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Machine Learning Predictive Model to Guide Treatment Allocation for Recurrent Hepatocellular Carcinoma After Surgery

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IMPORTANCE Clear indications on how to select retreatments for recurrent hepatocellular carcinoma (HCC) are still lacking.

OBJECTIVE To create a machine learning predictive model of survival after HCC recurrence to allocate patients to their best potential treatment.

DESIGN, SETTING, AND PARTICIPANTS Real-life data were obtained from an Italian registry of hepatocellular carcinoma between January 2008 and December 2019 after a median (IQR) follow-up of 27 (12-51) months. External validation was made on data derived by another Italian cohort and a Japanese cohort. Patients who experienced a recurrent HCC after a first surgical approach were included. Patients were profiled, and factors predicting survival after recurrence under different treatments that acted also as treatment effect modifiers were assessed. The model was then fitted individually to identify the best potential treatment. Analysis took place between January and April 2021.

EXPOSURES Patients were enrolled if treated by reoperative hepatectomy or thermoablation, chemoembolization, or sorafenib.

MAIN OUTCOMES AND MEASURES Survival after recurrence was the end point.

RESULTS A total of 701 patients with recurrent HCC were enrolled (mean [SD] age, 71 [9] years; 151 [21.5%] female). Of those, 293 patients (41.8%) received reoperative hepatectomy or thermoablation, 188 (26.8%) received sorafenib, and 220 (31.4%) received chemoembolization. Treatment, age, cirrhosis, number, size, and lobar localization of the recurrent nodules, extrahepatic spread, and time to recurrence were all treatment effect modifiers and survival after recurrence predictors. The area under the receiver operating characteristic curve of the predictive model was 78.5% (95% CI, 71.7%-85.3%) at 5 years after recurrence. According to the model, 611 patients (87.2%) would have benefited from reoperative hepatectomy or thermoablation, 37 (5.2%) from sorafenib, and 53 (7.6%) from chemoembolization in terms of potential survival after recurrence. Compared with patients for which the best potential treatment was reoperative hepatectomy or thermoablation, sorafenib and chemoembolization would be the best potential treatment for older patients (median [IQR] age, 78.5 [75.2-83.4] years, 77.02 [73.89-80.46] years, and 71.59 [64.76-76.06] years for sorafenib, chemoembolization, and reoperative hepatectomy or thermoablation, respectively), with a lower median (IQR) number of multiple recurrent nodules (1.00 [1.00-2.00] for sorafenib, 1.00 [1.00-2.00] for chemoembolization, and 2.00 [1.00-3.00] for reoperative hepatectomy or thermoablation). Extrahepatic recurrence was observed in 43.2% (n = 16) for sorafenib as the best potential treatment vs 14.6% (n = 89) for reoperative hepatectomy or thermoablation as the best potential treatment and 0% for chemoembolization as the best potential treatment. Those profiles were used to constitute a patient-tailored algorithm for the best potential treatment allocation.

CONCLUSIONS AND RELEVANCE The herein presented algorithm should help in allocating patients with recurrent HCC to the best potential treatment according to their specific characteristics in a treatment hierarchy fashion.

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Supplemental content

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Although hepatocellular carcinoma (HCC) treatment relies on surgery, this is affected by a high rate of recurrence up to 60% at 5 years.[1] Several therapies have been investigated extensively in the literature to improve survival after recurrence (SAR); however, no clear indications are available on which treatment should be chosen according to the recurrent tumor presentation. Few guidelines[2,3] provide an indication for those events, suggesting that the treatment should be selected according to the stage. However, this approach may be reductionist: it subclassifies patients' risk across a few risk profiles, suggesting only 1 treatment per stage. Moreover, this approach has been noted as being far from a real scenario in the era of multidisciplinary approaches.[4]

