Real-world role of performance status in surgical resection for hepatocellular carcinoma: A multicenter study[☆]

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ABSTRACT

Background: The Barcelona Clinic Liver Cancer (BCLC) categorizes a patient with performance status (PS)-1 as advanced stage of hepatocellular carcinoma (HCC) and surgical resection is not recommended. In real-world clinical practice, PS-1 is often not a contraindication to surgery for HCC. The aim of current study was to define the impact of PS on the surgical outcomes of patients undergoing liver resection for HCC.
Methods: 1,531 consecutive patients who underwent a curative-intent resection of HCC between 2005 and 2015 were identified using a multi-institutional database. After categorizing patients into PS-0 (n = 836) versus PS-1 (n = 695), perioperative mortality and morbidity, overall survival (OS) and recurrence-free survival (RFS) were compared.
Results: Overall perioperative mortality and major morbidity among patients with PS-0 (n = 836) and PS-1 (n = 695) were similar (1.4% vs. 1.6%, $P = 0.525$ and 9.7% vs. 10.2%, $P = 0.732$, respectively). In contrast, median OS and RFS was worse among patients who had PS-1 versus PS-0 (34.0 vs. 107.6 months, and 20.5 vs. 60.6 months, both $P < 0.001$, respectively). On multivariable Cox-regression analyses, PS-1 was independently associated with worse OS (HR: 1.301, 95% CI: 1.111—1.523, $P < 0.001$) and RFS (HR: 1.184, 95% CI: 1.034—1.358, $P = 0.007$).
Conclusions: Patients with PS-1 versus PS-0 had comparable perioperative outcomes. However, patients with PS-1 had worse long-term outcomes as PS-1 was independently associated with worse OS and RFS. Routine exclusion of HCC patients with PS-1 from surgical resection as recommended by the BCLC guidelines is not warranted.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide [1]. The primary cause of HCC in Asia, especially China, is hepatitis B virus (HBV) [2,3]. Although surveillance for HCC in high-risk populations is recommend, only a minority of asymptomatic HCCs is detected on surveillance [4—6]. Most HCCs are initially diagnosed due to symptoms after tumor progression and overall prognosis is poor [7,8]. The Barcelona Clinic Liver Cancer (BCLC) staging, which links tumor staging with recommended treatment strategies defines the standard of care for each HCC tumor stage [9,10]. The BCLC staging is approved and recommended by the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) [9,10]. One of the unique advantages of the BCLC staging is in the incorporation of performance status (PS), determined according to the Eastern Cooperative Oncology Group (ECOG) scale, into the BCLC staging algorithm [11]. PS scoring reflects the degree of cancer-related symptoms, categorizing patients from 0 to 5 [11,12]. Specifically, PS-0 denotes normal activity, PS-1 some symptoms yet still near fully ambulatory, PS-2 less than 50% ability to do activities of daily living, PS-3 more than 50% of daytime in bed, PS-4 completely bedridden, and PS-5 is dead [13]. These criteria are extensively used by clinicians to evaluate progression of a variety of malignant diseases and direct treatment options relative to the daily living ability of patients [14—20].

The BCLC staging defines advanced HCC (BCLC stage C) as the presence of macroscopic vascular invasion (VI), extrahepatic spread (ES), or a poor PS (score 1—2). In turn, the BCLC recommends sorafenib or other targeted drugs alone, but not surgical resection, for patients with advanced HCC. Since being proposed, the BCLC staging system has been updated and adjusted several times, especially with regards to the definition of BCLC A and B stages [21—27]. The role of PS in HCC staging relative to different treatment recommendations has, however, never been revised [21—27]. Specifically, BCLC staging still considers patients with PS score of 1—2 as advanced-staged HCC and notes that surgical resection is contra-indicated in the treatment guideline [28—31]. In real clinical practice, however, PS is often not used as an absolute contraindication to surgical resection for HCC [32—35]. In fact, even a minority of patients with PS 3—4, such as selected patients with ruptured HCC and hemorrhagic shock, can have favorable long-term survival after surgical resection [14,29].

The impact of PS on perioperative and long-term prognosis after surgical resection of HCC remains unclear. Therefore, the objective of the current study was to define the impact of PS on the short- and long-term outcomes among patients who underwent surgical resection of HCC. Such data may provide evidence to challenge the existing BCLC guidelines for the management of patients with advanced HCC (BCLC C stage) with PS-1.

Patients and methods

Study population

Consecutive patients who underwent surgical resection for HCC with curative intent at six medical institutions in China from January 2005 to December 2015 were identified using a multi-institutional database. The six medical centers were the Eastern Hepatobiliary Surgery Hospital, Ziyang First People's Hospital, Pu'er People's Hospital, Liuyang People's Hospital, Fourth Hospital of Harbin, and Mengchao Hepatobiliary Hospital. The study was approved by the institutional review boards and ethics committees at each institution. Inclusion criteria included 1) newly diagnosed HCC without previous anti-cancer treatment, 2) HCC confirmed by postoperative histopathological examination, 3) curative liver resection for HCC, which was defined as a R0 resection, 4) PS 0—1 and 5) complete records on all the important prognostic variables. Exclusion criteria included 1) recurrent HCC or combined HCC-cholangiocarcinoma, 2) R1 or R2 resection, 3) loss to follow-up immediately after liver resection, 4) patients with PS $\geq$ 2. PS was assessed using ECOG criteria based on the first consultation with a clinician at each respective hospital. The consistency and accuracy of the data were checked by the group coordinator (T.Y.). Any clarification or additional information was obtained, if required, from the involved participating institutions.

