,700)	0.343
Surgical factors						
Operating time (min)	291 (50–797)	228 (48–730)	<0.001	255 (50–797)	257 (83–730)	0.650
Operative blood loss (ml)	560 (0–17,000)	300 (0–15,000)	<0.001	430 (0–5,100)	400 (0–3,425)	0.216
Blood transfusion (+/−)	112/511	44/558	<0.001	39/309	38/304	1.000
Laparoscopic hepatectomy (+/−)	27/616	37/584	0.160	16/339	19/335	0.608
Complications						
Morbidity (+/−)	168/475	111/511	<0.001	78/277	68/287	0.403
Mortality (+/−)	6/637	1/621	0.124	3/352	1/354	0.624
Pathological factors						
Maximum tumor size (cm)	3.3 (0.7–6.5)	2.5 (0.8–5.5)	<0.001	2.9 (0.7–6.5)	3.0 (0.9–5.5)	0.496
Histological tumor differentiation (well/mod/poor/necrosis)	106/425/104/7	121/411/83/3	0.194	58/242/52/3	55/244/51/2	0.974
Microscopic surgical margin (positive/negative)	19/624	21/591	0.634	5/350	17/332	0.009
Microscopic vascular invasion in portal vein and/or hepatic vein (+/−)	168/475	129/493	0.024	83/272	83/272	1.000
Microscopic bile duct invasion (+/−)	30/613	8/614	<0.001	2/353	8/347	0.107
Associated liver disease (normal liver/chronic hepatitis or liver fibrosis/cirrhosis)	57/373/211	39/312/270	<0.001	22/208/123	29/188/137	0.256
The UICC/AJCC 7th Staging System (I/II)	607/36	604/18	0.018	225/130	212/143	0.355

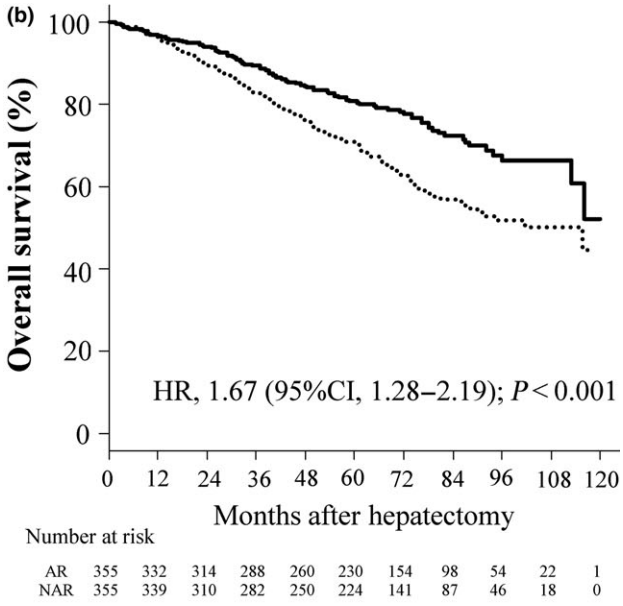
AFP alpha-fetoprotein, *ALT* alanine aminotransferase, *AR* anatomic resection, *HBsAg* hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *J* Japan, *K* Korea, *NAR* non-anatomic resection, *PIVKA-II* protein induced by vitamin K absence or antagonist-II, *PSM* propensity score matching

Propensity score analysis

To avoid confounding differences due to baseline varieties between AR and NAR, we established a propensity score-matched subset. Propensity score analysis was used to build a matched group of patients for comparison of oncological and short-term outcomes between AR and NAR. The propensity scores were generated using perioperative characteristics, including sex; age; underlying liver disease [hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus antibody (HCV Ab) positivity]; preoperative serum total bilirubin concentration, alanine aminotransferase (ALT) concentration, albumin concentration, platelet count, ICGR15, Child–Pugh class, and serum α-fetoprotein concentration; and intraoperative blood loss, operating time, maximum tumor size, and microscopic vascular invasion in the portal and/or hepatic vein and/or bile duct invasion. Propensity scores were matched using a caliper



	DFS (%)				
Variables	1-yrs	3-yrs	5-yrs	7-yrs	10-yrs
All	79.4	52.4	44.6	38.5	31.2
AR	82.7	55.9	47.9	39.7	32.8
NAR	76.1	48.9	41.4	37.4	30.0



