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Defining the chance of cure after resection for hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer guidelines: A multi-institutional analysis of 1,010 patients

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ABSTRACT

Background: Surgery is considered the only potentially curative treatment option for patients with hepatocellular carcinoma. However, the chance that patients will eventually be "cured" after liver resection for hepatocellular carcinoma remains ill defined.
Methods: Patients who underwent curative-intent hepatectomy for hepatocellular carcinoma between 1998 and 2017 were identified using an international multi-institutional database. A nonmixture cure model was used with disease-free survival as a primary measure to estimate cure fractions after matching patients with the general population by age, race, and sex.
Results: Among 1,010 patients, the median and 5-year disease-free survival were 2.8 years and 36.6%, respectively. The probability of being cured after hepatocellular carcinoma resection was 42.2% and the median time to cure was 3.35 years. The multivariable cure model revealed preoperative alpha-fetoprotein level, tumor size, tumor number, and margin status as independent predictors of cure. The cure fraction for patients with an alpha-fetoprotein level $\leq$ 10 ng/mL, largest tumor size $\leq$5 cm, $\leq$3 nodules, and R0 resection was 61.6%. In contrast, patients who had all 4 unfavorable prognostic factors (ie, alpha-fetoprotein >11 ng/mL, nodules $\geq$4, size >5cm, R1 resection) had a cure fraction of 15.8%. Although the probability of cure was 47.6% among Barcelona Clinic Liver Cancer-A patients, patients undergoing resection for Barcelona Clinic Liver Cancer-B hepatocellular carcinoma had a 37.6% cure fraction. Only alpha-fetoprotein levels predicted the probability of cure among Barcelona Clinic Liver Cancer-B patients.
Conclusion: Roughly 4 in 10 patients could be considered "cured" after liver resection for hepatocellular carcinoma. Although cure was achieved more often after resection for Barcelona Clinic Liver Cancer-A

Author contribution: Drs Tsilimigras and Bagante contributed equally to this work.

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hepatocellular carcinoma, surgery still provided a reasonable probability of cure among select patients with Barcelona Clinic Liver Cancer-B hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and accounts for more than 70% of primary liver malignancies.[1,2] Possible etiologies related to the development of HCC include cirrhosis, hepatitis B and C infection, alcohol abuse, and nonalcoholic fatty liver disease.[3] In the United States, HCC is the fastest rising cause of cancer-related deaths, with model-based simulations forecasting a continued increase in the incidence of HCC until at least 2030.[3,4] Surgery—in the form of liver resection or transplantation—is still considered the only potentially curative treatment option for patients with HCC. However, the percentage of patients who will eventually be “cured” after liver resection for HCC remains ill defined.

In epidemiologic studies, “cure” is often defined as the time when the mortality risk of patients treated for a particular disease reaches a level expected in the general population.[5,6] Although first introduced in the statistical literature, cure models have been particularly popular recently among clinicians because these models can help answer real-world questions about the probability of “cure” after treatment for cancer.[7] Indeed, previous investigators have reported on the probability of cure among patients with various types of tumors, including colorectal, pancreas, breast, and prostate cancer.[8] Our group has also assessed the probability of cure among patients undergoing resection for intrahepatic cholangiocarcinoma, extrahepatic biliary tract cancer, and neuroendocrine liver metastases.[9–11] Nevertheless, the possibility of cure after resection of HCC remains largely unknown.

The use of cure models may be particularly relevant to patients with HCC, especially given that surgical resection for patients beyond the Barcelona Clinic Liver Cancer (BCLC) guidelines has been a matter of great debate. According to the BCLC guidelines, liver resection should be offered only to patients with very early (ie, BCLC-0) and early stage (ie, BCLC-A) HCC.[12] Recently, however, a number of studies have advocated for resection beyond the BCLC criteria (ie, BCLC-B/C patients), with favorable results among select HCC patients.[13–15] However, although liver resection has been associated with acceptable long-term survival, whether it can provide a long-term “cure” for patients with early (BCLC-A) and especially intermediate stage (BCLC-B) HCC remains largely unknown. As such, the objective of the current study was to define the probability of cure after curative-intent resection for HCC. In addition, using a large multi-institutional database, we sought to identify factors associated with the probability of cure within (ie, BCLC-A) and beyond (ie, BCLC-B) the BCLC resection criteria.

Materials and Methods

Study population and data collection

Patients who underwent curative-intent resection for HCC between 1998 and 2017 were identified from an international multi-institutional database. Patients were treated at 1 of the 11 participating institutions:

- The Ohio State University Wexner Medical Center, Columbus, OH, USA
- Yokohama City University School of Medicine, Japan
- University of Verona, Italy
- Ospedale San Raffaele, Milano, Italy
- Curry Cabral Hospital, Lisbon, Portugal
- APHP, Beaujon Hospital, Clichy, France
- Westmead Hospital, Sydney, Australia
- Stanford University, Stanford, CA, USA
- Fundeni Clinical Institute, Bucharest, Romania
- University of Ottawa, ON, Canada
- The University of Sydney, School of Medicine, Australia

Patients were followed and outcomes were recorded in a multi-institutional database. Patients with very early (BCLC-0), early (BCLC-A), or intermediate (BCLC-B) stage HCC were included in the analytic cohort. According to the latest European Association for the Study of the Liver classification, BCLC-0 was defined as a single tumor <2 cm; BCLC-A was defined as a single tumor ≥2 cm or 2–3 nodules, all <3cm. BCLC-B was defined as 2–3 nodules ≥3 cm or ≥4 nodules.[12] Individuals with advanced stage (BCLC-C) HCC, an R2 resection, missing follow-up data, as well as individuals who died within 90 days from surgical resection were excluded ($n = 36$). The study was approved by the institutional review boards of all participating institutions.

