Original Article

Can Hepatic Resection Provide a Long-Term Cure for Patients With Intrahepatic Cholangiocarcinoma?

Gaya Spolverato, MD[1]; Alessandro Vitale, MD, PhD[2]; Alessandro Cucchetti, MD[3]; Irinel Popescu, MD[4]; Hugo P. Marques, MD[5]; Luca Aldrighetti, MD[6]; T. Clark Gamblin, MD[7]; Shishir K. Maithel, MD[8]; Charbel Sandroussi, MD[9]; Todd W. Bauer, MD[10]; Feng Shen, MD[11]; George A. Poultsides, MD[12]; J. Wallis Marsh, MD[13]; and Timothy M. Pawlik, MD, MPH, PhD[1]

BACKGROUND: A patient can be considered statistically cured from a specific disease when their mortality rate returns to the same level as that of the general population. In the current study, the authors sought to assess the probability of being statistically cured from intrahepatic cholangiocarcinoma (ICC) by hepatic resection. **METHODS:** A total of 584 patients who underwent surgery with curative intent for ICC between 1990 and 2013 at 1 of 12 participating institutions were identified. A nonmixture cure model was adopted to compare mortality after hepatic resection with the mortality expected for the general population matched by sex and age. **RESULTS:** The median, 1-year, 3-year, and 5-year disease-free survival was 10 months, 44%, 18%, and 11%, respectively; the corresponding overall survival was 27 months, 75%, 37%, and 22%, respectively. The probability of being cured of ICC was 9.7% (95% confidence interval, 6.1%-13.4%). The mortality of patients undergoing surgery for ICC was higher than that of the general population until year 10, at which time patients alive without tumor recurrence can be considered cured with 99% certainty. Multivariate analysis demonstrated that cure probabilities ranged from 25.8% (time to cure, 9.8 years) in patients with a single, well-differentiated ICC measuring $\leq$5 cm that was without vascular/periductal invasion and lymph nodes metastases versus $<$0.1% (time to cure, 12.6 years) among patients with all 6 of these risk factors. A model with which to calculate cure fraction and time to cure was developed. **CONCLUSIONS:** The cure model indicated that statistical cure was possible in patients undergoing hepatic resection for ICC. The overall probability of cure was approximately 10% and varied based on several tumor-specific factors. ***Cancer*** **2015;121:3998-4006**.

KEYWORDS: cure, hepatic resection, intrahepatic cholangiocarcinoma, surgery.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common malignant hepatic tumor after hepatocellular carcinoma (HCC) and accounts for 5% to 30% of all primary liver malignancies.[1-4] ICC arises in the hepatic parenchyma either directly from cholangiocytes or from transdifferentiation of hepatocytes.[5] Although complete surgical resection remains the best hope for cure, the overall 5-year survival rate is reported to range from 30% to 35% after surgical resection.[6] Before the current 7th edition of the American Joint Committee on Cancer (AJCC) staging system was published,[7] ICC was staged exclusively based on data derived from patients with HCC.[8] However, these 2 tumors are distinct entities with different molecular underpinnings and biological behavior.[8] As such, the classification of ICC using a staging schema based on HCC data was inappropriate and led to inadequate stratification with minimal prognostic discrimination.[9-11] In the current 7th edition of the AJCC manual,[7] ICC has a distinct staging system based in part on data reported by Nathan et al.[9] The 7th edition of the AJCC staging system consists of factors including tumor number

Corresponding author: Timothy M. Pawlik, MD, MPH, PhD, Division of Surgical Oncology, Department of Surgery, Johns Hopkins Hospital, 600 N. Wolfe St, Blalock 688, Baltimore, MD 21287; Fax: (410) 502-2388; tpawlik1@jhmi.edu

[1]Division of Surgical Oncology, Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Unit of Hepatobiliary Surgery and Liver Transplantation, University of Padua Medical Center, Padua, Italy; [3]Department of Medical and Surgical Sciences, S. Orsola-Malpighi Hospital, Alma Mater Studiorum, University of Bologna, Bologna, Italy; [4]Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania; [5]Hepato-Biliary- Pancreatic and Transplantation Centre, Curry Cabral Hospital, Lisbon, Portugal; [6]Hepatobiliary Surgery, San Raffaele Hospital, Milan, Italy; [7]Division of Surgical Oncology, Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin; [8]Division of Surgical Oncology, Department of Surgery, Emory University School of Medicine, Atlanta, Georgia; [9]Department of Surgery, University of Sydney, Sydney, New South Wales, Australia; [10]Division of Surgical Oncology, Department of Surgery, University of Virginia, Charlottesville, Virginia; [11]Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai, China; [12]Department of Surgery, Stanford University, Stanford, California; [13]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

The first 2 authors contributed equally to this article.

