2-18-2022

Dynamic risk profiling of HCC recurrence after curative intent liver resection

Tommy Ivanics
Henry Ford Health, tivanic1@hfhs.org

Carla Fiorella Murillo Perez

Marco P. A. W. Claasen

Madhukar S. Patel

Gabriela Morgenshtern

See next page for additional authors

Recommended Citation

Ivanics T, Murillo Perez CF, Claasen MP, Patel MS, Morgenshtern G, Erdman L, Shwaartz C, Rajendran L, O'Kane GM, Hansen BE, Cleary SP, and Sapisochin G. Dynamic risk profiling of hepatocellular carcinoma recurrence after curative intent liver resection. Hepatology 2022.

Authors

Tommy Ivanics, Carla Fiorella Murillo Perez, Marco P. A. W. Claasen, Madhukar S. Patel, Gabriela Morgenshtern, Lauren Erdman, Chaya Shwaartz, Luckshi Rajendran, Grainne M. O'Kane, Bettina E. Hansen, Sean P. Cleary, and Gonzalo Sapisochin

Received: 22 October 2021 | Revised: 7 February 2022 | Accepted: 8 February 2022

DOI: 10.1002/hep.32411

ORIGINAL ARTICLE

Dynamic risk profiling of HCC recurrence after curative intent liver resection

Tommy Ivanics[1,2,3] | **Carla Fiorella Murillo Perez**[1,4] | **Marco P. A. W. Claasen**[1,5] | **Madhukar S. Patel**[1,6] | **Gabriela Morgenshtern**[7] | **Lauren Erdman**[7] | **Chaya Shwaartz**[1,8] | **Luckshi Rajendran**[8] | **Grainne M. O'Kane**[9] | **Bettina E. Hansen**[4,10] | **Sean P Cleary**[11] | **Gonzalo Sapisochin**[1,8]

[1]Multi-Organ Transplant Program, University Health Network Toronto, Toronto, Ontario, Canada

[2]Department of Surgery, Henry Ford Hospital, Detroit, Michigan, USA

[3]Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden

[4]Toronto Centre for Liver Disease, Toronto Western & General Hospital, University Health Network, Toronto, Ontario, Canada

[5]Department of Surgery, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands

[6]Division of Surgical Transplantation, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA

[7]Department of Computer Science, University of Toronto, Toronto, Ontario, Canada

[8]Division of General Surgery, University of Toronto, Toronto, Ontario, Canada

[9]Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada

[10]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

[11]Division of Hepatobiliary and Pancreatic Surgery, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Gonzalo Sapisochin, Multi-Organ Transplant Program, University Health Network Toronto, 585 University Avenue, 11PMB184, Toronto, M5G 2N2, ON, Canada.
Email: Gonzalo.sapisochin@uhn.ca

Abstract

Background and Aims: Following liver resection (LR) for HCC, the likelihood of survival is dynamic, in that multiple recurrences and/or metastases are possible, each having variable impacts on outcomes. We sought to evaluate the natural progression, pattern, and timing of various disease states after LR for HCC using multistate modeling and to create a practical calculator to provide prognostic information for patients and clinicians.

Approach and Results: Adult patients undergoing LR for HCC between January 2000 and December 2018 were retrospectively identified at a single center. Multistate analysis modeled post-LR tumor progression by describing transitions between distinct disease states. In this model, the states included surgery, intrahepatic recurrence (first, second, third, fourth, fifth), distant metastasis with or without intrahepatic recurrence, and death. Of the 486 patients included, 169 (34.8%) remained recurrence-free, 205 (42.2%) developed intrahepatic recurrence, 80 (16.5%) developed distant metastasis, and 32 (7%) died. For an average patient having undergone LR, there was a 33.1% chance of remaining disease-free, a 31.0% chance of at least one intrahepatic recurrence, a 16.3% chance of distant metastasis, and a 19.8% chance of death within the first 60 months post-LR. The transition probability from surgery to first intrahepatic recurrence, without a subsequent state transition, increased from 3% (3 months) to 17.4% (30 months) and 17.2% (60 months). Factors that could modify these probabilities included tumor size, satellite lesions, and microvascular invasion. The online multistate model calculator can be found on https://multistatehcc.shinyapps.io/home/.

Conclusions: In contrast to standard single time-to-event estimates, multistate modeling provides more realistic prognostication of outcomes after LR for HCC by taking into account many postoperative disease states and transitions between

Abbreviations: IQR, interquartile range; LR, liver resection; MELD, Model for End-Stage Liver Disease; MWA, microwave ablation; RFA, radiofrequency ablation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TACE, transarterial chemoembolization.

them. Our multistate modeling calculator can provide meaningful data to guide the management of patients undergoing postoperative surveillance and therapy.

INTRODUCTION

HCC represents a leading cause of cancer death worldwide.[1] Liver resection (LR) is reserved for patients with preserved liver function in the absence of extrahepatic disease.[2–4] Although cure can be achieved with LR, up to 70% of patients develop disease recurrence within 5 years of resection, with the majority occurring in the liver.[5] If standardized treatment algorithms are applied, the median survival of all comers with recurrence is approximately 21 months.[5]

Postsurgical oncologic outcomes are typically reported as solitary binary events, such as dead versus alive or presence versus absence of disease. While these estimates offer information to evaluate the impact of patient, tumor, and treatment variables, they do not consider disease progression for pathologies where recurrence is not universally fatal. Because prognosis is contingent upon the disease state a patient is in and the patient's path to that state, these types of assumptions may yield oversimplified estimates of outcomes. Prognostication that incorporates various disease states (e.g., first, second, third, fourth, and fifth intrahepatic recurrences; both intrahepatic and distant metastases; distant metastases alone) may offer more realistic probabilities for patients in a specific disease state after curative-intent treatment in efforts to guide individualized treatment strategies. Though multistate modeling has been used to model progression of liver fibrosis due to hepatitis C after liver transplantation, it has not previously been used to model disease progression in HCC.[6]

Given that the likelihood of disease and survival post-LR for HCC is dynamic, we sought to evaluate the natural progression, pattern, and timing of the various disease states after LR for HCC using multistate modeling and to create a practical calculator in order to provide prognostic information for patients and clinicians.