Demographic and clinical data included sex; age; BCLC stage; histologic evidence of cirrhosis; Child-Pugh class; type of surgical resection (ie, minor or major); alpha-fetoprotein (AFP) levels; tumor grade, size, and number; pathologic lymphovascular invasion; and liver capsule involvement, as well as margin status (ie, R0, R1). Major hepatectomy was defined as resection of 3 or more Couinaud segments. For the purpose of this study, AFP levels were categorized into 3 groups (≤10 ng/mL, 11–400 ng/mL, and >400 ng/mL) based on earlier studies.[16,17] Assessment of postoperative morbidity was performed according to the Clavien-Dindo classification system.[18]

Statistical analysis

Descriptive statistics were presented as median (interquartile range) and frequency (%) for continuous and categorical variables, respectively. Univariate survival analyses were performed using the log-rank test and presented using Kaplan-Meier curves. Variables significant on univariate analysis were entered into the multivariable Cox regression model and backward step selection was used to eliminate nonsignificant variables based on a P value <.10. The level of statistical significance was set at $\alpha = 0.05$. All analyses were performed using STATA v 12.0 (StataCorp LP, College Station, TX).

Disease-free survival and cure fraction model

Disease free-survival (DFS) was defined as the time interval between the date of hepatectomy and the date of disease relapse or last follow-up. Overall survival (OS) was defined as the time interval between the date of hepatectomy and the date of death by any cause or last follow-up. To estimate the statistical chance of “cure,” we utilized the cure models defined as

$$S(t) = \pi + (1 - \pi)^{*} S_u(t)$$

Where π is the proportion of cured patients and $S_u(t)$ is the survival function for the uncured individuals. Cure models presume

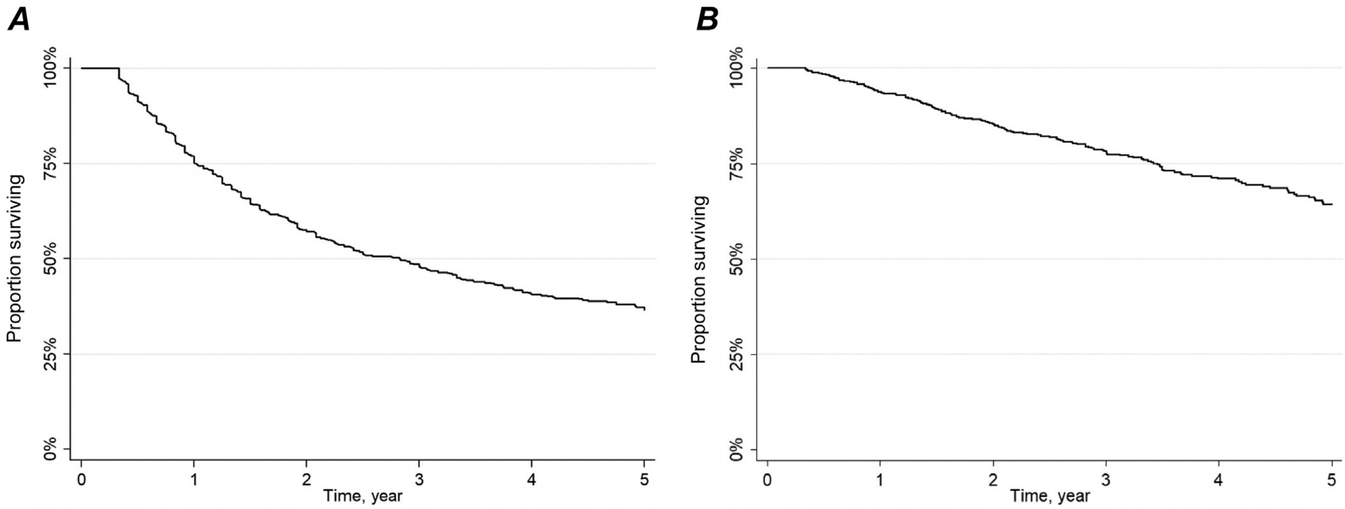

Fig 1. Kaplan-Meier curve depicting (*A*) the DFS and (*B*) the OS of patients who underwent liver resection for HCC.

that a group of patients can be considered "cured" when the sum of their excess and expected hazards of death (observed hazard rate) is equal to the hazard of death of the general population (matched by age, race, and sex) and, consequently, the risk of death among these individuals reaches that of the general population.

Application of a cure model presumes the concept that the statistical plausibility of cure can be fulfilled.[5] As presented in Fig 1, *A*, a plateau of DFS is reached after a period of time for certain individuals who underwent liver resection for HCC. Cure models define "cure" as occurring when the survival time tends to infinite. In this study, the nonmixture cure fraction model was applied to identify the fraction of patients who can be considered "cured" after liver resection for HCC.[6,19,20] As described elsewhere,[10,11] the nonmixture cure model is a parametric cure model that estimates an asymptote for the survival function at the cure proportion. In addition, time to cure was calculated. It is considered as the minimum time after HCC resection that an individual survives before being considered "cured." In the context of the current study, time to cure was calculated assuming a 99% level of confidence (α = 0.01). To implement the cure model, expected survival and the hazard of death among the general population was estimated using the data of population survival from US life tables, matched by age, race, and sex.[21]