	OS (%)				
Variables	1-yrs	3-yrs	5-yrs	7-yrs	10-yrs
All	96.4	86.1	75.4	64.1	48.3
AR	96.6	89.3	80.6	72.2	52.1
NAR	96.3	82.9	70.5	56.8	44.6

Fig. 1 Long-term survival outcomes after anatomic resection and non-anatomic resection in propensity score adjustment. (**a**) Disease-free survival rate. (**b**) Overall survival rate. *AR* anatomic resection, *CI* confidence interval, *HR* hazard ratio, *NAR* non-anatomic resection

width of 0.25 multiplied by the standard deviation of values calculated by a logistic regression model. One patient who underwent AR was matched to one patient who underwent NAR using a greedy nearest-neighbor matching algorithm without replacement.

Statistical analysis

Continuous variables were divided into two groups according to the median value. The clinical characteristics of the two groups were compared by either the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. The DFS and overall survival (OS) rates after hepatectomy were calculated by the Kaplan–Meier life table method, and the hazard ratio (HR) for OS and DFS and its 95% confidence interval (CI) were calculated using the stratified Cox model. Twenty-seven clinical variables, including AR and NAR, were evaluated by univariate analysis using the log-rank test to determine the risk factors for OS after hepatic resection. The DFS and OS rates, which were stratified according to age, hepatitis virus infection status, ICGR15, maximum tumor size, histological tumor differentiation, associated liver disease, microscopic vascular invasion in the portal vein and/or hepatic vein and/or bile duct, and staging system, were compared between the two groups.

Significant variables with a *P*-value of <0.05 by univariate analysis were subjected to multivariate analysis using a Cox proportional hazards regression model. Significance tests were two-tailed, and a *P*-value of <0.05 was considered statistically significant. Propensity score analysis and survival analysis were performed using R (version 3.3.1: 2016 and 3.1.1: 2014) with R package "Matching (version 4.9-2: 2015)" and "Survival (2.40-1: 2016)," respectively. Cox proportional hazards regression analyses were performed with a 2015 JMP software package (version 12.2.0; SAS Institute, Cary, NC, USA).

Results

Using our criteria, we identified a total number of 1,847 patients from Japan and Korea. The number of patients from Japan was 1,126 (534 in the AR group and 592 in the NAR group). The number of patients from Korea was 721 (354 in the AR group and 367 in the NAR group). Patients with insufficient data were excluded (107 patients

from Japan and 475 patients from Korea), decreasing the total to 1,265 patients. Finally, 710 patients were enrolled using PSM and divided into the AR group ($n = 355$; Japan, 279; Korea, 76) and NAR group ($n = 355$; Japan, 299; Korea, 56).

Table 1 summarizes the perioperative characteristics of both groups before and after PSM. There were substantial differences in background variables between the two groups before PSM. No difference was detected between the two groups with respect to sex, age, HBsAg, HCV Ab, serum total bilirubin, ALT, albumin, or ICGR15. The platelet count and Child–Pugh class differed significantly before matching. Conversely, the serum AFP and PIVKA-II concentrations were higher in the AR group. The operation time, operative blood loss, and requirement for blood transfusion were significantly lower in the NAR group. Complications attributable to surgery were noted in 111 (17.8%) patients in the NAR group and 168 (26.1%) patients in the AR group. The pathologic features of each group before PSM are listed in Table 1. Patients in the AR group had a significantly greater maximum tumor size and higher incidence of positive microscopic vascular invasion in the portal vein and/or hepatic vein and/or bile duct. Examination of the resected nontumorous liver tissue demonstrated a significantly higher incidence of cirrhosis in the NAR group. The TNM stage differed significantly between the two groups.

Paired PSM was carried out to classify patients into the AR and NAR groups, resulting in 355 patients in each group. Operative procedures in the AR group consisted of right hemihepatectomy ($n = 42$), left hemihepatectomy ($n = 43$), central bisectionectomy ($n = 6$), left lateral sectionectomy ($n = 103$), left medial sectionectomy ($n = 40$), right anterior sectionectomy ($n = 52$), and right posterior sectionectomy ($n = 70$). Comparison between the two groups revealed no significant differences in preoperative background or surgical factors (Table 1). Of the pathological factors, only the incidence of the surgical margin differed significantly between the two groups after matching.