Baseline characteristics and operative variables

Baseline characteristics and operative variables were collected and reviewed from the medical records. Cirrhosis was confirmed by postoperative histopathological examination. Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a low platelet count of $<100 \times 10^9$/L. The tumor staging at diagnosis was presented for both the TNM (the 8th edition) and BCLC staging systems. A major hepatectomy was defined as resection of three or more Couinaud liver segments, while minor hepatectomy was resection of less than three segments. An anatomical resection was defined by the Brisbane 2000 Nomenclature of Liver Anatomy, while non-anatomical resections included a wedge resection or a limited resection.

Follow-up

Patients had routine followed-up at each participating institution. The postoperative surveillance strategy for HCC recurrence consisted of a physical examination, serum AFP, ultrasonography or contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest and abdomen every two months for the first 6 months, every 3 months thereafter for the next 18 months, and then once every 6 months at 2 years or later after resection at each institution. Tumor recurrence was defined as new appearance of intra- or extra-hepatic tumor nodule(s) with or without a rise in serum AFP level, as well as the presence of intrahepatic nodules that had typical imaging features consistent with characteristics of HCC on contrast-enhanced CT or MRI examination. Treatment of HCC recurrence was based on the pattern of the recurrent tumor, residual hepatic functional reserve, and general condition of the patient.

Statistical analysis

The baseline characteristics and operative variables between HCC patients in the PS-0 and PS-1 groups were summarized using frequencies and percentages for categorical variables and mean $\pm$ standard deviation (SD), or median (range) for continuous variables. Categorical variables were compared using the χ [2] test with the Yates correction or Fisher's exact test. Continuous variables were compared using the Student's *t*-test or Mann-Whitney ranked *U* test. Overall survival (OS) and recurrence-free survival (RFS) were estimated using the Kaplan-Meier curves and compared using the log rank test. Univariable and multivariable Cox regression analyses were used to identify any independent predictive factor that was associated with OS and RFS. Statistical analysis was performed using the IBM SPSS Statistics v25.0 (SPSS, Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and operative variables

Among the 2,037 patients identified from the six centers, 1,531 patients underwent curative surgical resection for HCC and comprised the analytic cohort Fig. 1. Patients were evenly distributed with regards to PS (PS-0: n = 836, 54.6% vs. PS-1: n = 695, 45.4%). Baseline characteristics and operative variables among PS-0 and PS-1 patients are reported in Table 1. According to the BCLC criteria, all 695 patients in the PS-1 group were categorized as BCLC stage C or advanced-stage HCC. The 836 patients in the PS-0 group were comprised of patients with early HCC (n = 466, 55.7%), intermediate HCC (n = 295, 35.3%), and advanced HCC (n = 75, 9.0%).

Short- and long-term outcomes after surgical resection

Short- and long-term outcomes after curative resection for HCC among patients who were PS-0 versus PS-1 are noted in Table 2. Perioperative mortality was similar (PS-0: 1.6% vs. PS-1: 1.4%; $P = 0.525$), however overall perioperative morbidity among PS-1 patients was higher compared with PS-0 patients (37.1% vs. 25.6%; $P < 0.001$). While there was no difference in the incidence of major morbidity (PS-0: 10.2% vs. PS-1: 9.7%; $P = 0.732$), minor morbidity was higher among patients in the PS-1 group (PS-0: 15.9% vs. PS-1: 26.9%; $P < 0.001$).

With a median follow-up of 51.3 months, 962 of 1,531 (62.8%) patients had developed HCC recurrence and 869 (56.8%) patients had died. Of note, the overall incidence of recurrence and death among PS-1 patients (68.9% and 70.2%, respectively) were higher compared with PS-0 patients (57.8% and 45.6%, respectively) (both $P < 0.001$). OS and RFS survival comparing PS-0 and PS-1 patients are shown in Fig. 2A and B. The PS-1 group had a worse median OS and RFS compared with the PS-1 group (34.0 vs. 107.6 months, $P < 0.001$; and 34.0 vs. 107.6 months, respectively, $P < 0.001$).

Univariable and multivariable analyses of OS and RFS

Univariable and multivariable analyses of OS and RFS after curative resection for HCC are detailed in Table 3 and Table 4. On multivariable Cox-regression analyses with robust estimators, PS-1 was strongly associated with decreased OS (HR: 1.301, 95% CI: 1.111−1.523, $P < 0.001$) and RFS (HR: 1.184, 95% CI: 1.034−1.358,

$P = 0.007$) after curative resection for HCC.