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and presence of vascular invasion, as well as direct invasion of adjacent structures and the presence/absence of a periductal-infiltrating component.[12]

Although some reports have noted an improved trend in the long-term survival of patients undergoing resection of ICC,[13] to the best of our knowledge the question of whether surgery can provide a "cure" for patients has not been formally investigated. Specifically, although surgery for a malignant indication can often provide a therapeutic benefit, it is important to determine whether resection can provide "cure."[14] Cure models have been well developed in the statistical literature, but these models are not common in the clinical literature. In population-based cancer studies, cure is said to occur when the mortality rate in the diseased group of individuals returns to the same level as that expected in the general population.[15] Cure models have been advocated as a useful measure with which to monitor trends in survival of curable disease and are of great interest to patients and health care providers. Cure models are different from the standard Cox proportional hazards models. Rather than assuming a proportional hazards of death for the entire cohort over time, cure models allow for the investigation of the heterogeneity between patients with cancer who are long-term survivors (ie, "cured") versus those who are not (ie, "not cured").[16] In doing this, the nonmixture cure model can provide a clinically useful measure of the probability of cure among patients with cancer after treatment.[17] In a recent study by Cvancarova et al, cure models were applied to major cancer sites recorded in the Cancer Registry of Norway between 1963 and 2007, including a wide array of cancers including those of the esophagus, stomach, pancreas, liver, colon, bladder, and central nervous system, among others.[18] In this study, although cancers of bladder and central nervous system had the highest percentage of cured patients (67.4% and 64.0%, respectively), those of the pancreas and liver had among the lowest rates (5.7% and 9.9%, respectively).[18] A separate study conducted among 818,902 Italian patients with cancer confirmed a low cure rate for patients with liver and pancreatic cancers (<10%).[19] However, to our knowledge, cure models have not been used to date to define a statistical cure for ICC. As such, the objective of the current study was to use a nonmixture cure model to estimate the probability of being cured of ICC after hepatic resection.

MATERIALS AND METHODS

Patient Demographic and Clinical Data

A total of 584 patients who underwent liver resection with curative intent for ICC from 1990 to 2013 were identified from a multiinstitutional database including 12 major hepatobiliary centers in the United States, Europe, Australia, and Asia (Johns Hopkins Hospital, Baltimore, Md; Medical College of Wisconsin, Milwaukee, Wis; Stanford University, Stanford, Calif; University of Virginia, Charlottesville, Va; Emory University, Atlanta, Ga; University of Pittsburgh, Pittsburgh, Pa; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; University of Geneva Hospital, Geneva, Switzerland; San Raffaele Hospital, Milan, Italy; Royal Prince Alfred Hospital, University of Sydney, Sydney, New South Wales Australia; and Eastern Hepatobiliary Surgery Hospital, Shanghai, China). The Institutional Review Board of the participating institutions approved the study. Only patients with histologically confirmed ICC who underwent curative liver resection were included in the study group. Patients with metastatic disease, as represented by AJCC stage IVB, were excluded, whereas patients with AJCC T4N0M0 or any T, N1M0 (AJCC stage IVA) disease were included in the study cohort.

Standard demographic and clinicopathologic data were collected including age, sex, race, American Society of Anesthesiologists score, carbohydrate antigen 19-9 (CA 19-9) level, presence of underlying cirrhosis, and tumor-specific characteristics. In particular, data were collected regarding the T and N classifications according to the 7th edition of the AJCC staging system,[7] including information regarding direct invasion of contiguous organs and the presence of microvascular or major vascular invasion, perineural invasion, biliary invasion, and periductal invasion. Tumor grade was categorized as well, moderate, or poor based on the grade of differentiation; if the histologic grade varied in a specific specimen, the "worst" grade was used as the index tumor grade. Data concerning the overall AJCC tumor stage were also collected. Data regarding treatment-related variables such as the extent of surgical resection were obtained. Major hepatectomy was defined as resection of $\geq$3 liver segments according to the classification of Couinaud.[20] The resection margin was ascertained based on final pathology. The date of last follow-up and vital status were collected for all patients.

Cure Fraction Model

When a patient's observed hazard rate (excess and expected hazards combined) returns to that of the general population, that patient may be considered to be cured of the disease, because they are just as likely to die as a member of the general population. The cure fraction was defined as the time interval after diagnosis when the

hazard rates of patients with ICC resembled the risk of death of the general population; specifically, the cure rate was defined as having occurred when the hazard rate in the ICC population was ≤1 percentile above that of the general population. Application of a cure model relies on the concept that statistical plausibility of cure can be fulfilled. In essence, if a percentage of patients can reasonably be expected not to die as a consequence of their disease, the survival curve will trend toward a plateau with the passage of time.[21] Among patients who underwent resection for ICC, a subset did experience a plateauing of their survival after a period of time (Fig. 1).[16] For the purpose of analyses, disease-free survival (DFS) after surgery was used as the primary survival measure for the cure model in the current study. Rather than disease-specific survival or overall survival (OS), DFS was chosen as the primary outcome because the endpoint was cure. Unlike disease-specific survival and OS, DFS defines the survival "event" relative to whether a patient did (not cured) or did not (potentially cured) experience a tumor recurrence after surgery.[22] DFS was calculated from the time of the hepatectomy until clinical evidence of disease recurrence or patient death.