Long-term outcomes

The median follow-up period was 67.7 months in the AR group and 66.1 months in the NAR group. Figure 1 shows a comparison of the long-term outcomes between AR and NAR in the PS-adjusted population. The OS in the AR group was significantly better than that in the NAR group (HR 1.67, 95% CI 1.28–2.19, $P < 0.001$), while DFS showed no significant difference (HR 1.18, 95% CI 0.97–1.44, $P = 0.083$).

HCC recurrence was observed in 191 (53.8%) patients in the AR group and 206 (58.0%) in the NAR group (Table 2). In the stratified analyses for HCC recurrence, the number of patients with intrahepatic HCC recurrence in the AR group was significantly smaller than that in the NAR group. The number of patients with multiple intrahepatic recurrence in the AR group was also significantly smaller than that in the NAR group. With respect to treatment for intrahepatic recurrence, repeat hepatectomy or percutaneous ablation therapy as curative therapy was performed more frequently in the AR group, while transcatheter arterial chemoembolization or other palliative therapies were performed more frequently in the NAR group. The incidence of extrahepatic recurrence, the incidence of both intrahepatic and extrahepatic recurrence, and the number of patients who developed recurrence within 2 years after hepatectomy were significantly smaller in the AR than NAR group (Table 2).

We performed several subgroup analyses of DFS and OS between the two groups (Figs 2,3). With respect to the hepatitis viral infection status, the forest plots show that patients with HCV who underwent AR had better

Table 2 Clinical characteristics of recurrent tumors in AR and NAR groups

Factors	AR ($n = 355$)	NAR ($n = 355$)	P value
Number of patients with HCC recurrence	191 (54)	206 (58)	
Intrahepatic recurrence (+/−)	177/14	201/5	0.032
Number of intrahepatic recurrences			
1	105	95	0.019
2	30	32	
≥3	42	74	
Treatment for intrahepatic recurrence			
Repeat hepatectomy or percutaneous ablation	97	85	0.033
TACE or others	76	113	
None	4	3	
Extrahepatic recurrence (+/−)	28/163	46/160	0.049
Treatment for extrahepatic recurrence (+/−)	21/7	29/17	0.318
Both intra- and extrahepatic recurrence (+/−)	14/177	41/165	<0.001
Time to recurrence			
Recurrence within 2 years after hepatectomy (yes/no)	111/80	140/66	0.042
Number of deceased patients	87 (25)	141 (40)	
Cause of death			0.174
HCC-related	44	82	
Liver-related	12	18	
Others	25	39	
Unknown	6	2	

Data are presented as n (%) of patients

AR anatomic resection, *HCC* hepatocellular carcinoma, *NAR* non-anatomic resection, *TACE* transarterial chemoembolization