MATERIALS AND METHODS

Study population

We retrospectively studied consecutive adults (≥18 years) who underwent LR for HCC between January 2000 and December 2018 at a single academic institution (Toronto General Hospital). Patients with LR after 2018 were excluded, to allow for enough follow-up time to evaluate tumor recurrence after LR. At the time of analysis, patient data were up to date as of May 28, 2020. The diagnosis of HCC was established per the American Association for the Study of Liver Diseases guidelines.[7] Patients with preoperative tumor rupture, prior HCC treatment (including LR, liver transplant, and locoregional therapies such as radiofrequency ablation [RFA], transarterial chemoembolization [TACE], and microwave ablation [MWA]), missing pathology information, or fibrolamellar subtype on pathology were excluded. A Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)–compliant diagram of patients included and excluded is shown in Figure 1. This study complies with the STROBE statement for retrospective studies.[8] This study was approved by our institutional research ethics board (REB#16-5626), and a waiver of informed consent was obtained.

Data collection

We recorded patient demographics, age, sex, etiology of liver disease, preoperative degree of liver dysfunction (Model for End-stage Liver Disease [MELD] and Child-Pugh score), preoperative laboratory variables (albumin, total bilirubin, international normalized ratio, albumin-bilirubin grade, and platelet count), alpha-fetoprotein (categorized to reflect clinically relevant categories <20, 20–99, 100–999, and >1000),[9] preoperative tumor characteristics, pathology findings, and postoperative outcomes. Major hepatectomy was defined as complete resection of three or more liver segments according to the Brisbane 2000 terminology.[10] Pathology characteristics included the size of the largest tumor, tumor number, presence of satellite lesions, tumor differentiation, vascular invasion, surgical margin positivity, Laennec stage of adjacent liver fibrosis, and degree of liver steatosis. Tumor differentiation was defined according to the modified Edmondson criteria.[11] Treatments for recurrence were defined as ablation (including RFA, MWA, ethanol injection), TACE, LR, non-LR (including lung resection), systemic therapy, radiation, liver transplantation, and palliative care.

Follow-up, survival, and recurrence

Postoperatively, patients underwent surveillance with contrast-enhanced CT of the chest and abdomen or ultrasound every 3 months for the first 2 years. Subsequently, surveillance proceeded in 6-month intervals up to 5 years. Additional imaging studies were obtained in the case of a suspected recurrence and included contrast-enhanced CT, contrast-enhanced ultrasound, or MRI.[7] Additional information on recurrence

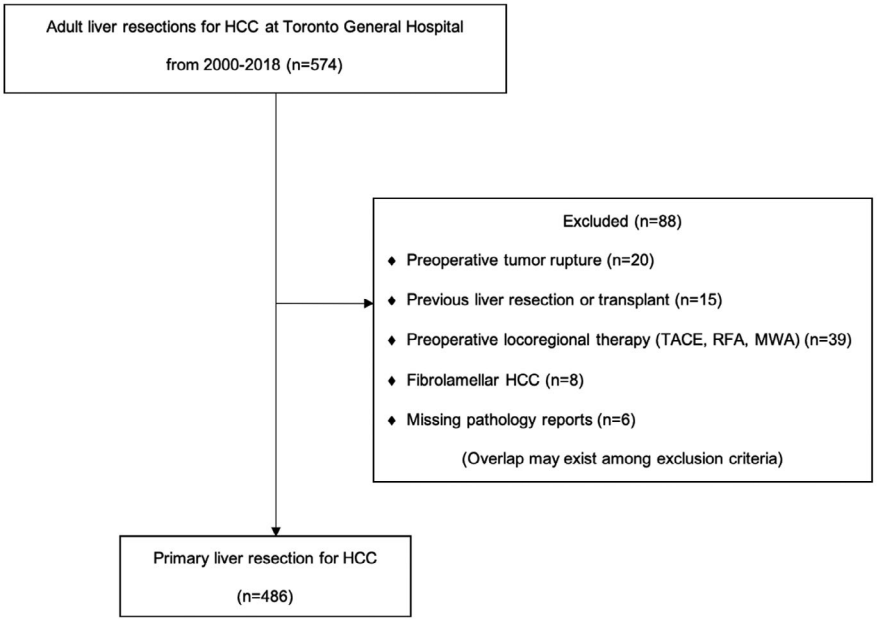

FIGURE 1 STROBE flow diagram of study cohort

included the date of recurrence and the location of recurrence. The latter was categorized as intrahepatic if the recurrence was confined to the liver and as extrahepatic if distant.

Outcome measures

The primary aim was to model disease progression after curative-intent primary HCC LR (HCC recurrence [intrahepatic or distant] and/or death).

Statistical analysis

Descriptive data were expressed as medians and interquartile ranges (IQR) for non-normally distributed variables. Normally distributed continuous variables were expressed as means with SD. Categorical variables were expressed using numbers and percentages. To visualize and estimate the incidence of first, second, third, fourth, and fifth intrahepatic recurrences, a Kaplan-Meier method with a clock-reset approach was applied. Patients without recurrence, distant metastasis, or death were censored. The demonstration of this Kaplan-Meier method was to illustrate the process and serve as a bridge between the traditional survival estimate method and the multistate modeling. To model post-LR tumor progression, a time-nonhomogeneous Markov multistate model was used to describe transitions between several well-defined, distinct states. In the selected model, the states included surgery, first intrahepatic recurrence, second intrahepatic recurrence, third intrahepatic recurrence, fourth intrahepatic recurrence, fifth intrahepatic recurrence, a separate state encompassing any intrahepatic and distant metastasis or distant metastasis alone, and death (absorbing state). Patients who did not progress to another state remained in their most recent state, regardless of treatment received (e.g., transplant). In this progressive multistate model, transitions are only allowed in the forward direction. Based on these transitions, a matrix was constructed and formed the basis for estimating the transition intensity functions used to estimate risk (transition probability) functions. These include rates of events, distributions of "sojourns" or times between events, the proportion of individuals in a particular "state," and transition probabilities between states of a specific period. Moreover, fixed covariate effects were evaluated through adjustments by age, sex, and post-LR pathology variables—these are reported as HRs. In the msm package used for the multistate modeling, individual-specific or time-dependent covariates were allowed to be fitted to transition intensities.[12] For the calculation of transition probabilities on which the likelihood depends, time-dependent covariates are assumed to be piecewise-constant. Models with intensities that change with time are referred to as *time-inhomogeneous*.[12] In the models, a variable to model the effect of a potentially curative therapy of recurrence was included. This was defined as any locoregional curative intent treatment (including ablation, LR, and transplant listing). All other treatments (TACE, systemic therapy, radiation therapy, nonliver surgery, and palliative care) were considered as not potentially curative therapy for recurrence. Moreover, we considered that the effect of sex is likely to be the same between states for higher-level recurrences. Consequently, we