The PS-1 group of patients were further sub-classified into patients with or without VI/ES. The typical MRI imaging of a male patient with HCC with PS-1 and without VI/ES is shown in Supplementary Fig. 1. The OS and RFS survival comparing PS-1 with and without VI/ES are shown in Fig. 2C and D. Median OS and RFS among PS-1 patients without VI/ES were better than PS-1 patients with VI/ES (54.5 vs. 8.3 months, $P < 0.001$, and 35.3 vs. 2.7 months, respectively; $P < 0.001$); 5-year OS and RFS among the PS-1 patients without ES/VI were 43.1% and 27.7%, respectively ($P < 0.001$). Univariable and multivariable Cox-regression analysis of OS and RFS after curative resection of HCC among PS-1 patients are demonstrated in Supplementary Tables 1 and 2 On multivariable Cox-regression analyses with robust estimators, VI/ES was strongly associated with decreased OS (HR 2.416, 95% CI: 1.925−3.031) and RFS (HR 2.658, 95% CI: 2.102−3.362) ($P < 0.001$).

Discussion

PS is an important factor that is often used by clinicians to determine the appropriateness of a given therapy for a particular patient. PS is commonly utilized by medical oncologist to determine whether patients will tolerate systemic chemotherapy. More recently, PS has been incorporated into other treatment algorithms. One such treatment algorithm is the BCLC staging system. In fact, the BCLC advocates that patients with HCC who have a PS-1 not be considered as possible surgical candidates. The current study was important because it examined a large cohort of patients with HCC using a multi-institutional database. In particular, using a cohort of 1,531 HCC patients with PS-0 or PS-1, we sought to determine the impact of PS on both short- (perioperative mortality and morbidity) and long-term (overall and recurrence-free survivals) outcomes after curative-intent liver resection for HCC. In real-world clinical practice, PS-1 status is rarely used alone as an absolute contraindication for surgical resection of HCC [29,36], colorectal liver metastases [37], pancreatic cancer [38], or gastric cancer [39]. In the present study, we found that perioperative mortality and major morbidity among PS-1 patients were similar PS-0 patients, suggesting that surgical resection for PS-1 patients was as safe as among PS-0 patients. By using univariable and multivariable Cox-regression analyses, the results of this study demonstrated that patients with PS-1 had worse long-term outcomes as PS-1 was independently associated with worse OS and RFS. Therefore, as we think, routine exclusion of HCC patients with PS-1 from surgical resection as recommended by the BCLC guidelines is not warranted. In addition, on subgroup analysis of PS-1 patients, VI/ES was strongly associated with poor outcomes. However, PS-1 patients who did not have VI/ES had acceptable long-term survival after curative-intent liver resection. Collectively, such results may provide evidence to challenge the existing BCLC guidelines for the management of advanced HCC, and PS-1 patients with HCC should not be considered for liver resection.

A subset of patients with PS-1 could indeed undergo surgical resection with acceptable perioperative outcomes, as well as long-term survival. For example, we presented an example of a typical PS-1 patient who presented with a single small HCC on MRI that was less than 3 cm in diameter that was located in the liver under the right diaphragm. This exophytic tumor compressed the diaphragm resulting in persistent right upper quadrant abdominal pain with radiation to the right shoulder. Given that the PS was 1, the BCLC staging would classify this tumor as an advanced-stage (BCLC C) and would recommended treatment with a molecular targeted drug such as sorafenib rather than surgery. However, surgical resection was carried out for this patient and he is still alive and disease-free 4 years after surgery. This example demonstrates
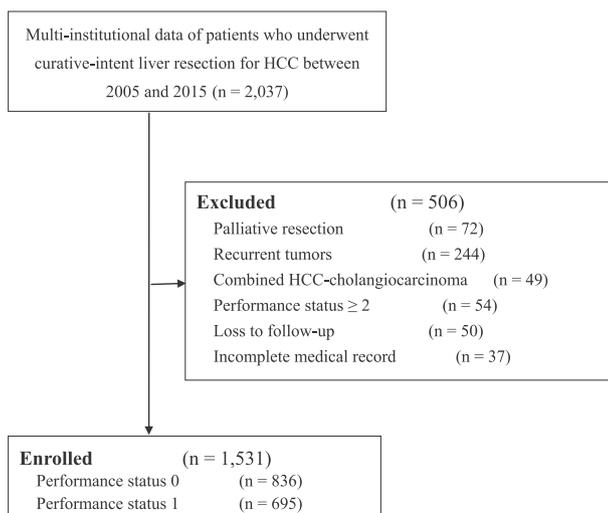

Fig. 1. Flow chart of study population. HCC, hepatocellular carcinoma.

Table 1
Comparison of patients' baseline characteristics and operative variables between performance status (ps)-0 and ps-1 patients with hepatocellular carcinoma.