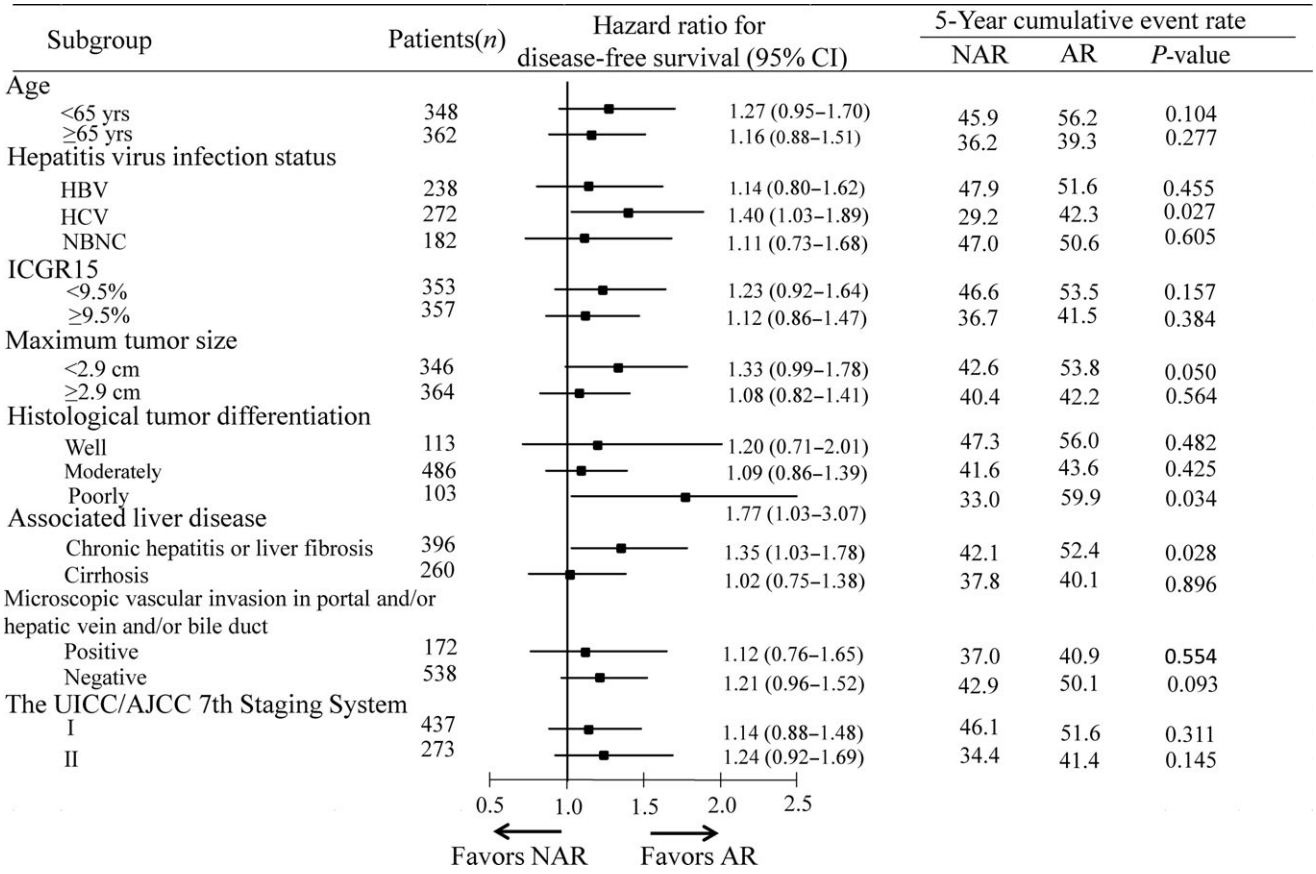


Fig. 2 Disease-free survival in selected subgroup. *AR* anatomic resection, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICGR15* indocyanine green retention rate at 15 min, *NAR* non-anatomic resection, *NBNC* negative for hepatitis B surface antigen and hepatitis C antibody

DFS and OS than those who underwent NAR. Among patients with non-B non-C HCC, the OS was significantly better in the AR than NAR group. Although the analysis of tumor size revealed no statistically significant difference in DFS or OS for patients with a tumor size of <2.9 cm between the AR and NAR groups, OS in patients with a tumor size of ≥2.9 cm was significantly better in the AR than NAR group. With respect to the histological tumor differentiation, the OS of patients with moderately differentiated HCC was significantly better in the AR than NAR group. Patients with poorly differentiated HCC who underwent AR had improved DFS and OS. With respect to associated liver disease, the DFS and OS of patients with chronic hepatitis or liver fibrosis were better in the AR than NAR group. The analysis of positive microscopic vascular invasion in the portal vein and/or hepatic vein and/or bile duct showed no similar effect of AR.

Prognostic factors related to OS rates after hepatic resection

Twenty-seven clinicopathologic variables were screened as risk factors for OS after hepatic resection using univariate analysis (Table 3). The following variables were not selected as prognostic factors: sex, habitual alcohol intake, serum total bilirubin concentration, ALT concentration, platelet count, prothrombin time, Child–Pugh class, operative blood loss, laparoscopic hepatectomy, morbidity, maximum tumor size, histological tumor differentiation, capsular formation, microscopic surgical margin, and associated liver disease status according to histological examination findings. The remaining 12 variables, including the surgical procedure, were significant risk factors for OS after hepatic resection. The final multivariate model identified six variables as independent prognostic factors (Table 4). The multivariate analysis revealed that AR was associated with a significantly better OS rate than was NAR (HR 1.69, 95% CI 1.29–2.22, $P < 0.001$).

