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Impact of tumor size on hepatectomy outcomes in hepatocellular carcinoma: a nationwide propensity score matching analysis

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Purpose: The aim of this study was to compare surgical outcomes after liver resection for hepatocellular carcinoma (HCC) according to tumor size using a large, nationwide cancer registry-based cohort and propensity score matching.
Methods: From 2008 to 2015, a total of 12,139 patients were diagnosed with liver cancer and registered in the Korean Primary Liver Cancer Registry. Patients without distant metastasis who underwent hepatectomy as a primary treatment were selected. We performed 1:1 propensity score matching between the small (<5 cm), large (≥5 cm and <10 cm), and huge (≥10 cm) groups.
Results: Overall, 265 patients in the small and large groups were compared, and 64 patients each in the large and huge groups were compared. The overall and progression-free survival rates were significantly lower in the large group than in the small group ($P < 0.001$ and $P < 0.001$, respectively). Overall survival tended to be poorer in the huge group than in the large group ($P = 0.051$). The progression-free survival rate was significantly lower in the huge group than in the large group ($P = 0.002$).
Conclusion: Although primary liver resection can be considered even in patients with huge HCC, greater caution with careful screening for recurrence is needed.
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Key Words: Disease progression, Hepatectomy, Hepatocellular carcinoma, Survival

INTRODUCTION

Liver resection is the first-line treatment for patients with single hepatocellular carcinoma (HCC) without cirrhosis, as well as for patients with cirrhosis but with adequate liver functional reserve [1-3]. The outcome of liver resection has been improved due to recent advances in preoperative examinations and surgical techniques, along with the accumulation of postoperative management [4,5]. According to recent reports, the 5-year survival rate after liver resection for HCC is 46%–69.5% and the 5-year disease-free survival rate is 23%–56.3% [6-8]. In general, liver resection is reported to have a good prognosis when performed in 1 or 2 small tumors [4,7]. Large tumor size, microvascular invasion (MVI), tumor rupture, severity of underlying cirrhosis, and tumor multiplicity are known to be associated with poor prognosis [5,9-12].

According to the studies reported so far, it is generally considered to be large if the tumor size is larger than 5 cm and huge if it is larger than 10 cm [11,13-17]. The American Joint Committee on Cancer staging system for HCC also includes a 5

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cm value in determining T3 [18].

However, some recent studies have shown that no MVI was observed in 1/3 of patients with tumors larger than 10 cm, indicating that the size solely itself did not adversely affect the prognosis [11,17]. Most of the existing studies are limited in that factors other than tumor size are not properly controlled, the sample size is small, they are not a comparative study, or their study was limited to single-center experience [11,12,17].

This study aimed to assess and compare outcomes after liver resection for HCC according to tumor size (<5 cm *vs.* ≥5 cm and <10 cm and ≥5 cm and <10 cm *vs.* ≥10 cm) using a large, nationwide cancer registry-based cohort and propensity score matching to adjust for differences between the groups.

METHODS

This study was conducted according to the ethical guidelines of the Declaration of Helsinki and exempted from further ethical review by the Institutional Review Board of Seoul National University Hospital (No. 2111-081-1272). The study population included 12,139 patients who were diagnosed with liver cancer and registered in the Korean Primary Liver Cancer Registry (KPLCR) from 2008 to 2015. Fig. 1 shows a schematic of the study. Patients who underwent hepatectomy as the primary treatment for HCC without distant metastasis were included. Patients with an Eastern Cooperative Oncology Group performance status other than 0 or missing were excluded. After exclusion of patients who had missing values for follow-up date, body mass index (BMI), serology, Child-Pugh score, number of tumors, size of tumor, platelet count, PT, or performance status, 1,390 patients were finally included in the study. We then divided the patients according to maximal tumor size, defined using preoperative imaging: small (<5 cm, n = 1,046), large (≥5 cm and <10 cm, n = 274), and huge (≥10 cm, n = 70). Progression-free survival (PFS) was measured from the day of initial treatment to the day of the second or last follow-up.

Statistical analysis

Categorical variables were presented as numbers and percentages, and continuous variables were presented as mean ± standard deviation or median (range). Continuous variables were compared using a Student t-test, whereas categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. Patient overall survival and PFS rates were calculated using the Kaplan-Meier method and compared