Results

Patient characteristics

A total of 1,010 patients who underwent curative-intent resection for HCC met the inclusion criteria and were included in the analytic cohort. Among the entire cohort, most patients were male (n = 769, 76.1%) and aged >65 years (n = 563, 55.7%; median age: 67 years, interquartile range:59–74) (Table I). History of cirrhosis was present in 41.4% (n = 418) of patients and most had Child-Pugh A liver function (n = 405 out of 418, 96.9%). The vast majority of patients had a solitary (n = 807, 79.9%), well/moderately differentiated tumor (n =824, 81.6%), size ≤5 cm (n = 564, 54.1%), and preoperative AFP levels ≤400ng/mL (n = 787, 77.8%). Roughly one-third of patients (n = 358, 35.4%) underwent major resection. Only 82 (8.1%) of patients underwent portal vein embolization before resection. On pathology, 39.5% (n = 399) of patients had lymphovascular invasion, and 22.4% (n = 226) had liver capsule involvement. The vast majority of patients had an R0 resection (n = 875, 86.6%).

Among the 1,010 patients, 830 (82.2%) had BCLC-0/A HCC; whereas 180 (17.8%) had BCLC-B HCC. Perhaps not surprising, patients undergoing resection for BCLC-B HCC were more likely to have a major resection (BCLC-B: n = 84, 46.7% versus BCLC-0/A: n = 274, 33.1%, P = .001), higher incidence of lymphovascular invasion (BCLC-B: n = 94, 52.2% versus BCLC-0/A: n = 305, 36.7%, P < .001), liver capsule involvement (BCLC-B: n = 60, 33.3% versus BCLC-0/A: n = 166, 20.0%, P < .001), and an R1 resection (BCLC-B: n = 34, 18.9% versus BCLC-0/A: n = 101, 12.2%, P = .016) (Table I).

Cure fraction model

After a median follow-up of 2.7 years, median and 5-year DFS were 2.8 years and 36.6% (95% CI 32.8–40.5), respectively (Fig 1, *A*, Supplemental Table I) and 5-year OS was 64.4% (95% CI 59.2–69.1) (Fig 1, *B*). Overall, the probability of being cured after HCC resection was 42.2% (95% CI 37.7–46.8). The time to cure was 3.35 years (95% CI 2.88–3.89), and the median survival of uncured patients was 1.44 years (95% CI 1.31–1.58) (Table II, Fig 2, *A*). In the entire group, the excess hazard of death began at 10% early after liver surgery (after 90 days) and increased to 30% in the first 2 postoperative years (Fig 2, *B*). In contrast, among uncured patients, the excess hazard of death began at 34% early after liver surgery (after 90 days) and progressively increased over time, reaching approximately 140% 5 years postoperatively. Among the entire cohort, the excess hazard of death progressively decreased until a 99% level of confidence at 3.35 years (95% CI, 2.88–3.89) postoperatively, indicating that patients who remained alive after this time point could be considered cured with 99% certainty.

Cure fractions, time to cure, and median survival of uncured patients stratified by different clinicopathologic factors are summarized in Table II. Factors determining the probability of cure included BCLC stage, AFP levels, tumor size, tumor number, presence of lymphovascular invasion, liver capsule involvement and margin status (all P < .05). After assessing these factors in a multivariable cure model, only AFP level, tumor size, tumor number, and margin status remained independent predictors of cure (Table III). For example, the cure fraction for patients with a preoperative AFP level ≤10 ng/mL, largest tumor size ≤5 cm, ≤3 nodules, and R0 resection was 61.6% (95% CI 54.4–68.7). This value represented the highest probability of cure that could be achieved

Table I
Baseline characteristics of 1,010 patients who underwent surgery for HCC

Variables	Entire cohort (n = 1,010)	BCLC 0-A (n = 830)	BCLC B (n = 180)	P value
Sex				
Female	241 (23.9%)	209 (25.2%)	32 (17.8%)	.035
Male	769 (76.1%)	621 (74.8%)	148 (82.2%)	
Age, y				
≤65	447 (44.3%)	372 (44.8%)	75 (41.7%)	.44
>65	563 (55.7%)	458 (55.2%)	105 (58.3%)	
BCLC				
0-A	830 (82.2%)	-	-	
B	180 (17.8%)			
Liver resection				
Minor	652 (64.6%)	556 (66.9%)	96 (53.3%)	.001
Major	358 (35.4%)	274 (33.1%)	84 (46.7%)	
Cirrhosis				
Absent	592 (58.6%)	495 (59.6%)	97 (53.9%)	.16
Present	418 (41.4%)	335 (40.4%)	83 (46.1%)	
Child-Pugh classification*				
A5	291 (69.6%)	234 (69.9%)	57 (68.7%)	.95
A6	114 (27.3%)	91 (27.2%)	23 (27.7%)	
B7	13 (3.1%)	10 (2.9%)	3 (3.6%)	
AFP, ng/mL				
≤10	464 (45.9%)	392 (47.2%)	72 (40.0%)	.14
11–400	323 (31.9%)	263 (31.7%)	60 (33.3%)	
>400	223 (22.1%)	175 (21.1%)	48 (26.7%)	
Size, cm				
≤5	546 (54.1%)	476 (57.4%)	70 (38.9%)	<.001
>5	464 (45.9%)	354 (42.6%)	110 (61.1%)	
Number of tumors				
1	807 (79.9%)	793 (95.5%)	-	<.001
2–3	149 (14.8%)	37 (4.5%)	126 (70.0%)	
≥4	54 (5.4%)	-	54 (30.0%)	
Grade				
Well-moderate	824 (81.6%)	679 (81.8%)	145 (80.6%)	.69
Poor	186 (18.4%)	151 (18.2%)	35 (19.4%)	
Lymph-vascular invasion				
Absent	611 (60.5%)	525 (63.3%)	86 (47.8%)	<.001
Present	399 (39.5%)	305 (36.7%)	94 (52.2%)	
Liver capsule involvement				
No	784 (77.6%)	664 (80.0%)	120 (66.7%)	<.001
Yes	226 (22.4%)	166 (20.0%)	60 (33.3%)	
Margin status				
R0	875 (86.6%)	729 (87.8%)	146 (81.1%)	.016
R1	135 (13.4%)	101 (12.2%)	34 (18.9%)	