constrained the effects of sex for all types of recurrence (i.e., transition from no recurrence to first intrahepatic recurrence = first intrahepatic recurrence to second intrahepatic recurrence transition, etc.; transition from no recurrence to distant recurrence = first intrahepatic recurrence to distant recurrence transition, etc.; transition from no recurrence to death = first intrahepatic recurrence to death transition, etc.). Hypothesis testing was performed using a log likelihood test comparing the sex coefficient–constrained model and the nonconstrained model. Given that the models were not statistically significantly different, the constrained model was selected as the final model. Finally, all analyses were performed using a complete-case analysis.

All two-sided p values < 0.05 were considered statistically significant. Statistical analyses were performed using R, version 4.0.3 (http://www.R-project.org/). Multistate modeling was performed using the msm and survival packages. An online interactive probability estimate calculator was developed using the R package shiny to provide prognostic information for patients at three time points—postsurgery, at first intrahepatic recurrence, and at second intrahepatic recurrence.

RESULTS

Study population

A total of 486 patients were included. The median follow-up was 41.8 (IQR, 19.1–84.2) months. The majority of patients were male (79.4%), with an underlying disease etiology of HBV (48.1%). The median preoperative MELD score was 7.0 (IQR, 6.4–8.0) (Table 1). The median preoperative tumor size was 5.0 cm (IQR, 3.5–7.9), and most tumors were solitary (Table 2).

TABLE 1 Overall patient cohort

	Overall (n = 486)
Age, median (IQR)	63 (55–71)
Missing, n (%)	2 (0.4%)
Gender, n (%)	
Male	386 (79.4%)
Missing, n (%)	0 (0%)
Etiology, n (%)	
No underlying liver disease	57 (11.7%)
HBV	234 (48.1%)
HCV	106 (21.8%)
EtOH	28 (5.8%)
NASH	22 (4.5%)
HBV and HCV coinfection	1 (0.2%)
Other	38 (7.8%)
Missing, n (%)	0 (0%)
BMI, median (IQR)	24.90 (22.00–28.00)
Missing, n (%)	85 (17.5%)
Ascites within 30 days prior to surgery, n (%)	
Yes	1 (0.2%)
Missing, n (%)	6 (1.2%)
Encephalopathy, n (%)	
No encephalopathy	407 (99.5%)
Grade 1–2	2 (0.5%)
Missing, n (%)	77 (15.8%)
HTN requiring medication, n (%)	
Yes	236 (49.2%)
Missing, n (%)	6 (1.2%)
BCLC stage, n (%)	
0	17 (3.5%)
A	425 (87.6%)
B	43 (8.9%)
Missing, n (%)	1 (0.2%)
LR completed laparoscopically, n (%)	83 (17.1%)
Missing, n (%)	0 (0%)
Major hepatectomy, n (%)	250 (51.4%)
Missing, n (%)	0 (0%)
Length of stay after surgery, median (IQR)	7.00 (5.00–9.00)
Missing, n (%)	26 (5.3%)

Abbreviations: BCLC, Barcelona Clinic liver cancer; BMI, body mass index; EtOH, ethyl alcohol, HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; IQR, interquartile range; LR, liver resection; NASH, Non-alcoholic steatohepatitis.

Postresection outcomes: recurrence and death

Of the 486 patients who underwent curative-intent liver resection, 169 patients remained recurrence-free throughout the follow-up period, 205 developed an intrahepatic recurrence, 80 developed distant metastasis, and 32 patients died without a diagnosis of any recurrence. Of the patients who developed a first intrahepatic recurrence, 64 remained in the first intrahepatic recurrence state, 111 developed a second intrahepatic recurrence, 16 developed a distant recurrence, and 14 died. A flow diagram of the state transitions and the number of patients in each state is shown in Figure 2 and Table S1. The various treatments for HCC recurrence in each state are shown in Table 3. The proportion of patients treated with ablation decreased with each subsequent intrahepatic recurrence (first, 49.7%; second, 40.5%; third, 35.0%; fourth, 28.6%; fifth, 23.8%). In contrast, the proportion of patients who received TACE increased from 14.1% after the first intrahepatic recurrence to approximately one third in subsequent intrahepatic recurrences (Table 3).

Using the clock-reset approach, the transition between states of intrahepatic recurrences accelerated with a