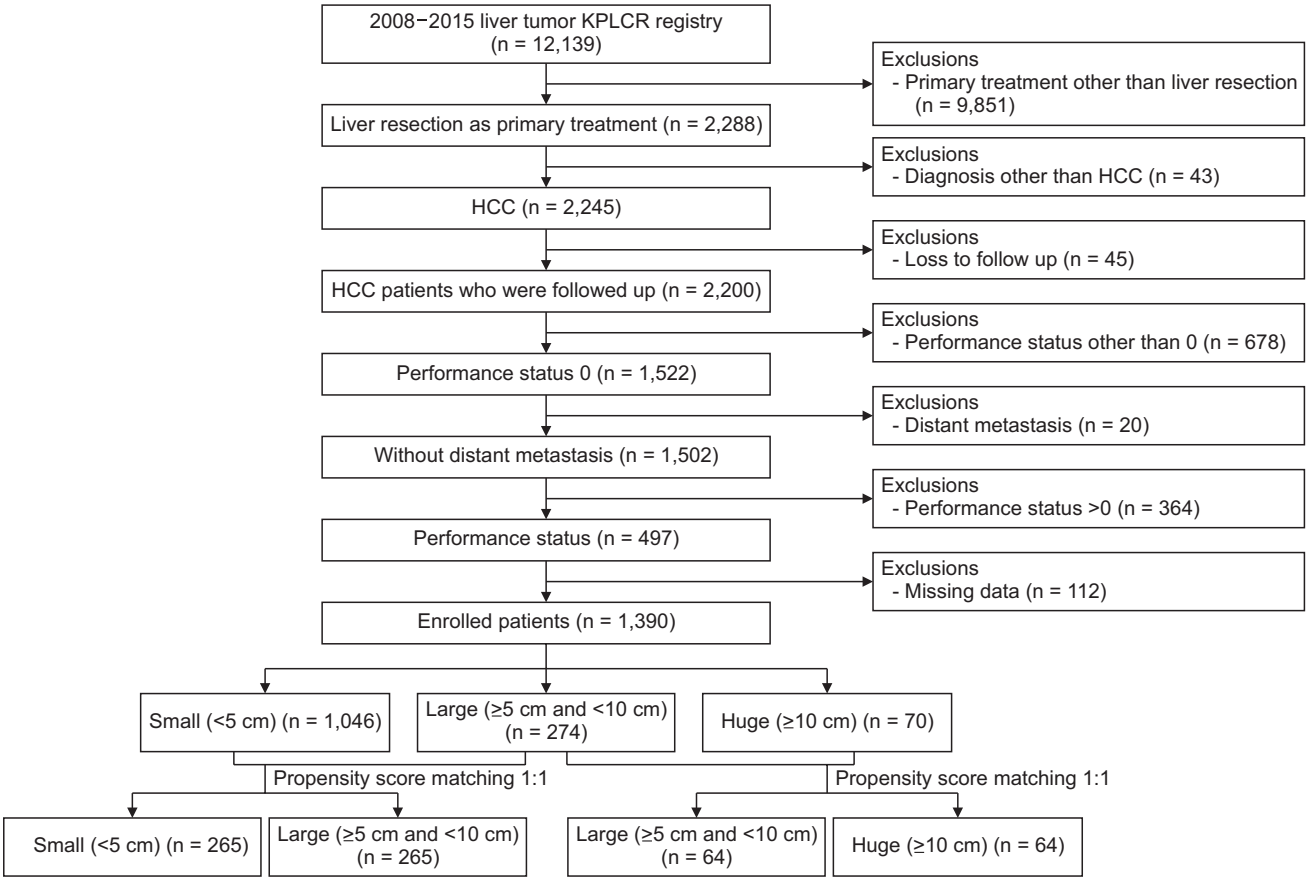

Fig. 1. Flowchart of the enrolled patients. KPLCR, Korean Primary Liver Cancer Registry; HCC, hepatocellular carcinoma.

using the log-rank test. To overcome possible selection bias, 1:1 propensity score matching between small and large and large and huge cohorts was applied using multiple logistic regression and a 1:1 matching requirement via the nearest-neighbor matching method. Factors such as age, sex, BMI, etiology (HBV, HCV, or non-B non-C), platelet count, PT, tumor number, and Child-Pugh score were matched. The absolute standardized differences method was used to diagnose the balance after matching, and all were checked to be less than 0.25. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Small (<5 cm) *vs.* large (≥5 cm and <10 cm)

A total of 1,046 patients in the small group and 274 patients in the large group were included (Table 1). After matching, 265 patients were included in each group. Before matching, the large group was older and had a higher proportion of etiology with non-B non-C than the small group. Platelet count was higher and PT was lower in the large group than in the small group. The large group had a higher proportion of patients with multiple tumors than the small group. After matching, there were no significant intergroup differences in relation to the 8 factors encompassing the baseline characteristics of the small and large groups.

The outcomes of demographic, radiologic, pathologic, and treatment variables are summarized in Table 2. Preoperative levels of α-FP (median [range]: 7.7 ng/mL [1.0–24,100.0 ng/mL] *vs.* 34.7 ng/mL [0.9–238,400.0 ng/mL], $P < 0.001$), protein induced by vitamin K absence-II (PIVKA-II) (43.0 mAU/mL [4.1–4,027.0 mAU/mL] *vs.* 508.0 mAU/mL [5.0–75,000.0 mAU/mL], $P < 0.001$), and the proportion of MVI was higher in the large group than in the small group. A higher proportion of patients experienced a second treatment after resection (31.3% *vs.* 48.7%, $P < 0.001$), most of which were non-radical treatments including transarterial therapy, chemotherapy, and radiation, in the large group than in the small group ($P = 0.021$).

Kaplan-Meier analysis showed that the 1-, 2-, 3-, and 5-year survival rates were 97.0%, 93.9%, 91.5%, and 88.7%, respectively, in the small group; and 90.5%, 78.4%, 71.2%, and 61.5%, respectively, in the large group ($P < 0.001$) (Fig. 2A). The 1-, 2-, 3-, and 5-year PFS rates were 84.8%, 74.2%, 69.1%, and 66.4%, respectively, in the small group; and 64.0%, 52.1%, 49.8%, and 48.0%, respectively, in the large group ($P < 0.001$) (Fig. 2B).