N (%)	Total (N = 1531)	PS-0 Group (N = 836)	PS-1 Group (N = 695)	P
Age, years*	50.6 ± 10.9	51.5 ± 10.4	49.5 ± 11.4	<0.001
Gender				
Male	1354 (88.4)	765 (91.5)	589 (84.7)	<0.001
Female	177 (11.6)	71 (8.5)	106 (15.3)	
Diabetes mellitus	89 (5.8)	48 (5.7)	41 (5.9)	0.913
Cigarette smoking	485 (31.7)	262 (31.3)	223 (32.1)	0.783
Alcohol drinking	292 (19.1)	155 (18.5)	137 (19.7)	0.601
Co-morbid illness**	368 (24.0)	176 (21.6)	192 (27.6)	0.003
ASA score				
≤ 2	1310 (85.6)	724 (86.6)	586 (84.3)	<0.001
>2	221 (14.4)	112 (13.4)	109 (15.7)	
Etiology of liver diseases				
HBV	1387 (90.6)	767 (91.7)	620 (89.2)	0.003
HCV	43 (2.8)	28 (3.3)	15 (2.2)	
HBV + HCV	20 (1.3)	12 (1.4)	8 (1.2)	
Others	81 (5.3)	29 (3.5)	52 (7.5)	
Cirrhosis	1066 (70.0)	586 (70.1)	480 (69.1)	0.696
Portal hypertension	475 (31.0)	252 (30.1)	223 (32.1)	0.437
Child-Pugh grade				
A	1376 (89.9)	782 (93.5)	594 (85.5)	<0.001
B	155 (10.1)	54 (6.5)	101 (14.5)	
Preoperative platelet count, × 10^9/L*	142 (19–610)	134 (21–610)	151 (19–561)	<0.001
Preoperative ALT, U/L*	59.2 (7.5–1371.7)	54.8 (7.5–467.2)	64.4 (8.3–1371.7)	0.006
Preoperative AST, U/L*	54.4 (13.3–965.7)	45.7 (13.3–332.2)	65.0 (13.3–965.7)	<0.001
Preoperative AFP level				
≤ 400 μg/L	955 (62.4)	597 (71.4)	358 (51.5)	<0.001
>400 μg/L	576 (37.6)	239 (28.6)	337 (48.5)	
Maximum tumor size, cm*	6.3 ± 4.2	4.5 ± 2.7	8.4 ± 4.6	<0.001
≤ 5 cm	770 (50.3)	591 (70.7)	179 (25.8)	<0.001
>5 cm	761 (49.7)	245 (29.3)	516 (74.2)	
Tumor number				
Solitary	1127 (73.6)	659 (78.8)	468 (67.3)	<0.001
Multiple	404 (26.4)	177 (21.2)	227 (32.7)	
Satellites nodules	434 (28.3)	164 (19.6)	270 (38.8)	<0.001
Macroscopic vascular invasion	209 (13.7)	50 (6.0)	159 (22.9)	<0.001
Microscopic vascular invasion	853 (54.5)	367 (43.9)	486 (69.9)	<0.001
Extrahepatic spread	12 (0.8)	5 (0.6)	7 (1.0)	0.397
Poor differentiation	1245 (81.3)	629 (75.2)	616 (88.6)	<0.001
Preoperative tumor rupture	72 (4.7)	5 (0.6)	67 (9.6)	<0.001
TNM stage				
I	561 (36.6)	400 (47.8)	161 (23.2)	<0.001
II	530 (34.6)	309 (37.0)	221 (31.8)	
III	440 (28.7)	127 (15.2)	313 (45.0)	
BCLC stage				
A (Early)	466 (30.4)	466 (55.7)	0 (0)	<0.001
B (Intermediate)	295 (19.3)	295 (35.3)	0 (0)	
C (Advanced)	770 (50.3)	75 (9.0)	695 (100)	
Intraoperative blood loss, ml *	530 (50–8000)	381 (50–3000)	708 (50–8000)	<0.001
Intraoperative blood transfusion	353 (23.1)	103 (12.3)	250 (36.0)	<0.001
Extent of hepatectomy				
Major hepatectomy	447 (29.2)	131 (15.7)	316 (45.5)	<0.001
Minor hepatectomy	1084 (70.8)	705 (84.3)	379 (54.5)	
Type of resection				
Anatomical	462 (30.2)	231 (27.6)	231 (33.2)	0.019
Non-anatomical	1069 (69.8)	605 (72.4)	464 (66.8)	

*Values are mean ± standard deviation or median (range) unless otherwise indicated.
** Co-morbid illnesses include hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and renal dysfunction.
AFP, alpha-fetoprotein; ALT, Alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, Aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; PS, performance status; TNM, tumor-node-metastasis.

that PS-1 should not be used as a surgical contraindication [28–31].