Recently, the introduction of machine learning algorithms in medicine drastically changed the potential to develop highly accurate prediction models[5,6]: those techniques changed our way of learning from data, identifying several profiles with efficient tailoring. The decision-making in oncology is the sum of the oncological knowledge and the physicians' experience: the first is the result of several years of research, while the second is intrinsically connected to the physician's skills, previous experiences, availability of services, but also the patient's will. While the last item cannot be predicted, the oncological benefit could be automatically evaluated, providing substantial support to make evidence-based medical decisions. Thus, to our knowledge, this study is the first national attempt to identify the best potential treatment among reoperative hepatectomy and thermoablation, chemoembolization, or sorafenib in predicting SAR by a machine learning and patient-tailored approach. Therefore, we trained and externally validated a potential outcome prediction algorithm for treatment selection and developed a web-based application for forecasting.

Key Points

Question How can the best potential oncological treatment be identified for recurrent hepatocellular carcinoma after surgery among curative approaches, chemoembolization, and sorafenib?

Findings In this prognostic study of 701 patients with recurrent hepatocellular carcinoma, a machine learning model was created to predict the survival after recurrence, and its area under the receiver operating characteristic curve was 78.5% at 5 years after recurrence; the model's area under the receiver operating characteristic curve reached 76.8% in another Italian cohort and 70.9% in a Japanese cohort. According to the model, most patients would have benefited from reoperative hepatectomy or thermoablation.

Meaning The herein presented algorithm should help in allocating patients with recurrent hepatocellular carcinoma to the best potential treatment according to their specific characteristics in a treatment hierarchy fashion.

Methods

Study Overview, Patient Selection, and Study Design

This is a secondary analysis of previously collected registry data prospectively enrolled by a national Italian register on hepatocellular carcinoma, the HE.RC.O.LE.S. (Hepatocarcinoma Recurrence on the Liver Study; NCT04053231) group, which includes participation by 30 surgical centers. The ethical committee of the coordinating center (Monza e Brianza Ethical Committee) approved the study protocol on December 21, 2018. Because of the retrospective and observational nature of the present study, the committee evaluated that written consent was not mandatory. Results are reported according to principles of Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline.[7] All consecutive adult patients (age ≥18 years) with a radiological and/or histologically proven HCC who underwent surgery between January 2008 and December 2019 were evaluated. Inclusion criteria for this study were (1) patients who underwent surgery for the first diagnosis of HCC without previous therapies, (2) patients who experienced a recurrence after surgery during the follow-up period, and (3) a recurrence treated by reoperative hepatectomy or thermoablation, transarterial chemoembolization, or sorafenib. Exclusion criteria were (1) a recurrence episode not following the absolute first treatment of the HCC, (2) missing data at follow-up, and (3) recurrence treatments other than those described in the inclusion criteria (included salvage liver transplant or being on a waiting list; using other tyrosin-kinase inhibitors or any type of immunotherapy). Selected patients were then divided into those who were treated for their recurrence by reoperative hepatectomy or thermoablation, those who were submitted to sorafenib, and those who were submitted to chemoembolization.

The primary study end point was SAR. The main aim was to assess the treatment of choice for HCC recurrence after surgery (among reoperative hepatectomy or thermoablation, chemoembolization, or sorafenib), which can lead to the best SAR according to different patient profiles.

Data of patients who had recurrence after a surgical treatment for HCC enrolled in another Italian national register on liver cancer (Italian Liver Cancer [ITA.LI.CA] study) were used as an external validation cohort. Another external validation cohort was obtained by the participation at the study of the surgeons attending the hepato-biliary-pancreatic surgery division of the University of Tokyo in Japan.

Definitions and Follow-up Protocol

Variables descriptions are provided in eMethods 1 in Supplement 1. The indication for reoperative hepatectomy or thermoablation, sorafenib, and chemoembolization was assessed by multidisciplinary meetings on a patient-by-patient basis and involved surgeons, hepatologists, oncologists, radiologists, interventional radiologists, and infectivologists as the sum of different evaluations about the underlying liver function, the tumor burden, and the comorbidities, creating tailored treatments for each individual case.