When performing subgroup analysis by excluding 96 patients with multiple HCCs, the 1-, 2-, 3-, and 5-year survival rates were 97.7%, 95.4%, 92.9%, and 92.2%, respectively, in the small group ($n = 217$); and 92.1%, 78.2%, 71.5%, and 62.7%, respectively, in the large group ($n = 217$) ($P < 0.001$) (Supplementary Fig. 1A). The 1-, 2-, 3-, and 5-year PFS rates were 87.9%, 77.1%, 71.9%, and 68.8%, respectively, in the small group; and 64.9%, 51.5%, 49.3%, and 48.6%, respectively, in the large group ($P < 0.001$) (Supplementary Fig. 1B).

Large (≥5 cm and <10 cm) *vs.* huge (≥10 cm)

A total of 274 patients in the large group and 70 patients in

Table 1. Baseline characteristics of patients with small or large hepatocellular carcinoma before and after propensity score matching

Variable	Before PSM				After PSM			
	Small (n = 1,035)	Large (n = 274)	P-value	SD	Small (n = 265)	Large (n = 265)	P-value	SD
Age (yr)	56.8 ± 9.7	58.9 ± 10.9	0.004	0.195	58.6 ± 10.0	58.7 ± 11.0	0.904	0.010
Sex, male:female	808:227	228:46	0.062	–0.137	227:38	221:44	0.471	0.060
Body mass index (kg/m^2)	24.1 ± 2.9	24.1 ± 3.0	0.837	–0.014	24.3 ± 2.9	24.1 ± 3.0	0.558	–0.050
Etiology								
HBV	777 (75.1)	171 (62.4)	<0.001	–0.261	176 (66.4)	170 (64.2)	0.584	–0.047
HCV	75 (7.2)	17 (6.2)	0.549	–0.043	13 (4.9)	17 (6.4)	0.452	0.062
Non B non C	189 (18.1)	88 (32.1)	<0.001	0.300	78 (29.4)	80 (30.2)	0.849	0.016
Platelet count (×10^9/L)	157.4 ± 59.5	197.7 ± 69.7	<0.001	0.579	190.9 ± 63.5	193.2 ± 64.7	0.876	0.033
PT, INR	1.1 ± 0.1	1.0 ± 0.1	0.001	–0.253	1.0 ± 0.1	1.0 ± 0.1	0.220	0.097
Tumor number			0.007	0.162			>0.999	<0.001
Single	911 (88.0)	224 (81.8)			217 (81.9)	217 (81.9)		
Multiple	124 (12.0)	50 (18.2)			48 (18.1)	48 (18.1)		
Child-Pugh score			0.974	–0.002			0.779	–0.026
A	1,012 (97.8)	268 (97.8)			258 (97.4)	259 (97.7)		
B or C	23 (2.2)	6 (2.2)			7 (2.6)	6 (2.3)		

Values are presented as mean ± standard deviation (SD) or number (%).
PSM, propensity score matching; INR, international normalized ratio.