As previously described,[22] we applied the nonmixture cure fraction model, chosen for its applicability in tumor recurrence modeling.[15,18,23] The nonmixture cure model is a parametric cure model that estimates an asymptote for the survival function at the cure proportion. In the nonmixture cure fraction model, the all-cause survival is: $S(t) = S^*(t) \exp\{\ln(\pi)Fz(t)\}$, in which π is the cure fraction and Fz is the cumulative distribution function chosen to be $1 - Sz(t)$ and in which $Sz(t)$ is the parametric survival function fitted using the Weibull distribution. The estimated cure fraction of patients occurs when t equals infinity, which is the asymptote of the Weibull curve. The survival function for the nonmixture model can also be written as: $S(t) = S^*(t)\,(\pi + (1-\pi)((\pi \hat{} Fz(t) - \pi)/(1-\pi)))$, which enables estimation of both the cure proportion (π) and the survival of the "uncured" patients ($1-\pi$). The λ (scale parameter) and γ (location parameter) coefficients of the Weibull model were appropriately fitted. The impact of the clinical and tumor variables in determining the cure fraction of the subgroups was also calculated using a proportional excess hazards model. The median survival of the uncured patients was obtained from the cure model by solving the following equation: $t\,\text{Median} = (-\ln(0.5)/\lambda) \hat{} (1/\gamma)$. Finally, time to cure was assessed. Time to cure is interpreted as the minimum time a patient must survive before a clinician can assess the patient for the possible presence of a cure. Cure models define cure as occurring when time tends to infinite and time to cure was calculated herein assuming a 99% level of confidence (alpha, .01). The estimations of expected survival, $S^*(t)$, and of the expected hazard of the general population, $h^*(t)$, at the time of patient event (death or disease recurrence) were derived from population survival tables obtained from the US life tables, matched by age, race, and sex.[24]

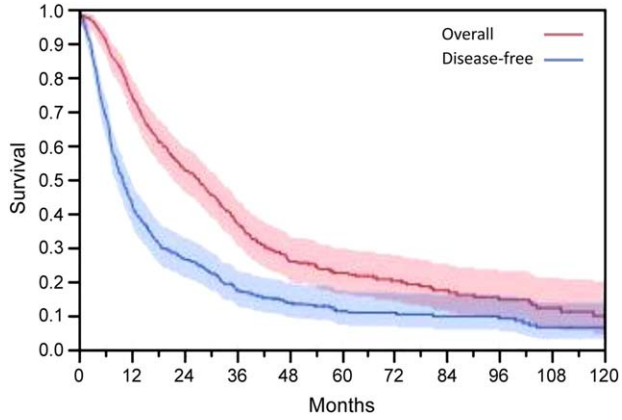

Figure 1. Overall and disease-free survival (DFS) of 584 consecutive patients who underwent surgical resection for intrahepatic cholangiocarcinoma (shaded areas represent 95% confidence intervals). As can be noted, the DFS curve had a tendency to flatten at the end of the fourth year after resection, confirming that the cure hypothesis can be accepted.

RESULTS

Demographic and Clinicopathologic Characteristics

A total of 584 patients undergoing hepatic resection for ICC who met the inclusion criteria were identified. Baseline characteristics of the population are summarized in Table 1. The median patient age was 60 years (interquartile range [IQR], 50.8-69.0 years), with an approximately equal sex distribution of males to females (311 males [53.3%] vs 273 females [46.7%]). A small subset of patients had a preoperative diagnosis of cirrhosis (58 patients; 9.9%). The median CA 19-9 level was 125 U/mL (IQR, 17.7-718.4 U/mL). The median tumor size was 6.6 cm (IQR, 4.8-9.0 cm) and the majority of patients had a solitary tumor (398 patients; 68.2%). At the time of surgery, the extent of hepatic resection consisted of either a major (408 patients; 69.9%) or minor (176 patients; 30.1%) hepatectomy. An R0 resection was achieved in the majority of patients (474 patients; 81.2%). On final pathology, approximately one-quarter of patients had a poorly differentiated tumor (152 patients; 26.0%). Vascular invasion (microinvasion or macroinvasion) was found in 194 patients (33.2%), whereas 119 patients (20.4%)

TABLE 1. Clinical and Pathologic Features of Patients (n = 584)