All patients were followed up using local protocols[8] every 3 months for the first 2 years and then every 6 months. SAR was defined as the time interval between the date of the assigned treatment for recurrence and any cause of death.

Time to recurrence was defined as the time interval in months from the first surgery to the date of recurrence. In case of no event, patients were censored at the last available visit. Patient surveillance was closed at the end of March 2019.

Statistical Analysis

The problem of missing values was tackled using multiple imputation by chained equations method. The selection of features that play a role as prognostic factors for SAR but also as treatment modifiers was performed by fitting a Cox model with least absolute shrinkage and selection operator (LASSO) penalization.[9] Ten-fold crossvalidation was used to choose the optimal value of the shrinkage parameter lambda.[10] All features that were retained by this procedure were used in the subsequent development of the prediction model.

The prediction model was built as a standard Cox model with all second-order interactions of treatment with the features selected by LASSO. The predictive performance of the model was evaluated using receiver operating characteristic (ROC) methodology (with bootstrap-validated area under the ROC curve index) and calibration plots (with Brier score).[11,12] The same procedures were adopted to perform an external validation of the model performance on data of patients with recurrence after surgery taken form the ITA.LI.CA and the Japanese cohorts.

For each patient, the model estimates were used to predict the potential SAR at 3 and 5 years under each treatment. Subsequently, the potentially optimal treatment within patients was determined as the one leading to the highest predicted SAR.

Considering the possible combinations of the 7 features included, the model was able to deal with potentially infinite different patients' risk profiles, and consequently it was built up as an R Shiny web application to let users calculate the potential SAR in time under each treatment for every profile of interest.

To simulate how the algorithm works in a clinical scenario, we also refitted the same prediction model described before but using variables' dichotomization to reduce the number of potential risk profiles obtainable in case of continuous variables. Thus, we only considered the 5 features showing the largest impact as treatment effect modifiers (age <75 or ≥75 years, cirrhosis: yes/no, number of recurrent nodules: 1 or >1, single/bilobar recurrence, and intra-/extrahepatic recurrence) and we created $2^5 = 32$ risk profiles from all possible combinations of the levels of these features (the remaining 2 features were fixed at size <50 mm and time to recurrence of 15 months). Potential SAR prediction at 3 and 5 years under each treatment was predicted for all these profiles.

When the difference in SAR between 2 treatments was less than 5%, both treatments were labeled as optimal. A tree diagram based on these simulations was drawn. The detailed description of statistical methods is provided as eMethods 2 in Supplement 1. Significance was considered when $P < .05$. All the analyses were carried out using R version 4.0.3 (R Foundation). Analysis took place between January and April 2021.

Results

During the study period, 2699 patients were enrolled in HE.RC.O.LE.S. Of these, 1235 (47.5%) experienced a recurrence after the first surgical treatment. Data on patients excluded were reported in eMethods 3 in Supplement 1. Finally, 701 patients (56.76%) were enrolled and further analyzed. For 293 patients (41.8%), recurrence was treated with reoperative hepatectomy or thermoablation, while 188 (26.8%) underwent sorafenib and 220 (31.4%) underwent chemoembolization. A flowchart is available in eFigure 1 in Supplement 1. The baseline characteristics among groups are summarized in **Table 1** (overall mean [SD] age, 71 [9] years; 151 [21.5%] female). SAR rates at 5 years from the first surgery in the 3 treatment groups for recurrence were 61.9% (95% CI, 53.6%-70.3%) for reoperative hepatectomy or thermoablation, 34.5% (95% CI, 23.8%-45.3%) for chemoembolization, and 32.3% (95% CI, 22.0%-42.7%) for sorafenib. Median SAR was not reached for reoperative hepatectomy or thermoablation and was 42.8 (95% CI, 32.9-50) months for chemoembolization and 17.9 (95% CI, 13.2-24) months for sorafenib. Median disease-free survival after the recurrence was 37 (95% CI, 31-56), 21.3 (95% CI, 16.9-27.6), and 15 (95% CI, 12.3-19) months for reoperative hepatectomy or thermoablation, chemoembolization, and sorafenib, respectively.