TABLE 2 Laboratory and tumor characteristics

	Overall (*n* = 486)
Preoperative variables	
Preoperative AFP (ng/ml), median (IQR)	17 (4–432)
Preoperative AFP (ng/ml), *n* (%)	
Missing	62
0–20	218 (51.4%)
20–99	60 (14.2%)
100–999	69 (16.3%)
>1000	77 (18.2%)
Preoperative MELD, median (IQR)	7.00 (6.43–8.00)
Preoperative platelet count (100,000), median (IQR)	193.00 (153.75–249.00)
Preoperative INR, median (IQR)	1.02 (0.97–1.07)
Preoperative total bilirubin (mg/dl), median (IQR)	10.00 (8.00–14.00)
Preoperative albumin (g/dl), median (IQR)	42.00 (39.00–44.00)
Preoperative creatinine (μmol/L), median (IQR)	77.00 (68.00–90.00)
Preoperative Child-Pugh grade, *n* (%)	
Missing	41
A5	410 (92.1%)
A6	29 (6.5%)
B7	6 (1.3%)
Preoperative ALBI, median (IQR)	−2.86 (−3.05 to −2.63)
Preoperative ALBI grade, *n* (%)	
Missing	42
1	344 (77.5%)
2	100 (22.5%)
Tumor size preoperatively (cm), median (IQR)	5.00 (3.50–7.90)
Tumor number preoperatively, median (IQR)	1.00 (1.00–1.00)
Missing	0 (0%)
Multiple	60 (12.3%)
Single	426 (87.7%)
Satellite lesions preoperatively, *n* (%)	26 (5.3%)
Pathology and postoperative variables	
Satellite lesions on pathology, *n* (%)	59 (12.1%)
Tumor size on pathology (cm), median (IQR)	5.20 (3.50–8.20)
Histologic grade, *n* (%)	
Missing	10
Well differentiated	21 (4.4%)
Moderate differentiation	351 (73.7%)
Poor differentiation	94 (19.7%)
Undifferentiated	1 (0.2%)
Not able to be assessed/nonviable	9 (1.9%)
Surgical margin positive, *n* (%)	17 (3.5%)
Missing	2
Macrovascular invasion on pathology, *n* (%)	70 (14.6%)
Missing	5
Microvascular invasion on pathology, *n* (%)	240 (50.0%)
Missing	6
Fibrosis, Laennec grade, median (IQR)	3.00 (2.00–4.00)
Cirrhosis	315 (64.9%)
Missing	1
Steatosis, median (IQR)	1.00 (0.00–1.00)
Tumor number on pathology, *n* (%)	
Missing	2
Multiple	117 (24.2%)
Single	367 (75.8%)
Postoperative AFP (ng/ml), *n* (%)	
Missing	98
0–20	302 (77.8%)
20–99	30 (7.7%)
100–999	29 (7.5%)
>1000	27 (7.0%)

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease.

higher intrahepatic recurrence (Figure 3). The 1-year intrahepatic recurrence-free probability was 76.2% after the first intrahepatic recurrence, 58.2% after the second, 48.7% after the third, 39.9% after the fourth, and 54.6% after the fifth. Similarly, transitions from each state to death accelerated with each intrahepatic recurrence (Figure S1). The maximum likelihood estimates of the mean sojourn time (average period [months] of single stay in a state—-i.e., temporary stay) for each nonabsorbing state are shown in Table S2. There was a progressive shortening in the estimates of the mean sojourn time (months) with the exception of the fourth and fifth intrahepatic recurrences (surgery 54.29, first intrahepatic recurrence 33.64, second intrahepatic recurrence 18.15, third intrahepatic recurrence 10.34, fourth intrahepatic recurrence 14.40, fifth intrahepatic recurrence 69.17) (Table S2).

The probability of making a transition from the surgery state over time is shown in Figure 4. The probability of remaining in the surgery state decreased from 94.6% at 3 months to 57.5% at 30 months and 33.1% at 60 months. In contrast, the probability of transitioning from the surgery state to a first intrahepatic recurrence increased from 3.0% at 3 months to 17.5% at 30 months and 17.3% at 60 months (Tables S3–S5). The 3-month, 30-month, and 60-month probabilities of transitioning to a distant recurrence and death from initial surgery were 1.3%, 10.3%, and 16.2% and 1.0%, 8.0%, and

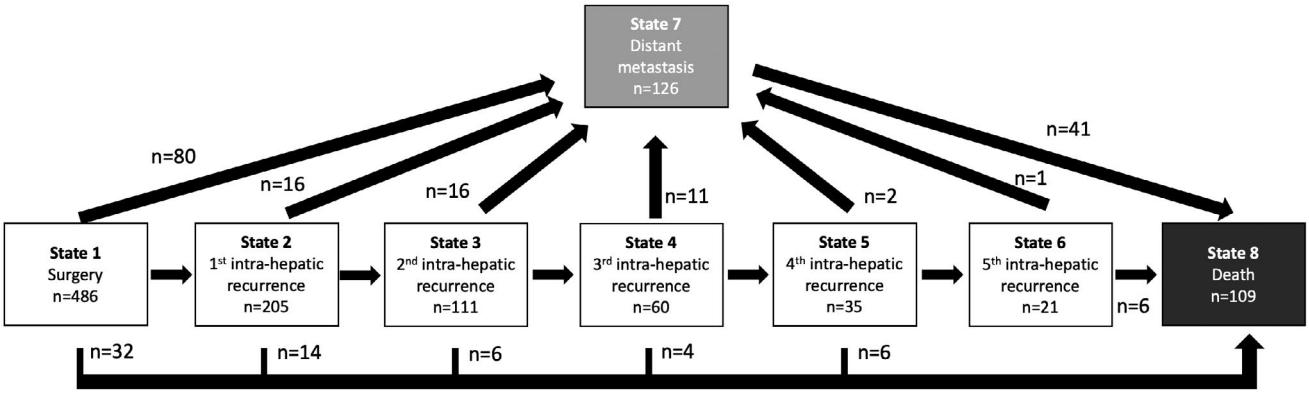

FIGURE 2 Number of patients in each state

19.8%, respectively (Tables S3–S5). In other words, a typical patient in the first state "surgery," disease-free after curative-intent LR, has a 33.1% probability of being disease-free, a 31.0% probability of having an intrahepatic recurrence (first, second, third, or higher), a 16.3% probability of having a distant recurrence (with or without intrahepatic recurrence), and a 19.8% probability of death in the first 60 months after surgery.

The probability of making a transition from the first intrahepatic recurrence over time is shown in Figure 5. The probability of remaining in the first intrahepatic recurrence state decreased from 91.5% at 3 months to 41.0% at 30 months and 16.8% at 60 months. In contrast, the probability of transitioning from the first intrahepatic recurrence state to the second intrahepatic recurrence progressed from 6.1% at 3 months to 20.1% at 30 months and 12.1% at 60 months. The 3-month, 30-month, and 60-month probabilities of transitioning to a distant recurrence or death from the first intrahepatic recurrence were 1.0%, 12.1%, and 19.3% and 1.0%, 12.1%, and 29.7%, respectively. The probability of transition from a distant recurrence is depicted in Figure S2. The probability of making a transition and reaching each state from the surgery state (post–curative-intent surgery) over the first 5 years depending on pathology covariates (including multiple tumors, large tumors [≥5 cm], satellite lesions, and microvascular invasion) is shown in Figure S3. The probability of making a transition and reaching each state from the first intrahepatic recurrence state over the first 5 years depending on receipt of curative-intent treatment for the first intrahepatic recurrence is shown in Figure S4.