Variables	Study Group (n = 584)
Median age (IQR), y	60.0 (50.8-69.0)
Female sex	273 (46.7%)
Nonwhite race	98 (16.4%)
Cirrhosis	58 (9.9%)
Median size (IQR), cm	6.6 (4.8-9.0)
Multiple lesions	186 (31.8%)
Bilobar tumor	189 (32.4%)
Median CA 19-9 level (IQR), U/mL	125.0 (17.7-718.4)
Vascular invasion (major or minor)	194 (33.2%)
Major vascular invasion	78 (13.4%)
Minor vascular invasion	169 (28.9%)
Biliary invasion	84 (14.4%)
Poor tumor grade	152 (26.0%)
Perineural invasion	119 (20.4%)
Direct invasion of contiguous organs	62 (10.6%)
Periductal invasion[a]	72 (12.3%)
Lymph node status	
N0	187 (32.0%)
N1	118 (20.2%)
Nx	279 (47.8%)
AJCC T classification	
T1	218 (37.4%)
T2a	91 (15.5%)
T2b	145 (24.8%)
T3	63 (10.8%)
T4	67 (11.5%)
AJCC stage[b]	
I	218 (37.4%)
II	179 (30.6%)
III	25 (4.3%)
IVA[a]	162 (27.7%)
Major surgical resection (≥3 segments)	408 (69.9%)
R0 resection margin	474 (81.2%)

Abbreviations: AJCC, American Joint Committee on Cancer; CA 19-9, carbohydrate antigen 19-9; IQR, interquartile range.
[a] Includes tumors with periductal-infiltrating or mixed mass-forming and periductal-infiltrating growth pattern.
[b] AJCC stage IVA (T4N0M0 or any TN1M0) tumors were included, whereas stage IVB (any T, any N, M1) tumors were excluded from the study cohort.

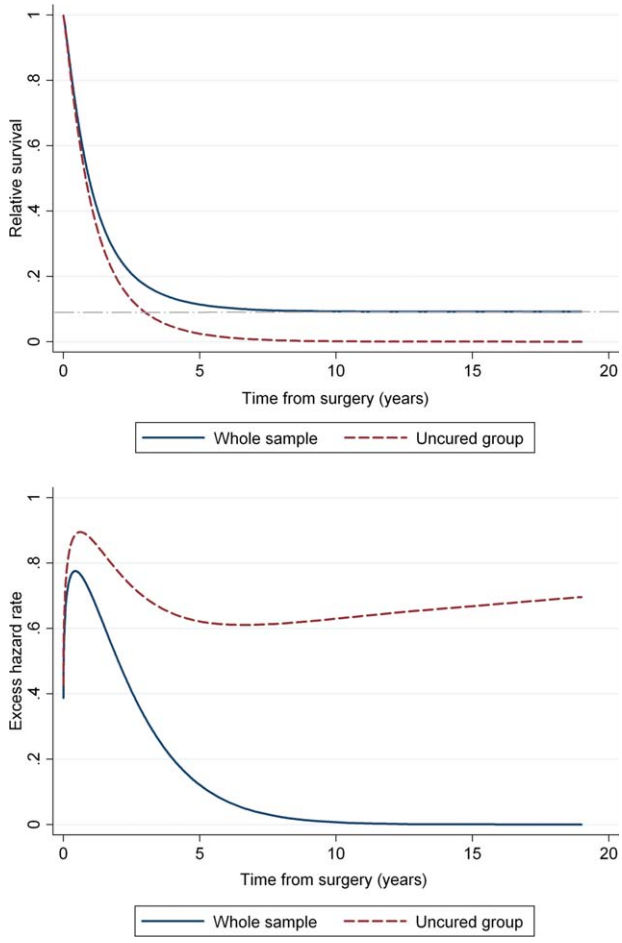

Figure 2. Cure model results. (*Top*) Relative survival of the entire group of patients and the uncured patients. In the entire group, from the sixth year after surgery onward, the survival curve reached a plateau at approximately 10%, which represents the cure fraction. (*Bottom*) Excess hazard rate of the entire study group and the uncured patients. At end of the first year after surgery, the excess of the hazard started to decrease until it approached zero at the end of 10 years after surgery. Conversely, in uncured patients, the excess of hazard progressively increased over time.

were found to have perineural invasion. Biliary invasion (84 patients; 14.4%), periductal invasion (72 patients; 12.3%), and direct invasion of contiguous organs (62 patients; 10.6%) were less common. Less than one-quarter of patients were found to have lymph node metastases (118 patients; 20.2%). The majority of patients were staged as having AJCC stage I disease (218 patients; 37.4%) or stage II disease (179 patients; 30.6%). Approximately one-half of the patients in the current study received adjuvant chemotherapy (300 patients; 51.3%), whereas a small subset of patients (68 patients; 11.7%) received adjuvant radiotherapy.