Discussion

Hepatocellular carcinoma is the fifth and seventh most commonly diagnosed cancer worldwide in men and women, respectively [24]. However, it accounts for an even higher level of cancer-related mortality because

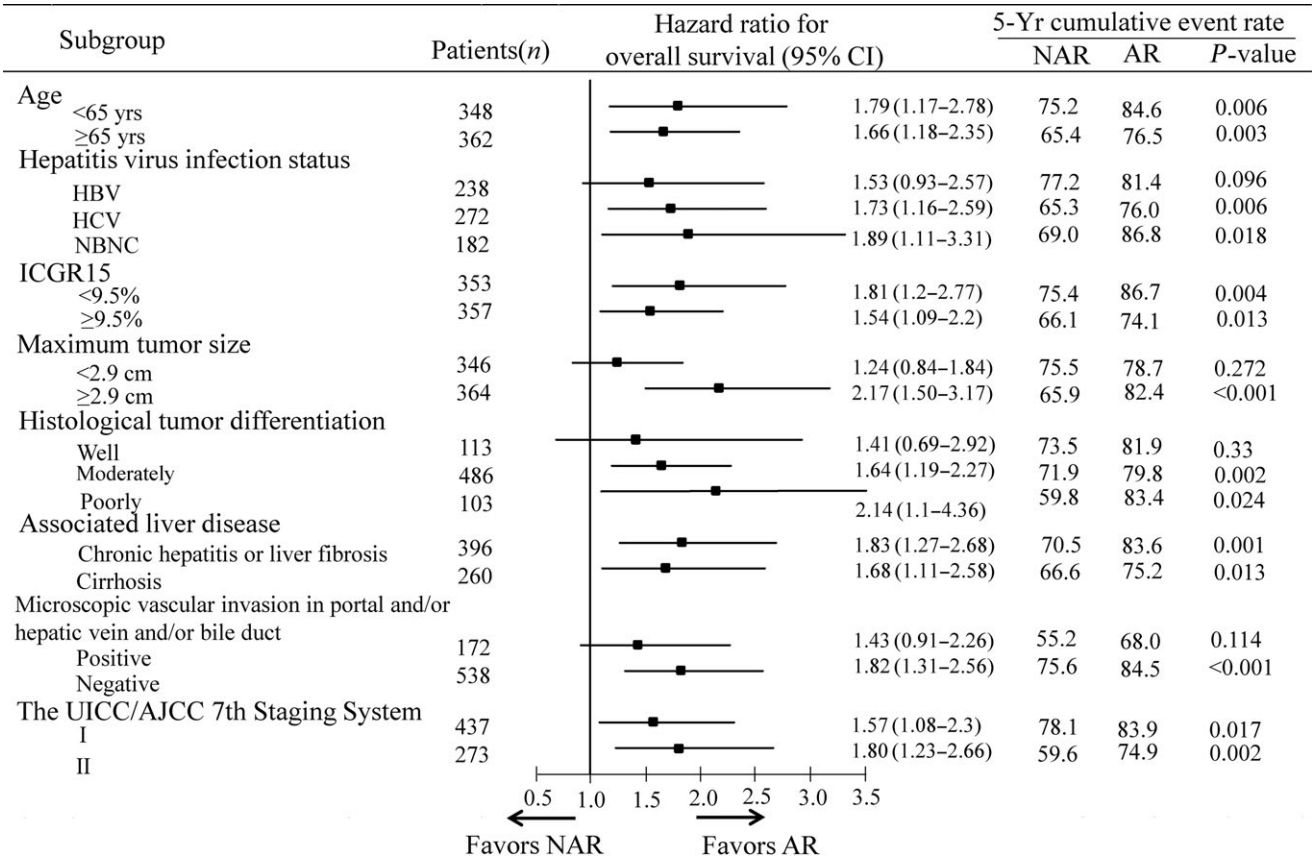


Fig. 3 Overall survival in selected subgroup. *AR* anatomic resection, *CI* confidence interval, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICGR15* indocyanine green retention rate at 15 min, *NAR* non-anatomic resection, *NBNC* negative for hepatitis B surface antigen and hepatitis C antibody