Transition intensities from surgery and first intrahepatic recurrence with HRs for various covariates are shown in Tables S6 and S7, respectively. Covariates associated with an increased HR of surgery to first intrahepatic recurrence transition included the presence of satellite lesion on pathology (HR, 2.64; 95% CI, 1.76–3.96) and the presence of microvascular invasion (HR, 1.54; 95% CI, 1.11–2.13). In contrast, while tumor number and presence of a satellite nodule were not associated with the transition from surgery to a distant recurrence (HR, 0.50; 95% CI, 0.22–1.16; and HR, 1.07; 95% CI, 0.52–2.19, respectively), larger tumor size (reference, <5 cm; HR, 2.55; 95% CI, 1.40–4.64) and microvascular invasion on pathology (HR, 4.16; 95% CI, 2.29–7.56) were covariates associated with this type of transition (Table S6).

The online interactive probability estimate calculator was developed to provide prognostic information for patients and clinicians at three time points—postsurgery, at first intrahepatic recurrence, and at second intrahepatic recurrence. Three models are provided: baseline, preoperative (based on variables that are known before surgery, such as age and sex), and postoperative variables (based on variables that are known postoperatively, such as tumor-specific variables; this calculator can be found at https://multistatehcc.shinyapps.io/home/).

DISCUSSION

This study presents an analysis of HCC recurrence post-LR using multistate modeling. Using this technique, a patient's prognosis is estimated based upon not only the disease state a patient is in but also the progression to that state. As opposed to standard time-to-one-event estimates, we found the postoperative course after initial HCC treatment to be highly variable and dependent on the timing and pattern of disease recurrence and/or metastasis. By incorporating these states in our model, we were able to calculate more realistic outcome probabilities of transitioning to a particular disease state and, in turn, develop a calculator that could be used to provide meaningful prognostic information for both patients and clinicians.

The development of HCC recurrence (intrahepatic and distant) after curative-intent LR is high, with estimates of 60%–70% at 5 years in major Western centers.[5,13] In our series, the estimate for disease-free survival at 5 years was 53.2% using a standard statistical binary time-to-one-event method (Kaplan-Meier). While these estimates provide general insight into

TABLE 3 Treatment received after each recurrence

	First intrahepatic recurrence (*n* = 205)	Second intrahepatic recurrence (*n* = 111)	Third intrahepatic recurrence (*n* = 60)	Fourth intrahepatic recurrence (*n* = 35)	Fifth intrahepatic recurrence (*n* = 21)	Distant or intrahepatic and distant recurrence (*n* = 80)
None, *n* (%)	18 (9.0)	8 (7.2)	3 (5.0)	5 (14.3)	1 (4.8)	10 (12.8)
Ablation, *n* (%)	99 (49.7)	45 (40.5)	21 (35.0)	10 (28.6)	5 (23.8)	3 (3.8)
TACE, *n* (%)	28 (14.1)	31 (27.9)	21 (35.0)	11 (31.4)	6 (28.6)	1 (1.3)
LR, *n* (%)	14 (7.0)	2 (1.8)	0	0	0	1 (1.3)
Resection (non-LR), *n* (%)	0	0	0	0	0	15 (19.2)
Liver transplantation (including bridging), *n* (%)	12 (6.0)	13 (11.7)	4 (6.7)	3 (8.6)	2 (9.5)	0
Systemic therapy, *n* (%)	10 (5.0)	4 (3.6)	5 (8.3)	3 (8.6)	3 (14.3)	24 (30.8)
Radiation, *n* (%)	3 (1.5)	1 (0.9)	0	0	2 (9.5)	2 (2.6)
Palliative care, *n* (%)	15 (7.5)	7 (6.3)	6 (10.0)	3 (8.6)	2 (9.5)	22 (28.2)
Missing, *n* (%)	6	0	0	0	0	2

disease recurrence postoperatively, they do not incorporate factors such as time to recurrence and other disease states known to influence outcomes. For example, an estimate of the expected probability of disease-free survival from curative LR may not be directly applicable to patients who have already developed their first recurrence. In this case, estimating subsequent oncologic events such as a second recurrence, distant recurrence, or death is contingent upon the development of the first recurrence. Within this context, multistate modeling provides meaningful prognostic estimates to individual patients, which is particularly useful in diseases such as HCC, where recurrence is not universally fatal.

Multistate modeling allows for adjustment of covariates, such as patient and tumor characteristics, that can offer more individualized estimates. For example, a patient who is 67 years old at the time of LR with two HCC tumors that are large with surrounding satellite nodules and microvascular invasion will have a different probability of transition to a first intrahepatic recurrence or distant recurrence than another patient who is 60 years old with one small focus of HCC without satellite nodules or vascular invasion. The differential prognostic estimates are reflected in the distinct probability shapes (Figures S3a–d and S4a,b). This provides an opportunity to tailor prognostic estimates to individual patients based on their clinicopathologic characteristics. By modeling disease progression after curative-intent LR, our calculator allows one to evaluate specific questions relevant to patient counseling and recurrent HCC behavior, including the following: (1) What is the probability of a first intrahepatic recurrence within 6 months after curative intent LR? (2) What is the probability of dying within 6 months after curative intent LR (with or without a recurrence)? and (3) What is the probability of dying within 6 months after the development of a distant recurrence? It thus offers dynamic insight into disease progression, pattern, and timing of HCC recurrence after curative-intent LR. Furthermore, given the changing landscape of systemic therapy for HCC and the potential for neoadjuvant and adjuvant therapies in these population, this model can better inform future clinical trials design because it may offer a means to improve the stratification of disease.[14] Incorporating information about disease states and the speed of progression between them may offer additional insight into optimal treatment selection strategies. For instance, a slow tumor progression in an 80-year-old patient may warrant a different management strategy from that for a younger patient with a faster disease progression. The concept of timing of disease progression and its relevance has been evaluated in other cancers such as colorectal liver metastases[15] and metastatic renal-cell carcinoma.[16] Nonetheless, it remains to be fully explored in HCC.