Cure Fraction Model

The median and 5-year DFS and OS for the entire cohort was 10 months and 11%, respectively, versus 27 months and 22%, respectively (Fig. 1). The cure model converged for the entire study population and for each subgroup analyzed ($P<.001$ in all cases). In the entire study population, the probability of being cured of ICC by hepatic resection was 9.7% (95% confidence interval, 6.1%-13.4%), and the median survival of uncured patients was 0.8 years (Fig. 2 *Top*). The excess of hazard after surgery is plotted in Figure 2 (*Bottom*) and started from a 35% increased risk of death early after surgical resection with respect to the general population. In the first postoperative year, the excess hazard increased to approximately 78% in the entire group and was up to 90% in uncured patients. At the end of the first year after surgery, the hazard of uncured

TABLE 2. Univariate Cure Fraction Calculation Stratified by Baseline Characteristics

Variable	Cure Fraction % (95% CI)	Time to Cure, Years (95% CI)	Median Survival of Uncured Patients, Years (95% CI)
Study population	9.7 (6.1-13.4)	9.50 (6.93-13.01)	0.81 (0.72-0.91)
Sex (P = .981)			
Male	9.8 (5.5-14.0)	9.49 (6.92-13.01)	0.81 (0.72-0.92)
Female	9.7 (5.5-13.9)	9.50 (6.93-13.01)	0.81 (0.71-0.92)
Age, y (P = 0.158)			
≤60	8.4 (4.6-12.1)	9.50 (6.95-13.00)	0.77 (0.68-0.88)
>60	11.5 (6.8-16.1)	9.31 (6.80-12.73)	0.85 (0.74-0.96)
Cirrhosis (P = .088)			
Yes	5.6 (4.0-10.8)	9.89 (7.16-13.67)	0.71 (0.57-0.88)
No	10.1 (6.3-13.9)	9.55 (6.96-13.12)	0.83 (0.74-0.93)
CA 19-9 >125 U/mL (P = .354)			
No	10.8 (6.3-15.3)	9.43 (6.89-12.90)	0.83 (0.73-0.95)
Yes	8.8 (4.9-12.7)	9.56 (6.98-13.09)	0.79 (0.69-0.89)
Positive resection margin (P = .015)			
Yes	5.2 (1.1-9.4)	10.02 (7.25-13.84)	0.70 (0.59-0.84)
No	10.4 (6.5-14.3)	9.62 (7.00-13.23)	0.84 (0.75-0.95)
Size, cm (P = .001)			
≤5	16.8 (10.3-23.3)	9.15 (6.70-12.49)	0.88(0.74-1.05)
>5	6.8 (3.6-9.9)	9.76 (7.13-13.36)	0.77(0.67-0.88)
Tumor no. (P <.001)			
Solitary	12.3 (7.8-16.8)	9.52 (6.94-13.06)	0.90 (0.79-1.02)
Multifocal	4.1 (1.3-7.0)	10.14 (7.36-13.98)	0.67 (0.58-0.77)
Poor tumor grade (P = .001)			
Absent	11.6 (7.4-15.9)	9.36 (6.84-12.80)	0.86 (0.76-0.97)
Present	4.9 (1.7-8.2)	9.85 (7.18-13.51)	0.68 (0.59-0.80)
Bilobar location (P = .010)			
Absent	11.6 (7.2-15.9)	9.35 (6.82-12.84)	0.85 (0.76-0.97)
Present	6.3 (2.7-9.9)	9.72 (7.07-13.37)	0.72 (0.63-0.83)
Lymph node metastasis (P <.001)			
Absent	11.3 (7.1-15.5)	9.70 (7.03-13.38)	0.89 (0.78-1.00)
Present	2.5 (1.8-4.8)	10.49 (7.56-14.55)	0.61 (0.51-0.72)
Major vascular invasion (P <.001)			
Absent	10.6 (6.6-14.6)	9.59 (6.97-13.19)	0.85 (0.75-0.96)
Present	3.3 (0.1-6.5)	10.21 (7.38-14.13)	0.63 (0.52-0.77)
Minor vascular invasion (P <.001)			
Absent	12.0 (7.6-16.4)	9.75 (7.09-13.40)	0.91 (0.80-1.04)
Present	2.9 (0.1-5.2)	10.52 (7.62-14.54)	0.64 (0.55-0.74)
Perineural invasion (P = .297)			
Absent	10.1 (6.3-13.9)	9.55 (6.97-13.09)	0.83 (0.73-0.93)
Present	7.6 (2.6-12.6)	9.73 (7.07-13.38)	0.77 (0.65-0.90)
Biliary invasion (P = .410)			
Absent	10.1 (6.3-13.9)	9.46 (6.92-12.94)	0.82 (0.73-0.92)
Present	7.8 (2.4-13.3)	9.61 (7.01-13.18)	0.76 (0.63-0.92)
Invasion of adjacent organs (P <.001)			
Absent	10.7 (6.7-14.6)	9.48 (6.94-12.97)	0.84 (0.75-0.94)
Present	3.0 (−0.1 to 0.6)	10.14 (7.38-13.94)	0.61 (0.49-0.76)
Periductal invasion (P <.001)			
Absent	10.9 (7.0-14.8)	9.34 (6.86-12.71)	0.84 (0.75-0.95)
Present	2.9 (0.0-5.8)	10.01 (7.33-13.68)	0.60 (0.49-0.75)
Major surgical resection (P = .103)			
Absent	12.6 (7.0-18.3)	9.43 (6.86-12.98)	0.88 (0.76-1.03)
Present	8.4 (4.7-12.1)	9.70 (7.04-13.37)	0.79 (0.70-0.88)