Table 2. Demographic and clinical characteristics of the included patients

Variable	Before PSM			After PSM		
	Small	Large	P-value	Small	Large	P-value
Demographic variable						
No. of patients	1,035	274		265	265	
Age (yr)	56.8 ± 9.7	58.9 ± 10.9	0.004	58.6 ± 10.0	58.7 ± 11.0	0.904
Sex, male:female	808:227	228:46	0.062	227:38	221:44	0.471
Body mass index (kg/m)[b]	24.1 ± 2.9	24.1 ± 3.0	0.837	24.3 ± 2.9	24.1 ± 3.0	0.558
Smoking			0.225			0.728
No	567 (54.8)	139 (50.7)		129 (48.7)	133 (50.2)	
Yes	467 (45.1)	135 (49.3)		136 (51.3)	132 (49.8)	
Unknown	1 (0.1)	0 (0)		0 (0)	0 (0)	
Alcohol			0.248			0.795
No	760 (73.4)	192 (70.1)		187 (70.6)	189 (71.3)	
Yes	266 (25.7)	80 (29.2)		78 (29.4)	75 (28.3)	
Unknown	9 (0.9)	2 (0.7)		0	1 (0.4)	
Diabetes			0.483			0.274
No	823 (79.5)	213 (77.7)		218 (82.3)	208 (78.9)	
Yes	210 (20.3)	61 (22.3)		47 (17.7)	57 (21.1)	
Unknown	2 (0.2)	0		0 (0)	0 (0)	
Hypertension			0.227			0.401
No	691 (66.8)	173 (63.1)		159 (60.0)	169 (63.8)	
Yes	340 (32.9)	101 (36.9)		105 (39.6)	96 (36.2)	
Unknown	4 (0.4)	0 (0)		1 (0.4)	0 (0)	
Etiology						
HBV	777 (75.1)[a]	171 (62.4)[b]	<0.001	176 (66.4)[c]	170 (64.2)[d]	0.584
HCV	75 (7.2)[a]	17 (6.2)[b]	0.549	13 (4.9)[c]	17 (6.4)[d]	0.452
Non B non C	189 (18.3)	88 (32.1)	<0.001	78 (29.4)	80 (30.2)	0.849
Child-Pugh score			0.974			0.779
A	1,012 (97.8)	268 (97.8)		258 (97.4)	259 (97.7)	
B or C	23 (2.2)	6 (2.2)		7 (2.6)	6 (2.3)	
MELD score	7.8 ± 1.9	7.8 ± 2.1	0.720	7.6 ± 1.8	7.8 ± 2.1	0.246
Laboratory variable						
Platelet count (×10^9/L)	189 (18.3)	88 (32.1)	<0.001	190.9 ± 63.5	193.2 ± 64.7	0.876
Total bilirubin (mg/dL)	0.9 ± 0.6	0.8 ± 0.5	0.157	0.8 ± 0.4	0.8 ± 0.5	0.756
Serum albumin (g/dL)	4.2 ± 0.5	4.2 ± 0.4	0.772	4.3 ± 0.5	4.2 ± 0.4	0.060
ANR (IU/L)	39.8 ± 31.8	42.8 ± 49.7	0.227	37.8 ± 29.2	42.5 ± 49.1	0.182
PT, INR	1.1 ± 0.1	1.0 ± 0.1	0.001	1.0 ± 0.1	1.0 ± 0.1	0.220
Creatinine (mg/dL)	0.9 ± 0.7	1.0 ± 0.8	0.335	1.0 ± 0.6	1.0 ± 0.8	0.905
Sodium (mmol/L)	140.1 ± 3.7	140.2 ± 3.1	0.687	140.1 ± 2.9	140.2 ± 3.1	0.809
α-FP (ng/mL)	14.9 (0.6–70,133.4)	33.7 (0.9–238,400.0)	<0.001	7.7 (1.0–24,100.0)	34.7 (0.9–238,400.0)	<0.001
PIVKA-II (mAU/mL)	41.0 (4.1–21,876.0.0)	538.0 (5.0–75,000.0)	<0.001	43.0 (4.1–4,027.0)	508.0 (5.0–75,000.0)	<0.001

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Table 2. Continued

Variable	Before PSM			After PSM		
	Small	Large	P-value	Small	Large	P-value
Radiologic variable						
Maximum tumor diameter (cm)	2.8 ± 1.0	6.6 ± 1.3	<0.001	2.9 ± 1.0	6.6 ± 1.3	<0.001
Tumor number			0.007			>0.999
Single	911 (88.0)	224 (81.8)		217 (81.9)	217 (81.9)	
Multiple	124 (12.0)	50 (18.2)		48 (18.1)	48 (18.1)	
Pathologic variable						
Maximum tumor diameter (cm)	2.8 ± 1.2	6.7 ± 1.8	<0.001	3.1 ± 1.4	6.7 ± 1.8	<0.001
Tumor number			0.005			0.687
Single	927 (89.6)	229 (83.6)		227 (85.7)	222 (83.8)	
Multiple	101 (9.8)	43 (15.7)		38 (14.3)	41 (15.5)	
Unknown	7 (0.7)	2 (0.7)		0 (0)	2 (0.8)	
Microvascular invasion			<0.001			<0.001
No	338 (32.7)	50 (18.2)		86 (32.5)	46 (17.4)	
Yes	98 (9.5)	60 (21.9)		20 (7.5)	59 (22.3)	
Unknown	599 (57.9)	164 (59.9)		159 (60.0)	160 (60.4)	
Treatment variable						
Second treatment			<0.001			<0.001
No	736 (71.1)	144 (52.6)		182 (68.7)	136 (51.3)	
Yes	299 (28.9)	130 (47.4)		83 (31.3)	129 (48.7)	
Second treatment modality			0.016			0.021
Resection	19 (1.8)	2 (0.7)		8 (3.0)	2 (0.8)	
Transplantation	5 (0.5)	0 (0)		2 (0.8)	0 (0)	
Local ablative therapy	67 (6.5)	27 (9.9)		21 (7.9)	27 (10.2)	
Transarterial therapy	184 (17.8)	79 (28.8)		44 (16.6)	78 (29.4)	
Chemotherapy	21 (2.0)	18 (6.6)		7 (2.6)	18 (6.8)	
Radiation	3 (0.3)	4 (1.5)		1 (0.4)	4 (1.5)	

Values are presented as number only, mean ± standard deviation, or number (%).
PSM, propensity score matching; MELD, model for end-stage liver disease; INR, international normalized ratio; PIVKA-II, protein induced by vitamin K absence-II.
[a]Four patients had underlying hepatitis B and C coinfections. [b]Two patients had underlying hepatitis B and C coinfections. [c]Two patients had underlying hepatitis B and C coinfections. [d]Two patients had underlying hepatitis B and C coinfections.