While survival is adversely impacted following recurrence, numerous treatments, including repeat

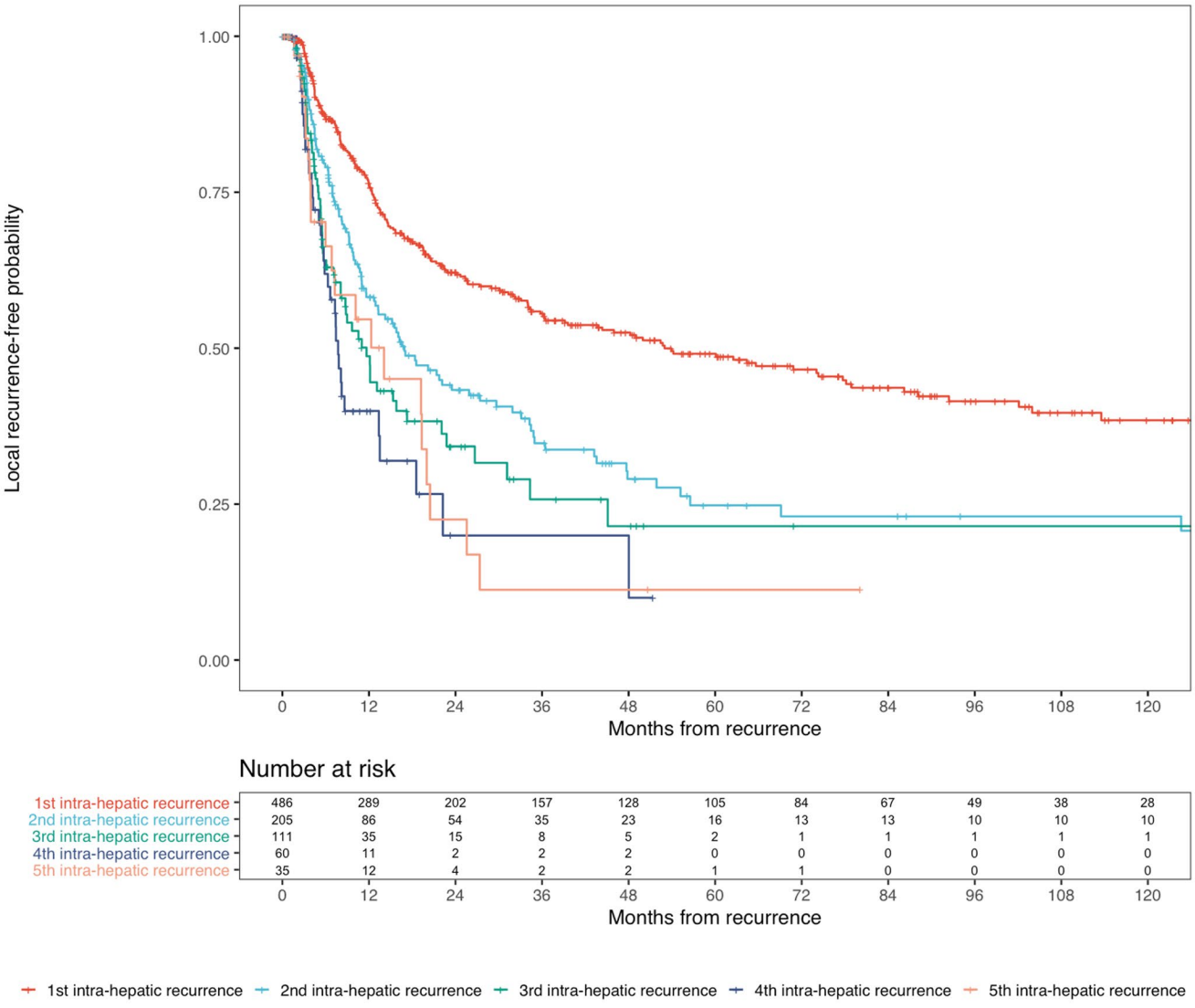

FIGURE 3 Kaplan-Meier estimates of time to intrahepatic recurrence in a clock-reset approach

resection, ablation, TACE, radiation, and liver transplantation, can offer cure and prolong patient survival. As the landscape of treating both primary and recurrent HCC has grown increasingly complex, algorithms have been applied to guide the management.[5,17] Nonetheless, the pursuit of any treatment should be based on an informed discussion between the patient and the clinician. To actively participate in such decision-making, patients must understand the risks and expected outcomes of any given procedure and their prognosis at any given clinical state and time. Traditional solitary time-to-event estimates, while useful, do not offer such prognostic insight in complex multidisease states, such as HCC recurrence, which involves multiple transitions and treatments over time. As such, they may skew a patient's understanding of the disease process and their prognosis. Using a multistate model and explaining the progression through possible disease states may help a patient make a more informed decision when considering different treatment modalities and enhance the understanding of the disease prognosis. Within this context, the patient counseling regarding prognosis will be different if the patient has just undergone a curative-intent LR or has just developed a second local recurrence following curative-intent LR. It is therefore critical to capture prognostic estimates that are relevant for individual patients because they differ based on recurrence and the number of recurrences. An accurate representation of covariate adjustment and the impact of treatment requires a large and heterogeneous patient sample to minimize selection bias and the effect of institutional treatment idiosyncrasies. This is necessary because prognostic estimates are not static and are likely to change depending on receipt and response to therapies. Consequently, the future direction of this analysis is external validation and refinement using a multi-institutional patient cohort.