Long-term prognosis of the PS-1 patients with HCC after curative resection was worse than the OS of PS-0 patients. In fact, on multivariable Cox-regression analysis, PS was an independent predictor of OS and RFS after curative liver resection for HCC. PS in general is considered to be a good physical parameter and prognostic indicator for cancer patients. Typically, PS has been used to assess short-term outcomes and anticipated ability of the patient to tolerate a therapy. Data from the current study were important as they demonstrated that PS was a strong predictor of long-term outcomes. Rather than being associated with perioperative

outcomes, in the current study, PS was more strongly associated with long-term outcomes. In addition, VI and ES affected long-term postoperative prognosis following resection of HCC [40–43]. In clinical practice, VI/ES are generally a contraindication to surgical resection. In the current study, 209 patients with VI and 12 patients with ES (including 5 with diaphragmatic metastasis, 4 with adrenal metastasis, and 3 with single intraperitoneal lymph node metastasis) underwent surgical resection with a curative intent (R0 resection). However, even among these patients who met the criterion of "curative-intent resection" (i.e. complete removal of all gross tumors with negative resection margins), postoperative

Table 2
Comparison of short-term and long-term outcomes between performance status (ps)-0 and ps-1 patients after curative resection of hepatocellular carcinoma.

N (%)	Total (N = 1531)	PS-0 Group (N = 836)	PS-1 Group (N = 695)	P
Perioperative death	23 (1.5)	12 (1.4)	11 (1.6)	0.525
Postoperative morbidity	472 (30.8)	214 (25.6)	258 (37.1)	<0.001
Minor morbidity (Clavien grade I-II)	320 (20.9)	133 (15.9)	187 (26.9)	<0.001
Major morbidity (Clavien grade III-V)	152 (9.9)	81 (9.7)	71 (10.2)	0.732
Period of follow-up, months*	60.0 ± 45.7	71.4 ± 44.3	46.3 ± 43.6	<0.001
Recurrence during the follow-up	962 (62.8)	483 (57.8)	479 (68.9)	<0.001
Death during the follow-up	869 (56.8)	381 (45.6)	488 (70.2)	<0.001
OS, months*	55.6 ± 3.1	91.2 ± 5.1	27.4 ± 1.7	<0.001
1-year OS rate	81.9	93.0	70.0	
3-year OS rate	60.3	76.3	43.3	
5-year OS rate	48.2	63.3	32.0	
10-year OS rate	29.0	38.2	19.1	
RFS, months*	29.4 ± 2.3	50.0 ± 4.0	15.2 ± 1.8	<0.001
1-year RFS rate	66.6	77.7	54.2	
3-year RFS rate	46.5	56.9	34.4	
5-year RFS rate	35.8	45.2	24.9	
10-year RFS rate	20.6	26.1	14.3	

*Values are median ± standard error.
OS, overall survival; PS, Performance status; RFS, recurrence-free survival.
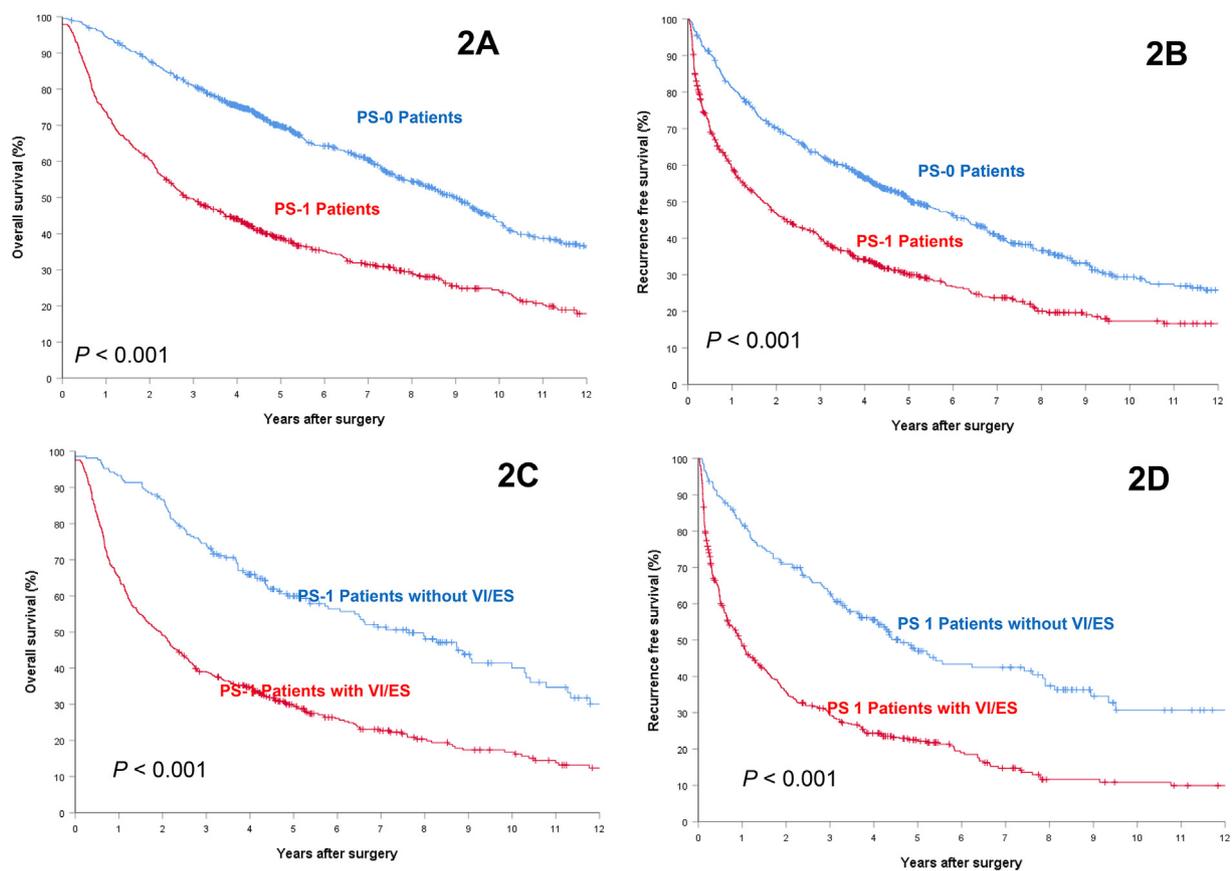
Fig. 2. Comparisons of overall survival (**2A**) and recurrence-free survival (**2B**) curves between patients with performance status (PS)-0 and PS-1, and comparison of overall survival (**2C**) and recurrence-free survival (**2D**) curves between PS-1 patients with and without macrovascular vascular invasion (VI)/extrahepatic spread (ES) (all *P* < 0.001, by log-rank test).