HCC is often only diagnosed at an advanced stage [25]. The incidence of HCC and performance of curative treatments such as hepatic resection in Japan and Korea appear to be among the highest worldwide [26, 27]. We believe that the present multicenter-based collaboration study of both Japan and Korea is of great clinical significance for HCC treatment. The main problem that surgeons face while operating on patients with cirrhosis is the balance between achieving a radical intervention while simultaneously preventing the development of postoperative liver failure that could ensue from removal of too much liver parenchyma. This problem is the basis of the dispute between which technique is more effective: AR, which should theoretically be a more radical procedure from an oncologic point of view, or NAR, which should reduce the risk of postoperative hepatic failure. In the present study, the patient eligibility criteria included tumor number, tumor size, and preoperative liver function. PSM analysis was applied to minimize selection bias between the groups. Tumors tended to be more advanced in the AR group in terms of size, tumor marker levels (AFP), and microscopic vascular invasion. Liver function as indicated by the platelet count and Child–Pugh class was more severely impaired in the NAR group. Moreover, the operative blood loss was greater and the operating time was longer in the AR group. The propensity scores in this study were calculated using 16 variables, most of which differed between the NAR and AR groups. These factors were determined before, during, and after the operation and could therefore potentially influence selection of the resection method.

According to two recent meta-analyses, AR is associated with better DFS than is NAR because the poorer liver function reserve in patients who undergo NAR significantly affects the prognosis [28, 29]. However, the available data remain insufficient to prove the prognostic advantage of AR because of substantial heterogeneity; the clinicopathologic features of patients who underwent AR or NAR are quite different among previous studies. To overcome the issue of selection bias, several case-controlled studies using PSM have recently been reported [30–33]. Cucchetti et al. [30] reported favorable outcomes of AR in PS-matched populations in terms of recurrence-free survival and OS. Shindoh et al. [31] reported that complete removal of the tumor-bearing third-order portal territories decreased the risk of tumor recurrence and improved the disease-specific survival in their patients with primary, solitary HCC. However,

Table 3 Risk factors for overall survival determined by univariate analysis in patients with hepatocellular carcinoma who underwent hepatic resection

Variables	Patients (*n*)	OS (%)			*P* value
		1-year	3-year	5-year	
All	710	96.4	86.1	75.4	
Sex					
Male	546	96.8	85.9	75.7	Reference
Female	164	95.1	86.8	74.5	0.990
Age (years)					
<65	348	97.7	88.4	79.6	Reference
≥65	362	95.2	83.8	71.1	<0.001
HBsAg					
+	256	97.3	86.5	78.7	Reference
−	454	96.0	85.8	73.5	0.017
HCV Ab					
+	290	94.7	82.6	70.7	Reference
−	420	97.6	88.4	78.6	0.006
Alcohol use					
Positive[a]	159	96.1	86.1	73.6	Reference
None	531	96.4	85.7	75.9	0.167
Total bilirubin (mg/dl)					
<0.7	309	96.4	86.4	75.5	Reference
≥0.7	401	96.5	85.8	75.4	0.959
Platelet count ($\times 10^4$/ml)					
<14.8	352	96.3	84.4	74.7	Reference
≥14.8	358	96.6	87.7	76.2	0.809
ALT (U/l)					
<36	350	98.0	87.2	75.6	Reference
≥36	360	94.9	85	75.2	0.775
Albumin (g/dl)					
<4.1	351	95.1	83.2	70.3	Reference
≥4.1	359	97.8	88.8	80.3	0.005
Prothrombin time (%)					
<92	348	95.6	83.2	72.5	Reference
≥92	354	97.1	88.8	78.1	0.105
Child–Pugh class					
A	703	96.5	86.1	75.5	Reference
B	7	85.7	85.7	71.4	0.286
ICGR15 (%)					
<9.5	353	98.3	90.6	81.1	Reference
≥9.5	357	94.6	81.6	69.9	0.001
AFP (ng/ml)					
<11.4	354	98.3	90.5	81.2	Reference
≥11.4	356	94.6	81.7	69.9	0.004
PIVKA-II (mAU/ml)					
<47	352	98.0	90.0	80.4	Reference
≥47	358	94.9	82.2	70.5	<0.001
Operative blood loss (ml)					
<409.5	355	98.3	89.8	79.1	Reference
≥409.5	355	94.5	82.3	71.7	0.071
Operating time (min)					
<255.5	355	98.0	90.5	79.1	Reference
≥255.5	355	94.9	81.7	71.9	0.047
Surgical procedure					
Non-anatomic resection	355	96.3	82.9	70.5	Reference
Anatomic resection	355	96.6	89.3	80.6	<0.001
Laparoscopic hepatectomy					
+	35	94.3	85.7	70.9	Reference
−	674	96.5	86.1	75.7	0.408
Blood transfusion					
+	80	87.2	75.7	59.0	Reference
−	630	97.6	87.4	77.4	0.014
Morbidity					
+	146	90.9	79.7	66.9	Reference
−	564	97.8	87.7	77.6	0.059
Maximum tumor size (cm)					
<2.9	346	98.3	87.9	77.1	Reference
≥2.9	364	94.7	84.4	73.9	0.131
Histological tumor differentiation					
Well	113	95.6	90.1	77.8	Reference
Moderate	486	96.9	86.6	75.7	0.185
Poor	103	95.1	78.7	71.4	0.132
Necrosis	5	100.0	80.0	60.0	0.620
Capsule formation					
Positive	552	96.5	85.7	75.1	Reference
None	147	95.8	86.4	75.5	0.708
Microscopic surgical margin					
Negative	682	96.6	86.4	76.2	Reference
Positive	22	95.5	86.4	67.2	0.304
Associated liver disease					
Normal liver	51	100.0	96.0	85.4	Reference
Chronic hepatitis or fibrosis	396	97.7	87.0	77.2	0.563
Cirrhosis	260	93.8	82.6	70.6	0.103
Microscopic vascular invasion in portal vein and/or hepatic vein and/or bile duct					
Negative	538	97.5	89.1	80.0	Reference
Positive	172	92.9	76.7	61.3	<0.001
UICC/AJCC 7th Staging System					
I	437	98.1	89.1	81.00	Reference
II	273	94.7	83.4	69.5	<0.001