BCLC, Barcelona Clinic Liver Cancer; *AFP*, alpha-fetoprotein; *HCC*, hepatocellular carcinoma
* Among 418 patients with cirrhosis.

for patients undergoing resection for HCC. In contrast, patients with an AFP level >11 ng/mL who underwent R0 resection for ≤3 nodules, with the largest one being >5 cm had a 38.9% probability of cure. Of note, when all 4 unfavorable prognostic factors were present (ie, AFP >11 ng/mL, nodules ≥4, size >5 cm, R1 resection) the cure fraction was only 15.8% (Table III).

BCLC-stage specific cure probabilities

The probability of being cured after BCLC-0/A HCC resection was 47.6% (95% CI 40.3–54.9). The time to cure was 3.56 years (95% CI 2.80–4.54), and the median survival of uncured patients was 1.70 years (95% CI 1.46–1.97). Among BCLC-B patients who underwent liver resection, the probability of being cured was 37.6% (95% CI 32.2–43.5). The time to cure was 3.12 years (95% CI 2.58–3.76), and the median survival of uncured patients was 1.26 years (95% CI 1.12–1.41) (P < .001, Table II).

To further identify subgroups of patients with favorable outcomes within BCLC-A and BCLC-B stage, a stage-specific subgroup analysis of cure fraction models was performed (Table IV). Of note, factors determining the probability of cure among BCLC-A patients included AFP level (<10 ng/mL: 48.7% versus 11–400 ng/mL: 41.7% versus >400 ng/mL: 38.0%, P = .002) tumor size (≤5 cm: 47.1% versus >5cm: 39.9%, P = .001), number of tumors (n = 1, 44.9% versus n = 2–3, 29.1%, P = .038), presence of lymphovascular invasion (absent: 49.6% versus present: 34.5%, P < .001), liver capsule involvement (absent: 46.2% versus present: 34.7%, P = .017), and margin status (R0: 46.5% versus R1: 25.8%, P < .001). In contrast, only AFP level (<10 ng/mL: 46.7% versus 11–400 ng/mL: 21.9% versus >400 ng/mL: 7.1%, P = 0.017) was associated with the probability of cure among BCLC-B patients.

Assessment of postoperative morbidity

Overall, 388 (38.4%) patients had a complication after resection for HCC, with the majority experiencing minor complications (Clavien-Dindo grade <III; n = 230, 59.3% of patients with complications). Perhaps not surprising, patients who underwent resection for BCLC-0/A HCC had a lower incidence of postoperative complications (n = 305, 36.8%) compared with patients undergoing resection for BCLC-B HCC (n = 83, 46.1%, P = .019). Nevertheless, the number of patients with severe complications (Clavien-Dindo grade ≥III) was similar between the 2 groups (BCLC-0/A, n = 123 out of 830, 14.8% versus BCLC-B, n = 35 out of 180, 19.4%, P = .76).

Table II
Cure fraction models based on DFS for the whole cohort of 1,010 patients