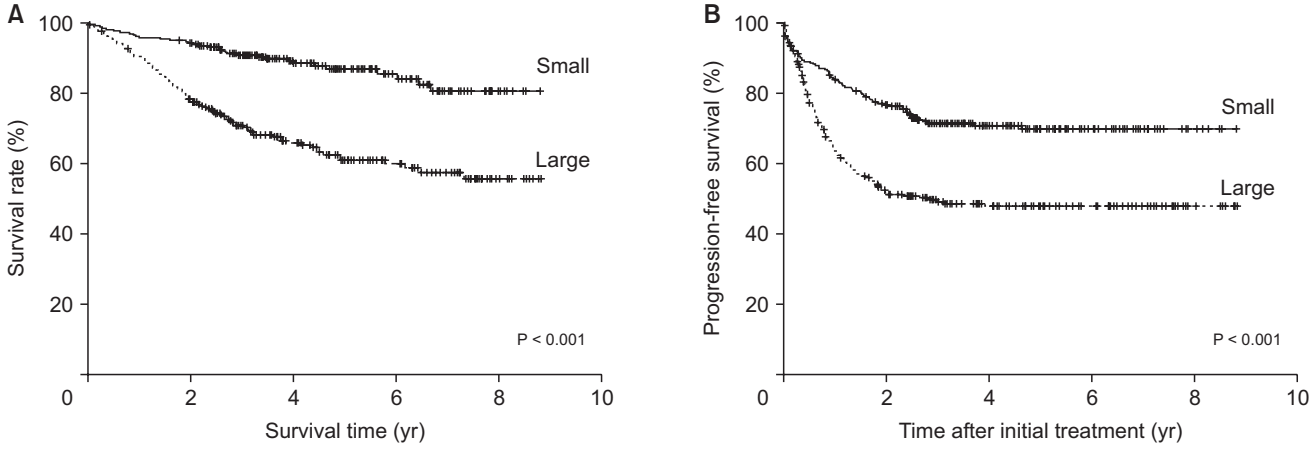

Fig. 2. Kaplan-Meier analysis of survival comparing small and large groups. (A) Overall survival, (B) progression-free survival.

Table 3. Baseline characteristics of patients with large or huge HCC before and after propensity score matching

Variable	Before PSM				After PSM			
	Large (n = 274)	Huge (n = 70)	P-value	SD	Large (n = 64)	Huge (n = 64)	P-value	SD
Age (yr)	58.9 ± 10.9	56.2 ± 13.7	0.131	–0.196	58.4 ± 11.0	57.6 ± 13.3	0.723	–0.056
Sex, male:female	228:46	63:7	0.160	–0.225	60:4	58:6	0.510	0.103
Body mass index (kg/m^2)	24.1 ± 3.0	23.7 ± 4.9	0.532	–0.079	23.7 ± 2.9	24.1 ± 4.9	0.576	0.082
Etiology								
HBV	171 (62.4)	41 (58.6)	0.556	–0.077	36 (56.3)	36 (56.3)	>0.999	<0.001
HCV	17 (6.2)	5 (7.1)	0.785	0.036	3 (4.7)	5 (7.8)	0.718	0.120
Non B non C	88 (32.1)	25 (35.7)	0.567	0.075	25 (39.1)	24 (37.5)	0.856	–0.032
Platelet count (×10^9/L)	197.7 ± 69.7	241.7 ± 88.8	<0.001	0.495	226.7 ± 78.3	227.0 ± 71.2	0.985	0.003
PT, INR	1.0 ± 0.1	1.0 ± 1.0	0.985	–0.002	1.0 ± 0.8	1.0 ± 0.1	0.680	0.064
Tumor number			0.382	0.109			0.544	–0.111
Single	224 (81.8)	54 (77.1)			46 (71.9)	49 (76.6)		
Multiple	50 (18.2)	16 (22.9)			18 (28.1)	15 (23.4)		
Child-Pugh			>0.999	–0.064			>0.999	0.131
A	268 (97.8)	69 (98.6)			64 (100)	63 (98.4)		
B or C	6 (2.2)	1 (1.4)			0 (0)	1 (1.6)		

Values are presented as mean ± standard deviation (SD) or number (%).
PSM, propensity score matching; SD, standard deviation; INR, international normalized ratio.

the huge group were included (Table 3). Before matching, the preoperative platelet count was higher in the huge group than in the large group. After matching, 64 patients were included in each group and they were well matched for age, sex, BMI, etiology, preoperative platelet count, PT, tumor number, and Child-Pugh score.

Table 4 summarizes the outcomes of the demographic, radiologic, pathologic, and treatment variables of the 2 groups. Serum albumin was significantly lower (4.2 *vs.* 4.0 g/dL, P = 0.022) and ALT was higher in the huge group than in the large group. Preoperative α-FP levels were similar between the 2 groups (P = 0.178), but the preoperative PIVKA-II level was higher in the huge group than in the large group (median [range]: 380.0 mAU/mL [25.0–48,000.0 mAU/mL] *vs.* 2,000.0 mAU/mL [26.0–100,000.0 mAU/mL], P = 0.023). The rate of MVI was higher in the huge group than in the large group (14.1% *vs.* 23.4%, P = 0.023).