AFP alpha-fetoprotein, *ALT* alanine aminotransferase, *AR* anatomic resection, *HBsAg* hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *NAR* non-anatomic resection, *PIVKA-II* protein induced by vitamin K absence or antagonist-II

[a]Intake of ≥86 g of alcohol daily for >10 years

Table 4 Independent risk factors for overall survival determined by Cox proportional hazard regression analysis (multivariate final model)

Variables	Patients (*n*)	HR (95% CI)	*P* value
Age (years)			
<65	348	Reference	—
≥65	362	0.66 (0.49–0.90)	0.008
HBsAg			
+	256	Reference	—
−	454	0.94 (0.65–1.36)	0.772
HCV Ab			
+	290	Reference	—
−	420	1.15 (0.84–1.59)	0.366
Albumin (g/dl)			
<4.1	351	Reference	—
≥4.1	359	1.24 (0.94–1.64)	0.113
ICGR15 (%)			
<9.5	353	Reference	—
≥9.5	357	0.74 (0.56–0.96)	0.029
AFP (ng/ml)			
<11.4	354	Reference	—
≥11.4	356	0.74 (0.56–0.98)	0.039
PIVKA-II (mAU/ml)			
<47	352	Reference	—
≥47	358	0.73 (0.55–0.96)	0.026
Operating time (min)			
<255.5	355	Reference	—
≥255.5	355	0.83 (0.63–1.08)	0.175
Surgical procedure			
Non-anatomic resection	355	Reference	—
Anatomic resection	355	1.69 (1.29–2.22)	<0.001
Blood transfusion			
+	80	Reference	—
−	630	1.38 (0.93–1.98)	0.103
Microscopic vascular invasion in portal vein and/or hepatic vein and/or bile duct			
Negative	538	Reference	—
Positive	172	1.67 (1.18–2.39)	0.004
UICC/AJCC 7th Staging System			
I	437	Reference	—
II	273	0.81 (0.59–1.14)	0.243

AFP alpha-fetoprotein, *AR* anatomic resection, *HBsAg* hepatitis B surface antigen, *HCV Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *NAR* non-anatomic resection, *PIVKA-II* protein induced by vitamin K absence or antagonist-II

Okamura et al. [32] and Marubashi et al. [33] found no prognostic advantage of AR. Although these studies were performed in an attempt to minimize selection bias and imbalances in baseline characteristics by using PSM, major issues may lie in the lack of quality control of surgery and insufficient analysis of oncologic features.