Abbreviations: 95% CI, 95% confidence interval; CA 19-9, carbohydrate antigen 19-9.

patients decreased until 5 years after hepatic resection to approximately 68% and then progressively increased over time, whereas the entire group demonstrated a progressive reduction until it approached zero. The excess of hazard in the entire group decreased until a 99% level of confidence in the general population at 9.50 years after hepatic resection, indicating that after this time point, a patient still alive without tumor recurrence could be considered cured with 99% certainty.

Cure fractions, time to cure, and the median survival of uncured patients stratified by clinical and tumor features are detailed in Table 2. The significant determinants of cure probabilities (P<.05) were positive surgical margins, tumor size >5 cm, multifocal tumor, poor tumor grade,

TABLE 3. Multivariate Cure Model in Relation to Clinical and Tumor Features

Variable	Coefficient (95% CI)	*P*
Constant	−1.057 (−1.574 to −0.541)	<.001
Positive resection margin	−0.292 (−1.104 to 0.521)	.482
Size >5 cm	− 0.763 (−1.305 to −0.220)	.006
Multifocal	−0.883 (−1.536 to −0.231)	.008
Poor tumor grade	−0.691 (−1.361 to −0.021)	.043
Bilobar	−0.029 (−0.650 to 0.591)	.926
Lymph node metastasis	−1.136 (−2.023 to −0.248)	.012
Major vascular invasion	−0.337 (−1.402 to 0.728)	.535
Minor vascular invasion	−1.333 (−2.097 to −0.568)	.001
Invasion of adjacent organs	−0.718 (−1.830 to 0.393)	.205
Periductal invasion	−1.352 (−2.406 to −0.297)	.012

Abbreviation: 95% CI, 95% confidence interval.
The final cure model was obtained after the backward exclusion/inclusion of each variable with a *P* value >.05 (order of exclusion: minor vascular invasion, lymph node metastases, multifocal, periductal invasion, invasion of adjacent organs, major vascular invasion, size, poor tumor grade, bilobar, and positive resection margin). The covariates effects for the cure fraction are expressed as log odds ratios and have an interpretation similar to those in logistic regression. A Web-based calculator of cure probability for each possible scenario is provided at http://www.livercancer.eu/CCCcuremodel.html.

bilobar location, lymph node metastasis, vascular invasion, invasion of adjacent organs, and periductal invasion. These variables were entered in the subsequent multivariate cure model (Table 3). It is interesting to note that cure fraction, time to cure, and median survival were not found to be associated with the receipt of adjuvant chemotherapy and therefore these variables were not included in the model. After backward removal of other nonsignificant variables, the final model included the following 6 covariates: vascular invasion, tumor size >5 cm, multifocal ICC, poor histological grade, lymph node metastasis, and periductal invasion. The cure fraction for patients with a single ICC measuring <5 cm, without vascular invasion, poor-grade ICC, lymph node metastases, and periductal histology was 25.8%. This value represented the highest achievable cure probability after liver resection for ICC based on this multicenter database. In such a favorable case (present in 13.5% of the study population), the time to cure was 9.85 years. Covariate effects were expressed as log odds ratios and a simple Web-based calculator of cure probability for each possible clinical scenario was developed (available at http://www.livercancer.eu/CCCcuremodel.html) (Fig. 3). For example, in patients with vascular invasion but none of the other 5 risk factors, the cure fraction was 8.4%; in patients with a tumor measuring >5 cm but none of the other 5 risk factors, the cure fraction was 13.9%. In the presence of all unfavorable prognostic factors (occurring in <1% of enrolled patients), the cure fraction dropped to <0.1% and the time to cure increased to 12.58 years.