Kaplan-Meier analysis showed that the 1-, 2-, 3-, and 5-year survival rates were 90.6%, 84.4%, 72.0%, and 62.3%, respectively, in the large group; and 82.8%, 73.4%, 62.0%, and 53.2%, respectively, in the huge group (P = 0.051) (Fig. 3A). The 1-, 2-, 3-, and 5-year PFS rates were 63.0%, 56.5%, 56.5%, and 56.5%, respectively, in the large group; and 43.1%, 36.2%, 28.9%, and 26.7%, respectively, in the huge group (P = 0.002) (Fig. 3B).

When performing subgroup analysis by excluding 33 patients with multiple HCCs, the 1-, 2-, 3-, and 5-year survival rates were

Table 4. Demographic and clinical characteristics of the included patients

Variable	Before PSM			After PSM		
	Large	Huge	P-value	Large	Huge	P-value
Demographic variable						
No. of patients	274	70		64	64	
Age (yr)	58.9 ± 10.9	56.2 ± 13.7	0.131	58.4 ± 11.0	57.6 ± 13.3	0.723
Sex, male:female	228:46	63:7	0.160	60:4	58:6	0.510
Body mass index (kg/m[b])	24.1 ± 3.0	23.7 ± 4.9	0.532	23.7 ± 2.9	24.1 ± 4.9	0.576
Smoking			0.747			0.860
No	139 (50.7)	34 (48.6)		33 (51.6)	32 (50.0)	
Yes	135 (49.3)	36 (51.4)		31 (48.4)	32 (50.0)	
Unknown	0 (0)	0 (0)		0 (0)	0 (0)	
Alcohol			0.026			0.267
No	192 (70.1)	39 (55.7)		43 (67.2)	37 (57.8)	
Yes	80 (29.2)	30 (42.9)		20 (31.3)	26 (40.6)	
Unknown	2 (0.7)	1 (1.4)		1 (1.6)	1 (1.6)	
Diabetes			0.141			0.174
No	213 (77.7)	60 (85.7)		49 (76.6)	55 (85.9)	
Yes	61 (22.3)	10 (14.3)		15 (23.4)	9 (14.1)	
Unknown	0 (0)	0 (0)		0 (0)	0 (0)	
Hypertension			0.792			0.465
No	173 (63.1)	43 (61.4)		42 (65.6)	38 (59.4)	
Yes	101 (36.9)	27 (38.6)		22 (34.4)	26 (40.6)	
Unknown	0 (0)	0 (0)		0 (0)	0 (0)	
Etiology						
HBV	171 (62.4)[a]	41 (58.6)[b]	0.556	36 (56.3)	36 (56.3)[c]	>0.999
HCV	17 (6.2)[a]	5 (7.1)[b]	0.785	3 (4.7)	5 (7.8)[c]	0.465
Non B non C	88 (32.1)	25 (35.7)	0.567	25 (39.1)	24 (37.5)	0.856
Child-Pugh score			>0.999			>0.999
A	268 (97.8)	69 (98.6)		64 (100)	63 (98.4)	
B or C	6 (2.2)	1 (1.4)		0 (0)	1 (1.6)	
MELD score	7.8 ± 2.1	7.9 ± 1.7	0.684	7.7 ± 1.5	7.9 ± 1.7	0.407
Laboratory variable						
Platelet count (×10^9/L)	197.7 ± 69.7	241.7 ± 88.8	<0.001	226.7 ± 78.3	227.0 ± 71.2	0.985
Total bilirubin (mg/dL)	0.8 ± 0.5	0.9 ± 0.5	0.114	0.8 ± 0.4	0.9 ± 0.5	0.093
Serum albumin (g/dL)	4.2 ± 0.4	4.0 ± 0.4	0.006	4.2 ± 0.4	4.0 ± 0.4	0.022
ALT (IU/L)	42.8 ± 49.7	67.6 ± 90.5	0.030	36.8 ± 19.6	62.4 ± 86.9	0.024
PT, INR	1.0 ± 0.1	1.0 ± 1.0	0.985	1.0 ± 0.1	1.0 ± 0.1	0.680
Creatinine (mg/dL)	1.0 ± 0.8	0.9 ± 0.3	0.710	1.0 ± 0.3	1.0 ± 0.3	0.873
Sodium (mmol/L)	140.2 ± 3.1	139.1 ± 2.8	0.007	139.6 ± 4.2	130.1 ± 2.8	0.395
α-FP (ng/mL)	33.7 (0.9–238,400.0)	243.7 (0.9–200,000.0)	0.033	10.4 (0.9–106,565.0)	127.9 (0.9–200,000.0)	0.178
PIVKA-II (mAU/mL)	538.0 (5.0–75,000.0)	2,000.0 (26.0–100,000.0)	0.057	380.0 (25.0–48,000.0)	2,000.0 (26.0–100,000.0)	0.023