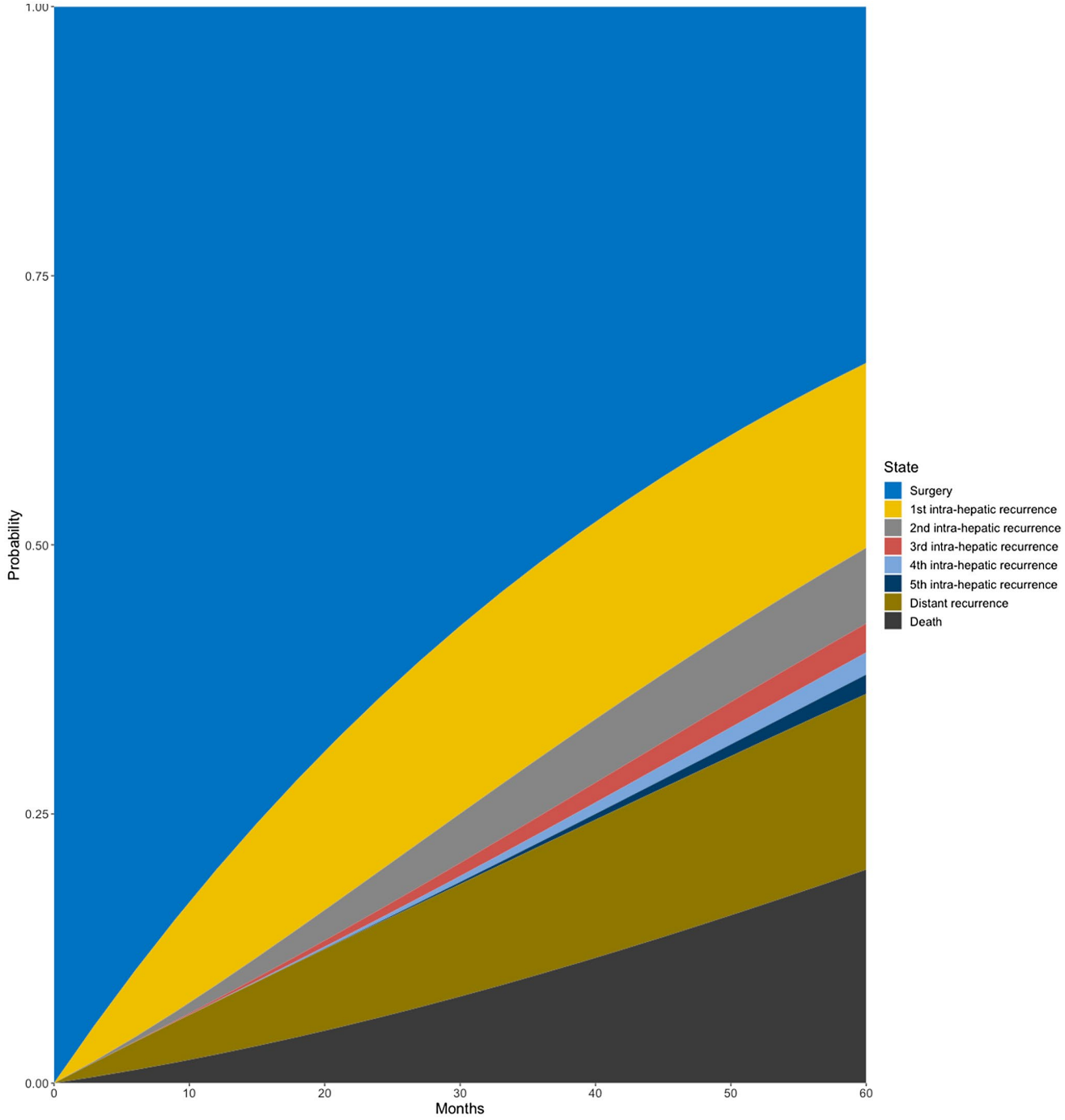

FIGURE 4 Probability of making a transition and reaching each state from the surgery state (postcurative-intent surgery) over the first 5 years. The *y* axis represents probability, and the *x* axis represents months from the beginning state (in this case surgery state [postcurative-intent surgery]). Each state is depicted by a different color. For the surgery state, depicted in blue, at time 0, the probability of being in that state is 1.0 (100%). Over time, the probability of remaining in this state diminishes. In contrast, the probability of having moved to (and stayed in) the first intrahepatic recurrence state (depicted in light yellow) progressively increases over time (e.g., the probability of being in the first intrahepatic recurrence state at time 0 is 0.0 [0%]). A similar interpretation can be applied to other states. For example, the probability of moving to (and staying in) the second intrahepatic recurrence state is negligible until a sufficient probability of the first intrahepatic recurrence transitions has occurred (as moving to a second local recurrence is contingent on having developed a first intrahepatic recurrence)

Limitations

This is a single-center retrospective nonrandomized study, with the potential for selection bias. However, the study population does represent one of the largest samples from a high-volume North American center. Given the diminishing number of transitions with each tumor progression transition, multiple covariate adjustments