recurrence was very high and survival rate was low. To this point, in the subgroup analysis of PS-1 patients, PS-1 patients with VI/ES had 1-year OS and RFS of 65.2% and 43.2% versus 93.3% and 79.4% among PS-1 patients without VI/ES. By 5-years, only roughly 1 in 4 patients (27.8%) who were PS-1 and had VI/ES were alive compared with 43.1% for PS-1 patients who did not have VI/ES. As such, patients who are PS-1 and are without VI/ES should be considered for surgical resection as they benefited the most for this therapy.

The current study had several limitations. As a retrospective study, there was undoubtedly some selection bias regarding how patients were chosen for surgery. In addition, patients included in the current study were treated exclusively in China. The majority of patients with HCC had a background of hepatitis B virus (HBV)-related cirrhosis. In the USA and Europe, hepatitis C and excessive alcohol are the main etiological factors [44–47]. As such, the results from the present study require an external validation, especially

Table 3
Univariable and multivariable cox-regression analyses of overall survival after curative liver resection for hepatocellular carcinoma in the entire cohort.

Variable	Median OS ± SE (months)	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Age					
≤ 60 years	49.1 ± 3.9	0.990 (0.832–1.178)	0.908		
> 60 years	52.4 ± 8.4				
Gender					
Male	77.0 ± 3.8	1.111 (0.907–1.361)	0.311		
Female	63.3 ± 18.9				
Diabetes mellitus					
Yes	52.2 ± 10.4	1.257 (0.954–1.656)	0.104		
No	77.4 ± 3.9				
Co-morbid illnesses					
Yes	41.6 ± 5.4	1.679 (1.450–1.945)	<0.001	1.329 (1.139–1.551)	<0.001
No	89.3 ± 4.7				
HBV (+)					
Yes	75.5 ± 3.8	1.026 (0.813–1.295)	0.829		
No	91.6 ± 17.5				
HCV (−)					
Yes	89.8 ± 22.2	1.216 (0.834–1.773)	0.309		
No	76.4 ± 3.8				
ASA score					
> 2	38.1 ± 15.2	1.616 (1.280–2.037)	<0.001	1.650 (1.290–2.110)	<0.001
≤ 2	73.9 ± 8.7				
Performance status					
1	34.0 ± 3.0	2.301 (2.011–2.633)	<0.001	1.301 (1.111–1.523)	<0.001
0	108.2 ± 5.0				
Child-Pugh grade					
B	36.6 ± 5.0	1.720 (1.410–2.099)	<0.001	1.103 (0.887–1.371)	0.377
A	83.5 ± 4.3				
Cirrhosis					
Yes	64.6 ± 3.9	1.443 (1.237–1.683)	<0.001	1.159 (0.981–1.369)	0.082
No	106.5 ± 8.5				
Portal hypertension					
Yes	55.2 ± 5.3	1.365 (1.188–1.568)	<0.001	1.332 (1.143–1.552)	<0.001
No	88.1 ± 5.3				
Preoperative platelet count					
≤ 100 × 10^9/L	65.4 ± 5.6	0.909 (0.787–1.051)	0.200		
> 100 × 10^9/L	79.6 ± 4.4				
Preoperative ALT					
> 40 U/L	68.2 ± 5.3	1.169 (1.020–1.340)	0.025	0.947 (0.808–1.111)	0.503
≤ 40 U/L	80.4 ± 6.0				
Preoperative AST					
> 40 U/L	52.8 ± 4.3	1.669 (1.458–1.911)	<0.001	1.013 (0.851–1.205)	0.886
≤ 40 U/L	97.5 ± 5.8				
Preoperative AFP level					
> 400 μg/L	38.8 ± 4.4	1.795 (1.569–2.054)	<0.001	1.272 (1.101–1.470)	0.001
≤ 400 μg/L	93.4 ± 5.2				
Tumor rupture					
Yes	18.4 ± 8.1	2.691 (2.072–3.496)	<0.001	1.800 (1.367–2.371)	<0.001
No	80.4 ± 4.1				
Tumor size					
> 5 cm	37.2 ± 3.5	2.477 (2.159–2.843)	<0.001	1.300 (1.095–1.542)	0.003
≤ 5 cm	114.6 ± 4.0				
Macroscopic vascular invasion					
Yes	10.9 ± 1.3	5.376 (4.547–6.357)	<0.001	2.875 (2.379–3.475)	<0.001
No	91.7 ± 4.1				
Microscopic vascular invasion					
Yes	43.6 ± 4.2	2.117 (1.840–2.435)	<0.001	1.113 (0.948–1.306)	0.190
No	112.4 ± 5.6				
Extrahepatic spread					
Yes	5.9 ± 2.3	6.021 (5.354–6.728)	<0.001	3.546 (2.723–4.372)	<0.001
No	77.1 ± 3.7				
Tumor differentiation					
Poorly	63.3 ± 3.6	1.820 (1.503–2.205)	<0.001	1.150 (0.983–1.346)	0.081
Well or moderately	120.0 ± 6.8				
Tumor number					
Multiple	27.4 ± 2.1	2.558 (2.222–2.944)	<0.001	1.096 (1.045–1.150)	<0.001
Solitary	100.7 ± 4.5				
Satellites					
Yes	25.7 ± 2.4	2.865 (2.495–3.291)	<0.001	1.528 (1.275–1.830)	<0.001
No	103.6 ± 4.6				
Intraoperative blood loss					
> 400 ml	42.2 ± 3.6	1.957 (1.711–2.237)	<0.001	0.942 (0.787–1.127)	0.511
≤ 400 ml	104.0 ± 4.2				
Perioperative blood transfusion					