Table 4. Continued

Variable	Before PSM			After PSM		
	Large	Huge	P-value	Large	Huge	P-value
Radiologic variable						
Maximum tumor diameter (cm)	6.6 ± 1.3	12.6 ± 2.5	<0.001	6.9 ± 1.5	12.5 ± 2.2	<0.001
Tumor number			0.382			0.544
Single	224 (81.8)	54 (77.1)		46 (71.9)	49 (76.6)	
Multiple	50 (18.2)	16 (22.9)		18 (28.1)	15 (23.4)	
Pathologic variable						
Maximum tumor diameter (cm)	6.7 ± 1.8	12.6 ± 3.5	<0.001	6.9 ± 1.6	12.3 ± 3.0	<0.001
Tumor number			0.373			0.558
Single	229 (83.6)	55 (78.6)		48 (75.0)	50 (78.1)	
Multiple	43 (15.7)	14 (20.0)		16 (25.0)	13 (20.3)	
Unknown	2 (0.7)	1 (1.4)		0 (0)	1 (1.6)	
Microvascular invasion			0.087			0.023
No	50 (18.2)	6 (8.6)		15 (23.4)	6 (9.4)	
Yes	60 (21.9)	17 (24.3)		9 (14.1)	15 (23.4)	
Unknown	164 (59.9)	47 (67.1)		40 (62.5)	43 (67.2)	
Treatment variable						
Second treatment			0.012			0.004
No	144 (52.6)	25 (35.7)		37 (57.8)	21 (32.8)	
Yes	130 (47.4)	45 (64.3)		27 (42.2)	43 (67.2)	
Second treatment modality			0.689			0.630
Resection	2 (0.7)	1 (1.4)		0 (0)	1 (1.6)	
Transplantation						
Local ablative therapy	27 (9.9)	8 (11.4)		5 (7.8)	7 (10.9)	
Transarterial therapy	79 (28.8)	25 (35.7)		19 (29.7)	24 (37.5)	
Chemotherapy	18 (6.6)	10 (14.3)		3 (4.7)	10 (15.6)	
Radiation	4 (1.5)	1 (1.4)		0 (0)	1 (1.6)	

Values are presented as number only, mean ± standard deviation, or number (%).
PSM, propensity score matching; MELD, model for end-stage liver disease; INR, international normalized ratio; PIVKA-II, protein induced by vitamin K absence-II.
[a]Two patients had underlying hepatitis B and C coinfections. [b]One patient had underlying hepatitis B and C coinfections. [c]One patient had underlying hepatitis B and C coinfections.

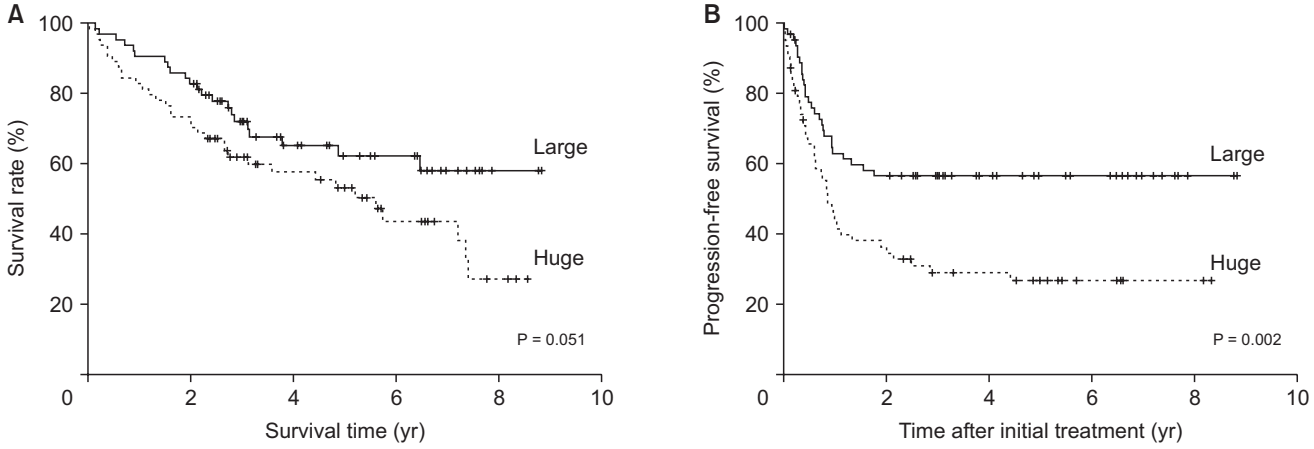

Fig. 3. Kaplan-Meier analysis of survival comparing large and huge groups. (A) Overall survival, (B) progression-free survival.

91.3%, 82.6%, 73.1%, and 67.2%, respectively, in the large group (n = 46); and 81.6%, 75.5%, 67.0%, and 59.0%, respectively, in the huge group (n = 49) (P = 0.088) (Supplementary Fig. 2A). The 1-, 2-, 3-, and 5-year PFS rates were 61.5%, 56.9%, 56.9%, and 56.9%, respectively, in the large group, and 48.6%, 41.7%, 34.1%, and 31.0%, respectively, in the huge group (P = 0.032) (Supplementary Fig. 2B).