DISCUSSION

Although a relatively rare disease, ICC is the second most common primary liver malignancy and its incidence is increasing worldwide.[4,25,26] ICC is associated with high mortality and only approximately one-third of patients who undergo curative-intent surgical resection survive 5 years after surgery.[6] A variety of factors have been proposed as independent predictors of worse survival such as extremes of age, larger tumor diameter, vascular invasion, cirrhosis of the underlying liver, lymph node metastasis, and the presence of multifocal disease.[6,27-29] In turn, several different staging/scoring systems have been used in an attempt to predict the prognosis of patients after surgery for ICC.[29,30] The most widely accepted means for stratifying patients with regard to prognosis is the AJCC staging system.[7] However, the AJCC staging system includes only a limited number of tumor-related variables and has been criticized for its inability to tailor prognosis to an individual specific patient. As such, our group and others have proposed nomogram-based strategies as a means with which to allow physicians to stratify the long-term survival of individual patients.[29,30] Although these models may be helpful in predicting prognosis, the majority of patients are particularly interested in the chance for "cure" after surgery. Although cure models have become an increasing topic of interest in the statistical literature, their application to specific disease-based cohorts of patients in the clinical setting has been more limited. In fact, to our knowledge, no previous study has specifically examined the chance of statistical cure among patients with ICC who undergo surgical resection. Therefore, the current study is important because, to the best of our knowledge, it is the first to apply statistical cure modeling to patients with ICC. Of particular interest was the finding that the overall chance of statistical cure of ICC with hepatic resection was quite low, at only approximately 10%. Indeed, even among patients with the most favorable characteristics (eg, a solitary, small tumor with no lymph node metastasis, etc), the chance for cure was still only approximately 25%.

Initially introduced by Boag[31] and Berkson and Gage,[32] cure models provide a method of modeling time to death when cure is possible, simultaneously estimating the death hazard of fatal cases and the percentage of cured cases.[33] The traditional assumption of standard proportional hazards models can fail when survival curves plateau at their tails. Compared with proportional hazards models, statistical cure models are able to distinguish between those patients who die of their cancer versus those who are cured and do not have any excess mortality compared with the