In the current study, the clinical advantage of completion of AR was confirmed by OS without DFS. With respect to the initial pattern of HCC recurrence in the two groups, the number of patients with intrahepatic HCC recurrence in the AR group was significantly smaller than that in the NAR group. Multiple intrahepatic recurrences also occurred significantly less frequently in the AR than NAR group. In terms of treatment for intrahepatic recurrence, curative therapy was performed more frequently in the AR group. Moreover, significantly fewer patients in the AR group developed recurrence within 2 years after hepatectomy (Table 2). These results suggest that AR influenced the outcomes not only by OS but also by recurrence of HCC, which did not reach a statistically significant difference. Indeed, the DFS curve in the AR group was significantly superior to that in the NAR group within 5 years after the operation (5-year DFS: AR, 47.9% vs. NAR, 41.4%; $P = 0.043$) (Fig. S1). If the number of patients in both groups had been higher after propensity score matching, we suggest that the DFS would have reached a statistically significant difference. The number of patients may have affected the results; however, the exact reason is unclear.

Oncological behavior, such as tumor size and histological differentiation, as well as liver function play important roles in patients' prognosis after initial hepatectomy for treatment of HCC [6, 34, 35]. In the present study, OS among patients with larger tumors was significantly better in the AR than NAR group. With respect to histological tumor differentiation, patients with poorly differentiated HCC who underwent AR had improved DFS and OS. Conversely, patients with HCV-positive HCC who underwent AR had improved DFS and OS. Moreover, among patients with moderate liver dysfunction, the DFS and OS were better in the AR group. The prognostic significance of poorly differentiated HCC for the risk of recurrence has been previously reported [36]. Additionally, some authors have reported that the recurrence rate after resection of HCC in patients with HCV infection was higher than in those with HBV infection, and this was attributed to a higher risk of multicentric occurrence in patients with chronic hepatitis C cirrhosis [37–39]. Our analysis of positive microscopic vascular invasion in the portal vein and/or hepatic vein and/or bile duct showed no similar effect of AR. If the numbers of patients in both groups had been higher after PSM, we assume that the analysis of positive microscopic vascular invasion may have reached statistical significance.

Twelve independent risk factors for OS, including the surgical procedure, were identified using Cox proportional hazards regression analysis. The most significant prognostic advantage of AR was noted among some oncological behaviors and levels of host liver function. To the best of our knowledge, this is largest and most well-defined study

exclusively conducted on patients with chronic hepatitis or cirrhosis in two East Asian countries.

In conclusion, we compared the post-hepatectomy prognosis of patients with HCC who underwent AR or NAR using combined data from Japan and Korea. Propensity score analysis successfully matched patients from each group with similar liver function and tumor characteristics. AR decreases the risk of tumor recurrence and improves OS in patients with a primary, solitary HCC of <5.0 cm in diameter.

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Conflict of interest None declared.

Appendix: author's affiliations

Masaki Kaibori, Masanori Kon, Department of Surgery, Kansai Medical University, Osaka, Japan; Tomoki Kitawaki, Takayuki Kawaura, Department of Mathematics, Kansai Medical University, Osaka, Japan; Kiyoshi Hasegawa, Norihiro Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Shunichi Ariizumi, Masakazu Yamamoto, Department of Surgery, Tokyo Women's Medical University, Tokyo, Japan; Toru Beppu, Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan; Hiroyuki Ishizu, Department of Surgery, Sapporo Kosei Hospital, Sapporo, Japan; Shoji Kubo, Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan; Toshiya Kamiyama, Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, Sapporo, Japan; Hiroyuki Takamura, Department of Gastroenterological Surgery, Kanazawa University, Ishikawa, Japan; Tsuyoshi Kobayashi, Department of Gastroenterological and Transplant Surgery, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; Dong-Sik Kim, Department of Surgery, Korea University College of Medicine, Seoul, Korea; Hee Jung Wang, Department of Surgery, Ajou University School of Medicine, Suwon, Korea; Jong Man Kim, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Dai Hoon Han, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea; Sang-Jae Park, Center for Liver Cancer, National Cancer Center, Goyang, Korea; Koo Jeong Kang, Department of Surgery, Keimyung University Dongsan Medical Center, Daegu, Korea; Shin Hwang, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; Younghoon Roh, Department of Surgery, Dong-A University College of Medicine, Busan, Korea; Young Kyung You, Department of Surgery, The Catholic University of Korea, Seoul, Korea; Jae-Won Joh, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Survival outcomes within 5 years after anatomic resection and non-anatomic resection in propensity score adjustment. (**a**) Disease-free survival rate. (**b**) Overall survival rate. *AR* anatomic resection, *CI* confidence interval, *HR* hazard ratio, *NAR* non-anatomic resection