DISCUSSION

Most previous studies demonstrating the impact of tumor size in HCC patients who underwent hepatectomy are limited by selection bias, small sample size, and/or single-center experience [11,12,17]. The present study has several strengths that can overcome these limitations. First, the patient cohort was sorted from a large nationwide cancer registry database to maintain statistical power. The samples registered in the KPLCR are guaranteed to be representative of all HCCs in Korea, and the statistics of HCC in Korea have been continuously reported using this registry [19]. Second, the propensity score matching method was used after excluding patients with a performance status other than 0, distant metastasis, or missing data to minimize selection bias. Third, the patients were classified into 3 groups (small, large, and huge) and they were serially compared (small *vs.* large, large *vs.* huge) to accurately identify the impact of maximum tumor size while maintaining adequate sample size. Comparing the 3 groups at once can lead to the weakness of tailoring to the huge group, which includes only 70 patients before matching. Instead, we serially compared the small group (n = 1,035) with the large group (n = 274) first, and then the large group (n = 274) with the huge group (n = 70).

Our study showed that patients with HCC larger than 10 cm showed a 5-year overall survival rate of 53.2% and a 5-year PFS rate of 26.7%, which are higher than those of previous reports showing recurrence-free survival rates after resection in patients with these huge tumors as 35.5%–42.9% and 9.7%–14.2% [13,20]. This can be explained by the inclusion and exclusion criteria of the study design. Patients who underwent hepatectomy as primary treatment were included, and patients with a performance status other than zero and those with distant metastasis were excluded. These inclusion and exclusion criteria may have improved the survival outcomes. As expected, our study showed significantly better overall survival and PFS in the small group than in the large group; and better PFS in the large group than in the huge group. There was also a clear tendency for better overall survival in the large group than in the huge group, but the difference was not statistically significant (P = 0.051). Altogether, this study confirmed once again that overall and PFS worsened as the maximal tumor size increased.

The α-FP and PIVKA-II are widely used serum tumor markers, despite that facts that approximately 40% of patients with HCC have negative α-FP, the positive predictive value of α-FP is about 9%–32%, and PIVKA-II levels are influenced by several factors other than HCC [21-25]. Previous studies have reported the correlations between serum α-FP and PIVKA-II levels and the size of HCC [21-25]. Similarly, the present study showed that serum α-FP and PIVKA-II levels in the large group were significantly higher than those in the small group. Serum PIVKA-II levels in the huge group were higher than those in the large group; however, serum α-FP levels were similar between the 2 groups. As expected, the present study showed that the median values of serum α-FP and PIVKA-II levels serially increased according to the size of HCC.

Although not significant when comparing the small group with the large group, serum albumin was higher and ALT levels were lower in the huge group compared to the large group. Larger HCCs are reported to be associated with lower albumin levels, possibly due to decreased liver function as a result of the

original liver disease, liver destruction by extensive HCC growth, and systemic inflammation [26,27]. These factors might have been dramatically aggravated as HCC grew to more than 10 cm. Elevation of serum ALT levels can also be explained in a similar context. ALT is a protein that is expressed in various human tissues and organs, with the highest expression observed in the mitochondria of hepatocytes [23]. ALT can be used as a biomarker evaluating hepatocyte destruction. Elevation of ALT level with a mean value of 62.4 IU/L in the huge HCC group may have resulted from liver destruction due to extensive HCC growth. Tarao et al. [27] reported a close correlation between ALT elevation and histological necroinflammation using biopsy specimens. Another explanation can be deduced from previous studies that reported an association between ALT elevation and risk of HCC [28-30]. Lin et al. [30] demonstrated that elevated serum levels of ALT were significantly associated with an increased HCC risk in a large cohort of chronic HBV carriers.

It has been reported that as the size of the tumor increases, the frequency of MVI increases and the prognosis is poor [9]. However, according to recent studies, MVI was not observed in approximately one-third of patients with tumors larger than 10 cm [11,17]. The present study showed a significant difference in the proportion of MVI between the small and large groups ($P < 0.001$) and large and huge groups ($P = 0.023$). There are several missing data on MVI because the registry began to include MVI data since 2013. When performing subgroup analysis including only the period after 2013, the rate of MVI was 18.9% in the small group and 56.2% in the large group. According to the comparison between the large and huge groups, the rate of MVI was 37.5% in the large group and 71.4% in the huge group. Similar to a previous study [11], approximately 30% of patients with huge HCC larger than 10 cm had no MVI.

This study has several limitations. First, it was a retrospective study using a national database registry that relied on the completeness of medical records. Second, Korea is an HBV endemic country, and it is also clear in the present study showing that 56.3%–64.2% of the patients had an etiology of HBV. Thus, our results may not be generalizable to patients with HCC with other etiologies. Third, recurrence-free survival could not be evaluated using this registry. Instead, PFS, which was calculated by the date of initial hepatectomy and the date of the second treatment, was used. Fourth, this study did not compare hepatectomy as an initial treatment with other treatment methods such as transarterial embolization. Despite these limitations, this study has a strength in that it is a large study using a national registry database and it minimized selection bias by excluding patients with certain conditions and using propensity score matching.

In conclusion, this study reports overall survival and PFS, which progressively increased with increasing size of HCC. However, at the same time, it showed a favorable outcome of primary liver resection even in HCCs larger than 10 cm. Primary liver resection should not be excluded based solely on tumor size. Of course, after performing primary liver resection in huge HCC patients, greater caution with careful screening for recurrence is needed.

SUPPLEMENTARY MATERIALS

Supplementary Figs. 1 and 2 can be found via https://doi.org/10.4174/astr.2022.102.4.193.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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