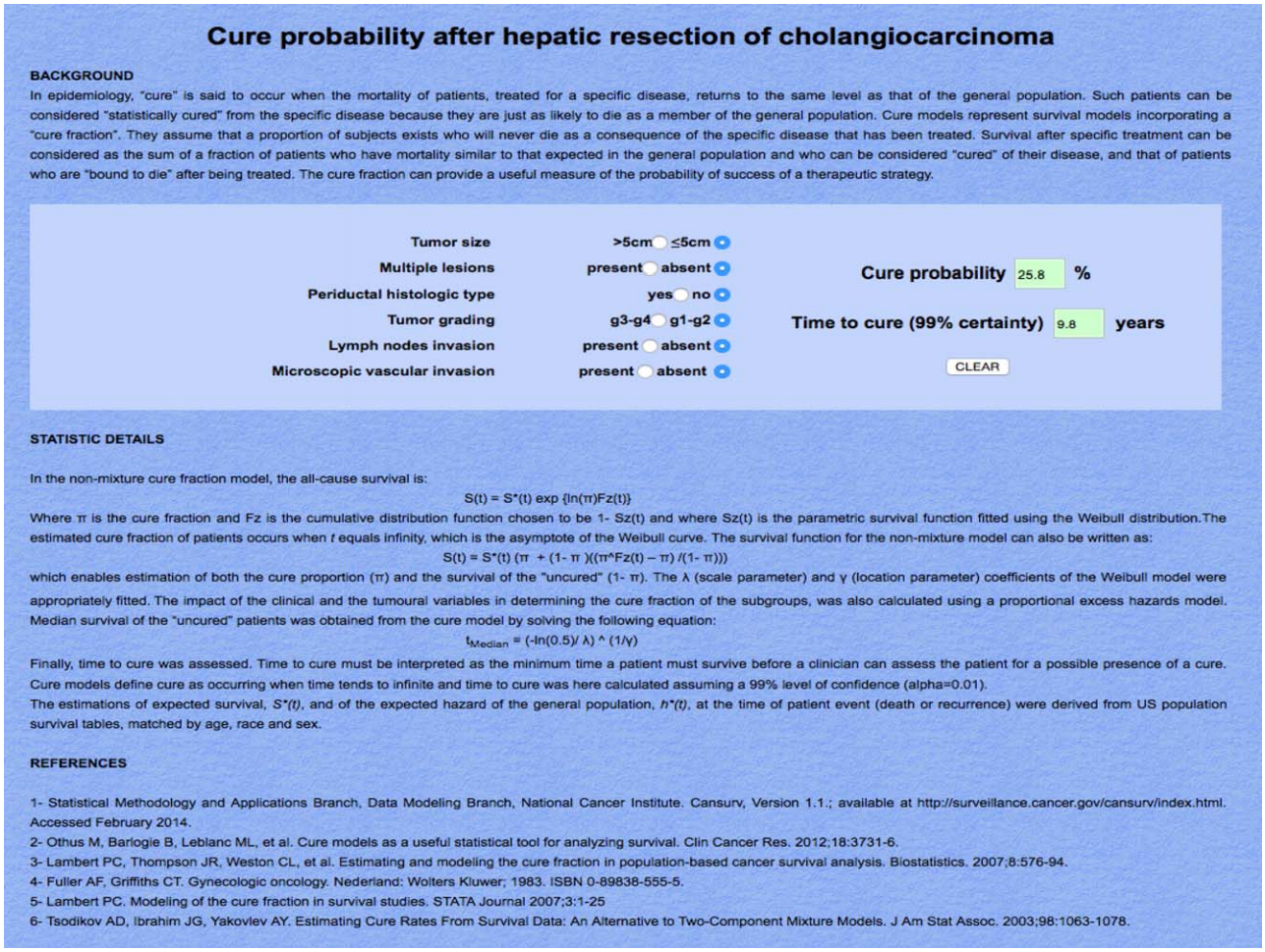

Figure 3. Web-based calculator of cure probability for each possible clinical scenario. Reprinted from the Bologna Liver Oncology Group (available at http://www.livercancer.eu/CCCcuremodel.html).

general population.[33] In effect, statistical cure models characterize more explicitly the heterogeneity in the plateau areas of standard survival plots. In addition, cure models also allow the investigation of which patient and tumor covariates may be associated with cure. This information is particularly relevant in the clinical setting, in which both physicians and patients frequently want information regarding the chance of cure after surgery. Therefore, in the current study, we have proposed an application of a nonmixture model of DFS for patients with ICC undergoing surgical resection.

Previous data have documented the general poor prognosis of patients with ICC.[6,28,34] When considered as a cohort, the OS for all patients undergoing resection of ICC ranges from 30% to 35% (Fig. 1).[27] The poor outcomes after surgery are related to the high incidence of disease recurrence, which is reported to be approximately 50% to 55%, with a recurrence-free survival of only 20 months.[35] Although the majority of patients will develop disease recurrence and ultimately die of their disease, a small percentage may derive a curative survival benefit from surgery. Using statistical cure modeling, we estimated that the probability of being cured of ICC by hepatic resection was 9.7%. Not surprisingly, several factors were found to be associated with the chance of cure and these factors mirrored some of the covariates previously included in the AJCC staging system, as well as ICC nomograms.[7,29] Specifically, tumor size >5 cm, multifocal ICC, vascular invasion, poor tumor grade, lymph node metastasis, and periductal invasion were found to be the most significant determinants of cure probabilities. By combining the effects of these pathological features, we were able to develop a simple Web-based calculator of cure probability for each possible scenario, which can assist in the prognostication of cure among patients undergoing surgery for ICC. For example, in the best-case scenario of a patient with a single, well-differentiated ICC measuring

<5 cm without vascular/periductal invasion as well as no lymph node metastases, the cure fraction was 25.8% and the time to cure was 9.85 years. In contrast, in the presence of unfavorable prognostic factors (eg, large tumor, poorly differentiated tumor, presence of lymph node metastases, etc), the cure fraction dropped to <0.1% and the time to cure increased to 12.58 years. These data serve to demonstrate the wide range of chance at a possible cure after surgical resection of ICC. The formula proposed in the current study may help to better estimate the chance of cure, thereby assisting physicians and patients in understanding the long-term benefit of surgery for ICC.

Juxtaposed to statistical cure modeling for other malignancies, the analyses presented herein also serve to emphasize the particularly poor prognosis of patients with ICC. For example, the results of the current study are different from the data previously reported by Cucchetti et al concerning patients undergoing hepatic resection for colorectal liver metastasis (CRLM).[22] Among patients with ICC, the probability of cure after liver resection was found to be dramatically lower than the probability of cure noted among patients who underwent surgical resection for CRLM (9.7% vs 20.0%). Similarly, the time to cure was longer in patients with ICC (9.50 years) compared with those with CRLM (6.48 years). It is interesting to note that the highest probability of cure for patients with ICC who underwent liver resection was only 25.8%, which was less favorable than the 41.9% probability of cure for patients with CRLM but better than the 5.7% probability of cure for patients with cancer of the pancreas.[18,22]

The current study had several limitations. The data were derived from 12 hepatobiliary centers in the United States, Europe, Australia, and Asia. Although the patients were heterogeneous with regard to their demographic, clinical, and tumor-related characteristics, this heterogeneity can allow for generalization. In addition, as with all retrospective studies of surgical procedures, the current cohort may have been subject to selection bias.

The cure model presented herein indicated that statistical cure was possible in patients undergoing hepatic resection for ICC. However, the overall probability of cure was only approximately 10% and varied considerably based on several tumor-specific factors. Although future validation of the proposed cure probability calculator is warranted, data from the current study provide patients and providers with an estimate of the long-term potential for cure when considering surgical resection for patients with ICC.

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