Variables	Cure fraction (95% CI)	Time to cure (95% CI)	Median survival of uncured (95% CI)	*P* value
Study population	42.2% (37.7–46.8)	3.35 y (2.88–3.89)	1.44 y (1.31–1.58)	—
Sex				
Female	45.6% (37.2–54.3)	3.07 y (2.34–4.01)	1.42 y (1.19–1.69)	.44
Male	40.9% (35.8–46.4)	3.45 y (2.89–4.13)	1.45 y (1.29–1.61)	
Age				
≤65	42.7% (36.3–48.8)	3.39 y (2.71–4.24)	1.36 y (1.18–1.56)	.94
>65	41.9% (35.5–48.6)	3.27 y (2.68–3.99)	1.50 y (1.33–1.70)	
BCLC				
0-A	47.6% (40.3–54.9)	3.56 y (2.80–4.54)	1.70 y (1.46–1.97)	< .001
B	37.6% (32.2–43.5)	3.12 y (2.58–3.76)	1.26 y (1.12–1.41)	
Liver resection				
Minor	42.8% (35.9–47.9)	3.69 y (3.02–4.50)	1.59 y (1.41–1.79)	.22
Major	42.1% (35.5–49.1)	2.80 y (2.26–3.47)	1.21 y (1.06–1.39)	
Cirrhosis				
Absent	45.4% (39.7–51.1)	3.06 y (2.53–3.70)	1.36 y (1.21–1.54)	.19
Present	37.2% (30.0–44.9)	3.79 y (2.96–4.85)	1.55 y (1.34–1.79)	
Child-Pugh classification*				
A5	30.1% (20.8–41.4)	4.87 y (3.35–7.06)	1.74 y (1.43–2.13)	.86
A6	45.1% (32.9–57.8)	2.94 y (2.07–4.19)	1.37 y (1.08–1.76)	
B7	-	-	-	
AFP, ng/mL				
≤10	49.5% (42.7–56.3)	3.13 y (2.53–3.87)	1.56 y (1.36–1.79)	.001
11–400	38.9% (31.9–46.6)	3.08 y (2.46–3.86)	1.36 y (1.18–1.56)	
>400	32.5% (23.2–43.4)	4.17 y (2.78–6.25)	1.34 y (1.06–1.69)	
Size, cm				
≤5	45.6% (39.2–52.2)	3.53 y (2.88–4.33)	1.66 y (1.46–1.88)	.002
>5	38.7% (32.7–45.2)	2.97 y (2.38–3.71)	1.21 y (1.06–1.38)	
Number of tumors				
1	44.5% (39.1–50.0)	3.49 y (2.87–4.25)	1.48 y (1.32–1.67)	< .001
2-3	30.6% (21.7–41.1)	3.19 y (2.38–4.28)	1.27 y (1.07–1.49)	
≥4	-	-	-	
Grade				
Well-moderate	42.6% (37.6–47.7)	3.39 y (2.90–3.97)	1.51 y (1.37–1.67)	.26
Poor	41.5% (31.7–52.0)	2.72 y (1.75–4.24)	1.09 y (0.85–1.39)	
Lymph-vascular Invasion				
Absent	47.5% (41.6–53.6)	3.29 y (2.70–4.01)	1.56 y (1.37–1.77)	< .001
Present	34.1% (27.6–41.3)	3.43 y (2.72–4.29)	1.29 y (1.12–1.49)	
Liver capsule involvement				
No	43.6% (38.4–49.0)	3.46 y (2.88–4.16)	1.48 y (1.33–1.66)	.031
Yes	36.4% (28.0–45.7)	3.07 y (2.38–3.97)	1.32 y (1.12–1.55)	
Margin status				
R0	44.8% (39.9–49.7)	3.27 y (2.78–3.86)	1.47 y (1.33–1.63)	.001
R1	26.7% (15.4–37.1)	3.84 y (2.68–5.49)	1.26 y (1.01–1.56)	

BCLC, Barcelona Clinic Liver Cancer; *AFP*, alpha-fetoprotein; *DFS*, disease-free survival; *CI*, confidence interval.
* Among 418 patients with cirrhosis.

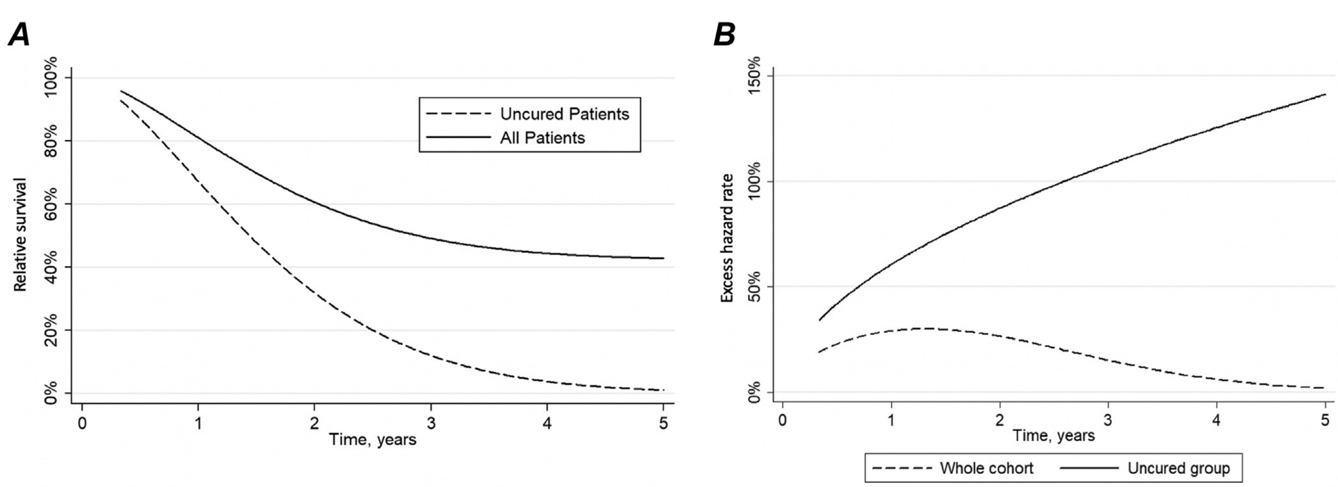

Fig 2. Cure model results depicting (*A*) the relative survival of patients in the total cohort and uncured patients. Cure model results demonstrating (*B*) the excess hazard of death of patients in the total cohort and uncured patients.

Table III
Multivariable cure model

Variables	Coefficient (95% CI)	*P* value
Constant	61.6% (54.4 to 68.7)	–
AFP, ≥11	−11.8% (−18.9 to −4.8)	.001
Size, >5 cm	−10.9% (−17.9 to −3.9)	.002
Number of tumors, ≥4	−11.9% (−19.7 to −4.2)	.003
Margin STATUS, R1	−11.2% (−19.6 to−2.8)	.008

CI, confidence interval; *AFP*, alpha-fetoprotein.