Table 3 (*continued*)

Variable	Median OS ± SE (months)	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P*
Yes	26.8 ± 2.7	2.327 (2.013–2.690)	<0.001	1.321 (1.090–1.601)	0.004
No	95.0 ± 4.1				
Extent of resection					
Major hepatectomy	28.3 ± 2.2	2.294 (1.997–2.635)	<0.001	1.226 (0.948–1.520)	0.074
Minor hepatectomy	97.5 ± 4.5				
Type of resection					
Anatomical	78.1 ± 8.7	1.108 (0.956–1.284)	0.172		
Non-anatomical	73.9 ± 4.5				

*Variables with a univariate P ≤ 0.10 were entered in the multivariate Cox regression model.

AFP, alpha-fetoprotein; ALT, Alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, Aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval; HR, hazard ratio; MV, multivariable; OS, overall survival; SE, standard error; UV, univariable.

Table 4
Univariable and multivariable cox-regression analyses of recurrence-free survival after curative liver resection for hepatocellular carcinoma in the entire cohort.

Variable	Median RFS ± SE (months)	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Age					
≤ 60 years	40.1 ± 2.7	0.964 (0.811–1.147)	0.683		
> 60 years	45.1 ± 6.6				
Gender					
Male	43.1 ± 2.7	1.113 (0.908–1.476)	0.302		
Female	35.8 ± 8.3				
Diabetes mellitus					
Yes	28.9 ± 6.0	1.154 (0.833–1.508)	0.296		
No	42.9 ± 2.6				
Co-morbid illness					
Yes	24.5 ± 3.5	1.646 (1.422–1.907)	<0.001	1.043 (0.892–1.221)	0.595
No	60.4 ± 5.1				
HBV (+)					
Yes	49.0 ± 3.6	1.145 (0.907–1.445)	0.254		
No	57.5 ± 21.1				
HCV (+)					
Yes	89.8 ± 22.2	1.243 (0.878–1.759)	0.220		
No	76.4 ± 3.8				
ASA score					
> 2	19.6 ± 7.8	1.655 (1.342–2.041)	<0.001	1.412 (1.130–1.767)	0.002
≤ 2	44.8 ± 9.6				
ECOG Performance status					
1	16.9 ± 2.0	2.264 (1.978–2.590)	<0.001	1.184 (1.034–1.358)	0.007
0	84.6 ± 5.2				
Child-Pugh grade					
B	19.2 ± 2.6	1.788 (1.465–2.181)	<0.001	1.226 (0.973–1.545)	0.084
A	55.2 ± 4.2				
Cirrhosis					
Yes	39.3 ± 3.7	1.483 (1.271–1.730)	<0.001	1.115 (0.957–1.298)	0.162
No	91.6 ± 12.8				
Portal hypertension					
Yes	36.0 ± 4.7	1.312 (1.142–1.507)	<0.001	0.980 (0.840–1.143)	0.796
No	58.5 ± 5.9				
Preoperative platelet count					
≤ 100 × 10^9/L	49.4 ± 6.4	0.928 (0.803–1.073)	0.313		
> 100 × 10^9/L	49.3 ± 4.1				
Preoperative ALT					
> 40 U/L	35.0 ± 3.3	1.247 (1.097–1.418)	0.001	1.077 (0.926–1.252)	0.338
≤ 40 U/L	40.0 ± 4.3				
Preoperative AST					
> 40 U/L	27.0 ± 3.2	1.745 (1.524–1.988)	<0.001	1.028 (0.872–1.212)	0.740
≤ 40 U/L	77.2 ± 7.0				
AFP					
> 400 µg/L	19.0 ± 3.3	1.777 (1.553–2.032)	<0.001	1.181 (1.028–1.356)	0.019
≤ 400 µg/L	69.8 ± 5.3				
Tumor rupture					
Yes	7.5 ± 4.2	2.458 (1.893–3.192)	<0.001	1.471 (1.109–1.950)	0.007
No	52.8 ± 4.2				
Tumor size					
> 5 cm	16.9 ± 1.7	2.467 (2.150–2.763)	<0.001	1.279 (1.093–1.496)	0.002
≤ 5 cm	91.6 ± 5.5				