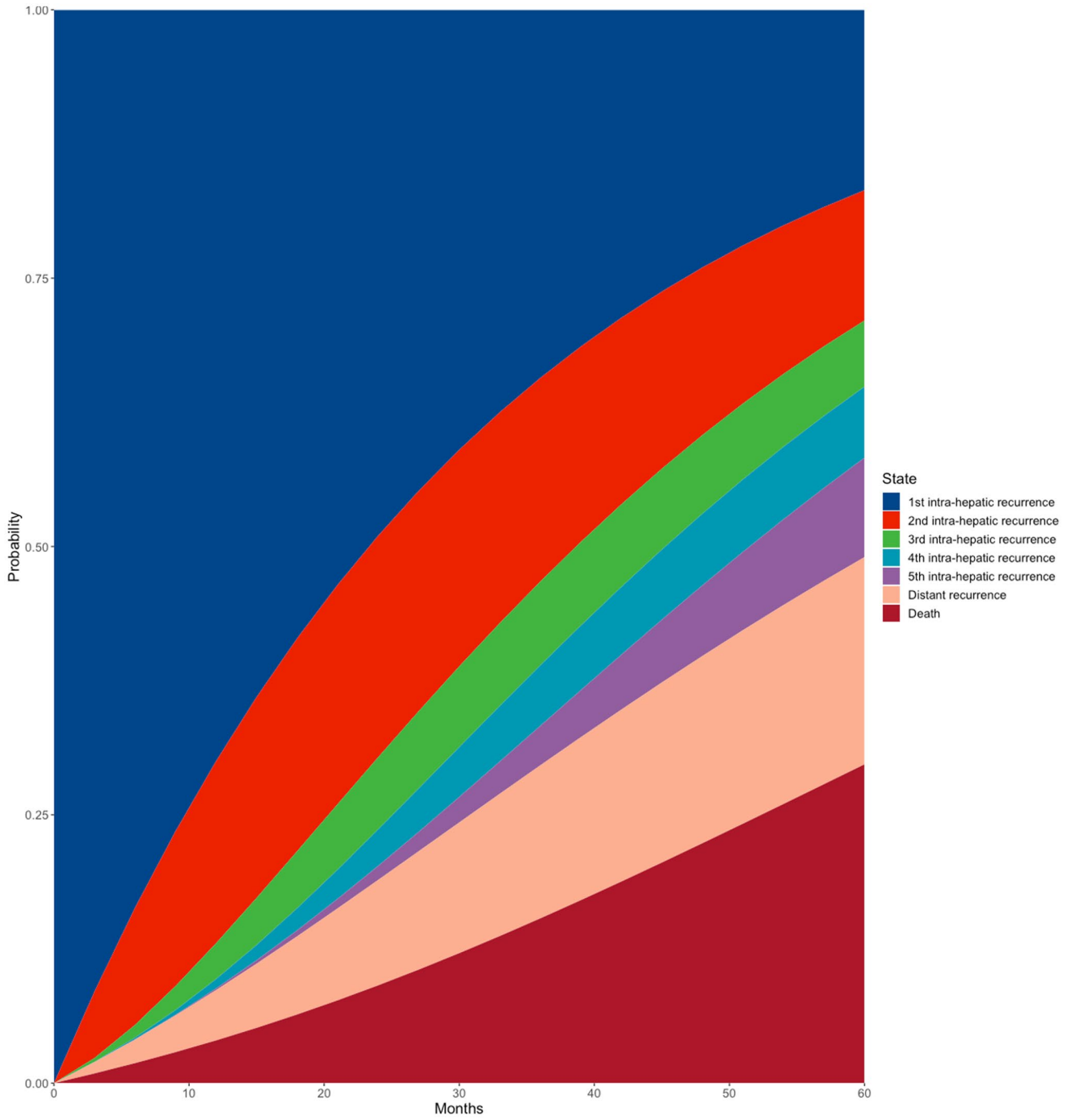

FIGURE 5 Probability of making a transition and reaching each state from the first intrahepatic recurrence state over the first 5 years

were limited. Further, because of the single-institution design, we cannot distinguish between the impact of institutional and provider-based practices (e.g., time to treatment of recurrence or selection of treatment modality for a given recurrence) from HCC disease biology. A larger multi-institutional cohort is planned to validate these findings and improve these results' external validity and generalizability.

In conclusion, multistate modeling of HCC recurrence can be used to account for the various disease states a patient can exist in and transition between after curative-intent LR. In contrast to standard single time-to-event estimates, multistate modeling provides a more realistic prognostication of outcomes after curative-intent surgery for HCC by taking into account a multitude of postoperative disease states and transitions between them. Our multistate modeling calculator can provide meaningful data to guide the management of patients undergoing postoperative surveillance and therapy.

CONFLICTS OF INTEREST

Dr. Sapisochin consults for Intercept. Dr. Sapisochin consults for and received grants from Roche. He consults for AstraZeneca, Novartis, and Integra. He received grants from Bayer.

AUTHOR CONTRIBUTIONS

Conception of project, literature review, analysis, interpretation of results, writing the manuscript: Tommy Ivanics, Carla Fiorella Murillo Perez, Sean P. Cleary, and Gonzalo Sapisochin. Interpretation of results and writing the manuscript: Marco P. A. W. Claasen, Madhukar S. Patel, Chaya Shwaartz. Interpretation of results, writing the manuscript, and online calculator development: Gabriela Morgenshtern and Lauren Erdman. Data collection, interpretation of results, and writing the manuscript: Luckshi Rajendran. Conception of project, analysis, interpretation of results, and writing the manuscript: Bettina E. Hansen. All authors gave final approval of the manuscript.

ORCID

Tommy Ivanics https://orcid.org/0000-0002-1312-4470
Carla Fiorella Murillo Perez https://orcid.org/0000-0001-7634-4537
Marco P. A. W. Claasen https://orcid.org/0000-0001-8218-3119
Madhukar S. Patel https://orcid.org/0000-0001-7508-899X
Gabriela Morgenshtern https://orcid.org/0000-0003-4762-8797
Lauren Erdman https://orcid.org/0000-0002-7106-2669
Chaya Shwaartz https://orcid.org/0000-0003-2841-9834
Luckshi Rajendran https://orcid.org/0000-0002-2716-7121
Grainne M. O'Kane https://orcid.org/0000-0002-8690-403X
Bettina E. Hansen https://orcid.org/0000-0001-8307-3341
Sean P Cleary https://orcid.org/0000-0002-5274-9983
Gonzalo Sapisochin https://orcid.org/0000-0001-9527-8723

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3:524–48.
2. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology. 2015;61:526–36.
3. Teh S, Christein J, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. J Gastrointest Surg. 2005;9:1207–15; discussion 1215.
4. Roayaie S, Jibara G, Tabrizian P, Park J-W, Yang J, Yan L, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 2015;62:440–51.
5. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261:947–55.
6. Bacchetti P, Boylan RD, Terrault NA, Monto A, Berenguer M. Non-Markov multistate modeling using time-varying covariates, with application to progression of liver fibrosis due to hepatitis C following liver transplant. Int. J. Biostat. 2010;6:7.
7. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68:723–50.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–9.
9. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol. 2017;3:493–500.
10. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg. 2005;12:351–5.
11. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer. 1954;7:462–503.
12. Jackson C. Multi-state modelling with R: the msm package. https://cran.r-project.org/web/packages/msm/vignettes/msm-manual.pdf (2019). Accessed 24 Aug 2021.
13. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, et al. Resection of hepatocellular cancer ≤2 cm: results from two Western centers. Hepatology. 2013;57:1426–35.
14. Pinato DJ, Fessas P, Sapisochin G, Marron TU. Perspectives on the neoadjuvant use of immunotherapy in hepatocellular carcinoma. Hepatology. 2021;74(1):483–90.
15. Vigano L, Darwish SS, Rimassa L, Cimino M, Carnaghi C, Donadon M, et al. Progression of colorectal liver metastases from the end of chemotherapy to resection: a new contraindication to surgery? Ann Surg Oncol. 2018;25:1676–85.
16. Rini BI, Dorff TB, Elson P, Rodriguez CS, Shepard D, Wood L, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol. 2016;17:1317–24.
17. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Ivanics T, Murillo Perez CF, Claasen MPAW, Patel MS, Morgenshtern G, Erdman L, et al. Dynamic risk profiling of HCC recurrence after curative intent liver resection. Hepatology. 2022;00:1–11. https://doi.org/10.1002/hep.32411