Discussion

In the United States, the incidence of HCC has been steadily increasing over the past 3 decades with a concomitant increase in HCC mortality rates.[1,3] Before implementing any treatment, clinicians and patients often desire information about the risk of recurrence, prognosis, and, in particular, the possibility of "cure" after relevant therapeutic interventions.[7] Although traditional survival analyses assess the long-term outcomes of patients after treatment for cancer, the use of cure models may be more appropriate in the determination of the chance to be cured.[5,20] As such, an increasing number of studies have applied these models for a variety of cancers, including gastrointestinal, breast, and prostate cancers.[8] To date, however, no study has assessed the chance of cure and the interaction of various clinicopathologic factors after resection for HCC. The current study was important because, using a large international multi-institutional database, we assessed the probability of cure after resection for HCC. Of note, the overall chance of cure among patients undergoing resection for HCC was 42.2%, which could be achieved after a median time of 3.35 years. Among patients with the most favorable characteristics (ie, AFP level ≤10 ng/mL, largest tumor size ≤5 cm, ≤3 nodules, and R0 resection), the chance of cure was 61.6%; whereas among patients with all 4 unfavorable prognostic factors (AFP level ≥11 ng/mL, largest tumor size >5 cm, ≥4 nodules, and R1 resection), the cure fraction was only 15.8%. Of note, patients with BCLC-0/A tumors had a 47.6% chance of cure; whereas the chance of cure decreased to 37.6% among BCLB-B patients who underwent liver resection.

First introduced by Boag[22] and Berkson and Gage,[23] cure models have recently gained popularity because of their significant advantages over traditional survival analyses. Indeed, the assumptions of traditional proportional hazards models often fail when survival curves plateau at their ends. In contrast, cure models are better able to characterize the heterogeneity in the plateau areas of survival plots.[5] In addition, cure models allow investigators to estimate the probability of cure based on separate clinicopathologic factors and even combine these factors in multivariable models.[6] Information on cure can be particularly relevant in the clinical setting because clinicians are frequently asked to answer the most challenging of prognostic questions: "What is my probability of being cured?" Data from the current study are important as empiric information to provide caregivers an objective—rather than arbitrary—estimation of the cure probability after HCC resection. In turn, such information can bridge the gap between patient and provider perception of "cure" after cancer surgery.[24]

Several studies have investigated the probability of cure for other diseases, including colorectal, pancreas, breast, and prostate cancers.[8] Of note, our own group had reported on the probability of cure among patients undergoing resection for hepatobiliary malignancies such as intrahepatic cholangiocarcinoma, extrahepatic biliary tract cancer, and neuroendocrine liver metastases.[9–11] To date, however, no study had explicitly investigated cure fraction, time to cure, and survival of uncured patients related to various clinical scenarios among patients undergoing resection of HCC. Using statistical cure modeling, we estimated that the probability of cure after liver resection was 42.2%. As expected, certain prognostic factors were identified as predictors of "cure" in the multivariable cure model, including preoperative AFP level, tumor size, tumor number, and margin status. Perhaps of more interest, even in the best-case scenario (ie, patients with AFP levels ≤10 ng/mL, largest tumor size ≤5 cm, ≤3 nodules, and R0 resection), approximately only 6 out of 10 patients achieved cure after liver resection (cure fraction: 61.6%), which was worse than the reported probability of cure after liver transplantation for HCC (74.1%).[25] Nevertheless, patients undergoing transplantation are selected even more rigorously than individuals who are typically offered resection. As such, direct comparison of these 2 surgical approaches are difficult to interpret and limited in nature.[25] Data from the current study did indicate that a patient who was alive and free of disease at 3.35 years after resection could be considered cured with 99% certainty. Although the reason for long-term cure is certainly multifactorial, in the current era, direct-acting antivirals against the hepatitis C virus may significantly improve the long-term outcomes of patients with hepatitis C virus-related decompensated cirrhosis.[26] Furthermore, the excess hazard of death in the entire cohort increased to 30% in the first 2 postoperative years and subsequently decreased to 0 at 3.35 years. In contrast, among uncured patients, the excess hazards of death steadily increased over the years, reaching 140% at 5 years postoperatively. Collectively, these data may assist physicians in determining appropriate postoperative surveillance protocols, as well as help patients understand their chance of cure after surgery for HCC.

To date, several systems have been proposed to inform prognosis and guide treatment decision-making for patients with HCC. The BCLC classification system has been traditionally used by clinicians in the West and has been endorsed in the most recent EASL guidelines.[12,27] Although the BCLC system suggests a stage-specific prognosis, data on the possibility of "cure" for each stage are lacking. In addition, although this system recommends surgery only for patients with very early (BCLC-0) and early (BCLC-A) HCC, several investigators have advocated that resection should be considered for select patients beyond the BCLC criteria (ie, BCLC-B or even BCLC-C HCC). The original BCLC system was updated in 2011 to designate single large tumors (≥5 cm) as BCLC-A rather than as BCLC-B HCC.[12] However, a number of studies have demonstrated acceptable outcomes even after resection of multinodular HCC (Table V). Matsukuma et al[28] reported a 5-year OS of 44.8% after resection for BCLC-B HCC; whereas other investigators reported a 5-year OS as high as 63% after resection for such patients.[13,29] Of note, our own group has demonstrated a comparable 5-year OS among patients undergoing resection for BCLC-B and BCLC-A1 (single tumor >5cm) HCC (49.9% vs 56.9%, $P = .259$).[30] Whether surgery can provide a long-term "cure" for these patients is largely unknown, however. In the current study, among 1,010 patients who underwent resection for HCC, 830 (82.2%) had BCLC-0/A and 180 (17.8%) had BCLC-B disease. Among BCLC-0/A patients, the probability of cure after resection was 47.6%; whereas, among BCLC-B patients, the probability of being cured was 37.6%. Although the chance of cure after resection of BCLC-B HCC lesions was lower than BCLC-0/A patients, a substantial subset of patients still had a chance at cure. As such, although some treatment recommendation algorithms claim that BCLC-B patients should not be considered for hepatic resection, data from the current study would suggest otherwise. In fact, patients with a low AFP <10 ng/mL had a probability of cure as high as 46.7%. In contrast, individuals with an AFP >400 ng/mL had less than a 10% chance of cure after liver resection for BCLC-B HCC. Of note, margin status did not appear to impact cure rates after resection for BCLC-B HCC; however, likely not enough power existed to identify a significant association because of the low number