Table 4 (*continued*)

Variable	Median RFS ± SE (months)	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Macroscopic vascular invasion					
Yes	2.9 ± 0.5	6.130 (5.166–7.273)	<0.001	3.249 (2.674–3.948)	<0.001
No	66.0 ± 4.5				
Microscopic vascular invasion					
Yes	21.6 ± 2.3	2.148 (1.867–2.471)	<0.001	1.116 (0.961–1.297)	0.149
No	93.5 ± 6.2				
Extrahepatic spread					
Yes	4.2 ± 3.1	7.023 (5.804–8.228)	<0.001	3.728 (2.953–4.527)	<0.001
No	40.1 ± 2.4				
Tumor differentiation					
Poorly	37.9 ± 3.3	1.893 (1.829–4.137)	<0.001	1.297 (1.118–1.505)	0.001
Well or moderately	99.5 ± 7.8				
Tumor number					
Multiple	11.6 ± 1.4	2.554 (2.218–2.940)	<0.001	1.063 (1.011–1.117)	0.016
Solitary	75.6 ± 5.6				
Satellites					
Yes	10.2 ± 1.1	2.954 (2.570–3.395)	<0.001	1.628 (1.367–1.939)	<0.001
No	79.8 ± 5.7				
Intraoperative blood loss					
> 400 ml	19.9 ± 2.5	1.891 (1.654–2.162)	<0.001	1.323 (0.968–1.303)	0.258
≤ 400 ml	79.9 ± 5.6				
Perioperative blood transfusion					
Yes	12.2 ± 2.0	2.232 (1.931–2.580)	<0.001	0.848 (0.716–1.004)	0.085
No	69.8 ± 5.0				
Extent of resection					
Major hepatectomy	12.8 ± 1.1	2.162 (1.890–2.472)	<0.001	1.186 (0.968–1.370)	0.082
Minor hepatectomy	59.5 ± 3.8				
Type of resection					
Anatomical	47.7 ± 3.9	1.096 (0.946–1.270)	0.223		
Nonanatomical	51.8 ± 7.8				

*Variables with a univariate P ≤ 0.10 were entered in the multivariate Cox regression model.
AFP, alpha-fetoprotein; ALT, Alanine aminotransferase; ASA, American Society of Anesthesiologists; AST, Aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; CI, confidence interval; HR, hazard ratio; MV, multivariable; RFS, recurrence-free survival; SE, standard error; UV, univariable.

from the West, to ensure the findings can be generalized to a broader population of patients. Last but not least, in the present study, we only enrolled patients undergoing liver resection for HCC, but not patients suffering from other therapies. Therefore, we could not compare long-term prognosis between patients with different therapeutic options, especially for patients with PS 1. More retrospective even and prospective studies on patients with PS 1 HCC undergoing different treatments need to be conducted to explore if surgical resection can be a better option or not for this specific population.

In conclusion, surgical resection for PS-1 HCC patients was as safe as PS-0 patients. PS-1 patients should not be routinely and necessarily considered as advanced stage of disease as recommended by the BCLC staging system. Although PS-1 was an independent risk factor of decreased OS and RFS after curative HCC resection, surgical resection was feasible with acceptable long-term survival outcomes in patients with PS-1 HCC, especially patients who did not have VI/ES. These results provided evidence to challenge the existing BCLC guideline for management of patients with advanced HCC (BCLC C stage) with PS-1.

Authors' contributions

Drs H. Wu, Xing, Liang, Huang and Li contributed equally to this work. Dr Tian had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** H. Wu, Xing, Li, Yang, Shen. **Acquisition, analysis, or interpretation of data:** H. Wu, Xing, Liang, Huang, Li, Zhou, Gu, H. Wang, Chen, Zhang, Zeng, M. Wang. **Drafting of the manuscript:** H. Wu, Xing, Lau, Shen, Yang. **Critical revision of the manuscript for important intellectual content:** Lau, Pawlik, M. Wu, Shen, Yang. **Statistical analysis:** H. Wu, Xing, Liang, Yang. **Obtained** funding**:** Yang. **Administrative, technical, or material** support**:** Zhou, Gu, H. Wang, Chen, Zeng, M. Wang, M. Wu, Shen, Yang. **Study supervision:** M. Wu, Shen, Yang.

Conflicts of interest

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.09.009.

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