Table IV
BCLC-stage (BCLC-A and B) specific cure fraction model

Variables	BCLC A Cure fraction (95% CI)	*P* value	BCLC B Cure fraction (95% CI)	*P* value
Sex				
Female	46.2% (36.4–56.2)	.48	35.5% (18.9–54.5)	.70
Male	42.3% (37.2–49.5)		27.2% (17.6–39.6)	
Age, y				
≤65	45.4% (38.4–52.5)	.29	24.5% (13.4–40.7)	.73
>65	42.2% (34.9–50.2)		35.1% (23.9–48.2)	
Liver resection				
Minor	43.1% (35.9–50.5)	.09	28.1% (17.9–41.3)	.84
Major	43.8% (36.3–51.7)		31.7% (18.1–49.3)	
Cirrhosis				
Absent	47.7% (41.2–52.3)	.16	28.1% (18.2–40.7)	.16
Present	38.2% (29.8–47.2)		28.5% (13.6–50.2)	
Child-Pugh classification*				
A5	30.2% (18.9–44.6)	.96	21.8% (5.2–58.6)	.71
A6	46.3% (32.4–60.8)		37.4% (17.1–63.3)	
B7	30.8% (9.1–66.6)		-	
AFP, ng/mL				
<10	48.7% (40.9–56.7)	.002	46.7% (33.2–60.8)	.017
11–400	41.7% (33.5–50.4)		21.9% (10.5–40.2)	
>400	38.0% (27.4–49.9)		7.1% (0.2–69.7)	
Size				
≤5 cm	47.1% (39.6–54.8)	.001	33.7% (21.4–48.8)	.09
>5 cm	39.9% (32.9–47.2)		32.4% (21.9–45.0)	
Number of tumors				
1	44.9% (39.3–50.2)	.038	35.1% (13.4–65.7)	.98
2-3	29.1% (14.4–50.1)		31.1% (20.8–43.6)	
≥4	-		49.6% (35.8–63.5)	
Grade				
Well-moderate	44.4% (38.7–50.2)	.18	31.5% (21.6–43.5)	.15
Poor	43.4% (31.9–55.7)		21.2% (8.5–43.3)	
Lymph-vascular invasion				
Absent	49.6% (42.8–56.5)	<.001	31.3% (19.8–45.5)	.77
Present	34.5% (27.1–42.9)		28.2% (16.4–44.2)	
Liver capsule involvement				
No	46.2% (40.3–52.2)	.017	25.6% (15.4–39.7)	.70
Yes	34.7% (24.4–46.6)		35.3% (21.9–51.4)	
Margin status				
R0	46.5% (40.8–52.2)	<.001	31.9% (22.6–42.9)	.19
R1	25.8% (15.3–39.9)		20.2% (5.9–50.1)	

BCLC, Barcelona Clinic Liver Cancer; *AFP*, alpha-fetoprotein; *CI*, confidence interval.
* Among 418 patients with cirrhosis.

of BCLC-B patients with positive margins ($n = 34$). These data highlight how surgery may indeed provide a chance of “cure” for select BCLC-B patients and that designation to BCLC-B per se should not be considered an absolute contraindication to surgery. Rather, preoperative AFP levels should be taken into consideration when planning surgery for patients outside the Barcelona criteria.

Several limitations should be considered when interpreting the results of this study. As with all retrospective studies, there may have been residual selection bias regarding which patients were offered surgery (ie, patients with potentially resectable tumors and more favorable tumor biology). In addition, all patients were treated at major tertiary referral centers and, therefore, the data may not be generalizable to the community setting. Furthermore, the vast majority of patients had well-differentiated to moderately differentiated tumors and did not have cirrhosis (or had Child-Pugh A liver function). As such, the conclusions cannot be extrapolated to patients with more severe underlying liver disease or more aggressive tumor differentiation status. Also, information on adjuvant treatments after resection was unavailable in this data set, although the incidence of such therapy was presumably low. The lack of a comparison group (ie, ablation for BCLC-0 and transarterial chemoembolization for BCLC-B patients) also did not allow us to draw definitive conclusions regarding which treatment approach might offer the highest chance of cure among patients treated for HCC.

Table V
Individual studies demonstrating acceptable long-term outcomes following resection beyond the current BCLC criteria

Author (year)	Number of patients	Findings
Tsilimigras et al (2019)[30]		5-y OS:
	157 BCLC-B versus	49.9% versus
	279 BLCC-A1 (single >5cm)	56.9%, *P* = .259
Matsukuma et al (2018)[28]		5-y OS:
	65 BCLC-B	44.8%
Kim et al (2017)[29]	160 BCLC-B:	5-y OS:
	80 surgery versus	63% versus
	80 nonsurgical treatment	22%, *P* < .001
Wada et al (2016)[13]		5-y OS:
	85 BCLC-B	63.4%

BCLC, Barcelona Clinic Liver Cancer; *OS*, overall survival.

In conclusion, up to 4 in 10 patients can be considered “cured” after liver resection for HCC. Specifically, in the best-case scenario, cure probability was roughly 60%. Even among individuals who had a BCLC-B HCC, approximately 30% of patients were estimated to achieve cure after liver resection with low preoperative AFP levels being the factor most associated with cure. These results indicate that statistical cure after resection for HCC is possible, but depends on tumor-specific factors, such as preoperative AFP levels, tumor size and number, as well as margin status. It is important to note that cure following surgical resection of HCC can be achieved even among patients who were beyond the BCLC criteria, further emphasizing the need for additional refinement of the current BCLC classification system.

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Supplementary materials

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References

1. Beal EW, Tumin D, Kabir A, et al. Trends in the mortality of hepatocellular carcinoma in the United States. *J Gastrointest Surg*. 2017;21:2033–2038.
2. Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. *Surg Oncol Clin N Am*. 2015;24:1–17.
3. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol*. 2018;68:526–549.
4. Petrick JL, Kelly SP, Altekruse SF, McGlynn KA, Rosenberg PS. Future of hepatocellular carcinoma incidence in the United States forecast through 2030. *J Clin Oncol*. 2016;34:1787–1794.
5. Othus M, Barlogie B, Leblanc ML, Crowley JJ. Cure models as a useful statistical tool for analyzing survival. *Clin Cancer Res*. 2012;18:3731–3736.
6. Lambert PC, Thompson JR, Weston CL, Dickman PW. Estimating and modeling the cure fraction in population-based cancer survival analysis. *Biostatistics*. 2007;8:576–594.
7. Kelly EP, Payne N, Pawlik TM. Understanding patient expectations around therapeutic benefits, risks, and the chance of cure. *Am J Surg*. 2019;217:410–412.
8. Dal Maso L, Guzzinati S, Buzzoni C, et al. Long-term survival, prevalence, and cure of cancer: A population-based estimation for 818 902 Italian patients and 26 cancer types. *Ann Oncol*. 2014;25:2251–2260.
9. Bagante F, Spolverato G, Merath K, et al. Neuroendocrine liver metastasis: The chance to be cured after liver surgery. *J Surg Oncol*. 2017;115:687–695.
10. Spolverato G, Vitale A, Cucchetti A, et al. Can hepatic resection provide a long-term cure for patients with intrahepatic cholangiocarcinoma? *Cancer*. 2015;121:3998–4006.
11. Spolverato G, Bagante F, Ethun CG, et al. Defining the chance of statistical cure among patients with extrahepatic biliary tract cancer. *World J Surg*. 2017;41:224–231.
12. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182–236.
13. Wada H, Eguchi H, Noda T, et al. Selection criteria for hepatic resection in intermediate-stage (BCLC stage B) multiple hepatocellular carcinoma. *Surgery*. 2016;160:1227–1235.
14. Guo H, Wu T, Lu Q, et al. Surgical resection improves long-term survival of patients with hepatocellular carcinoma across different Barcelona Clinic liver cancer stages. *Cancer Manag Res*. 2018;10:361–369.
15. Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. *Hepatology*. 2018;68:977–993.
16. She WH, Chan ACY, Cheung TT, Lo CM, Chok KSH. Survival outcomes of liver transplantation for hepatocellular carcinoma in patients with normal, high and very high preoperative alpha-fetoprotein levels. *World J Hepatol*. 2018;10:308–318.
17. Yang SL, Liu LP, Yang S, et al. Preoperative serum alpha-fetoprotein and prognosis after hepatectomy for hepatocellular carcinoma. *Br J Surg*. 2016;103:716–724.
18. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. *Ann Surg*. 2009;250:187–196.
19. Cvancarova M, Aagnes B, Fossa SD, Lambert PC, Moller B, Bray F. Proportion cured models applied to 23 cancer sites in Norway. *Int J Cancer*. 2013;132:1700–1710.
20. Tsodikov AD, Ibrahim JG, Yakovlev AY. Estimating cure rates from survival data: An Alternative to two-component mixture models. *J Am Stat Assoc*. 2003;98:1063–1078.
21. Centers for Disease Control and Prevention. Web site ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/NVSR/62_07/. Accessed July 30, 2019.
22. Boag JW. Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *J R Stat Soc [B]*. 1949;11:15–53.
23. Berkson J, Gage R. Survival curve for cancer patients following treatment. *J Am Stat Assoc*. 1952;47:501–515.
24. Winner M, Wilson A, Yahanda A, Kim Y, Pawlik TM. A cross-sectional study of patient and provider perception of "cure" as a goal of cancer surgery. *J Surg Oncol*. 2016;114:677–683.
25. Pinna AD, Yang T, Mazzaferro V, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. *Ann Surg*. 2018;268:868–875.
26. Cabibbo G, Celsa C, Calvaruso V, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. *J Hepatol*. 2019;71:265–273.
27. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68:723–750.
28. Matsukuma S, Sakamoto K, Tokuhisa Y, et al. Outcomes following liver resection for multinodular Barcelona Clinic liver cancer-B hepatocellular carcinoma. *Oncol Lett*. 2018;16:6383–6392.
29. Kim H, Ahn SW, Hong SK, et al. Survival benefit of liver resection for Barcelona Clinic liver cancer stage B hepatocellular carcinoma. *Br J Surg*. 2017;104:1045–1052.
30. Tsilimigras DI, Bagante F, Sahara K, et al. Prognosis after resection of Barcelona Clinic Liver Cancer (BCLC) stage 0, A, and B hepatocellular carcinoma: A comprehensive assessment of the current BCLC classification. *Ann Surg Oncol*. 2019;26:3693–3700.