A prediction model for SAR, treatment effect modifiers' identification, and a combination created the prediction algorithm. The association of SAR with the features selected by LASSO was investigated using univariate Cox models (eTable 1 in Supplement 1). The output of the application of LASSO penalization to the Cox model for the selection of predictive features is shown in eFigure 2 and eTable 2 in Supplement 1. Variables selected were treatment, age, cirrhosis, number and size of the recurrent nodules, bilobar presentation, extrahepatic spread, and time to recurrence. Treatment was associated with SAR, showing that patients treated with sorafenib (hazard ratio [HR], 3.68 [95% CI, 2.66-5.08]) or chemoembolization (HR, 1.99 [95% CI, 1.43-2.78]) were at a higher risk of death than patients receiving reoperative hepatectomy or thermoablation. Overall, the features showing the greatest prognostic association with outcomes were number of recurrent nodules more than 1 (HR, 2.15 [95% CI, 1.64-2.83]), size of the biggest recurrent nodule of 50 mm or more (HR, 2.89 [95% CI, 2.14-3.90]), and extrahepatic recurrence (HR, 2.95 [95% CI, 2.19-3.97]). Moreover, to explore the role of these features as treatment effect modifiers, the comparison of the association of treatments with SAR was evaluated in the subgroups defined by each feature (**Figure 1**). Sorafenib showed a worse performance with respect to reoperative hepatectomy or thermoablation in people younger than 75 years (HR, 5.03 [95% CI, 3.63-7.54]) than in those older than 75 years (HR, 2.01 [95% CI, 1.16-3.46]); a similar trend is shown also by chemoembolization vs no chemoembolization (HR, 2.23 [95% CI, 1.47-3.39] vs HR, 1.62 [95% CI, 0.94-2.82]).

The coefficients (ie, logarithm of the HR) of the multivariable Cox model used to estimate the potential SAR under each treatment are shown in **Table 2**. The number of recurrent

Table 1. Comparison of Features Among Groups of Treatment Actually Received and Groups of Best Potential Treatments

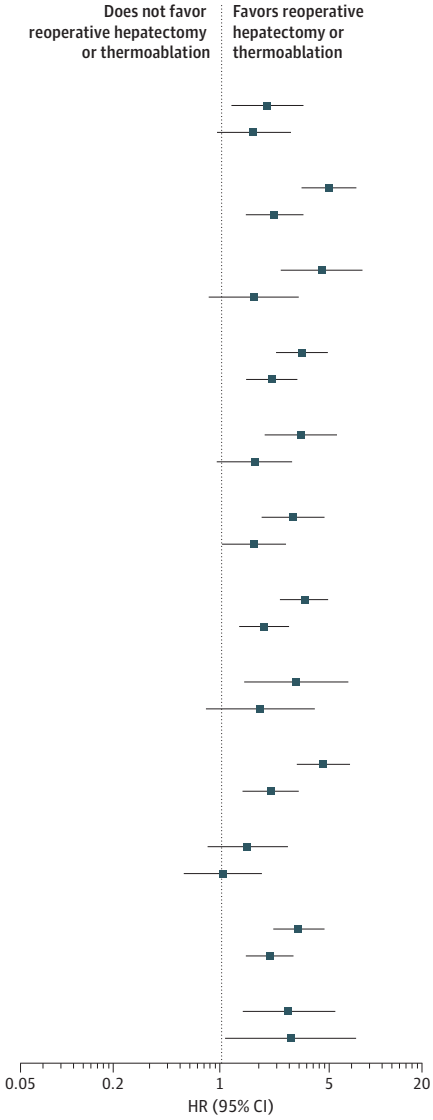
Features	Treatment received				Best potential treatment[a]			
	No. (%)				No. (%)			
	Reoperative hepatectomy or thermoablation (n = 293)	Sorafenib (n = 188)	Chemoembolization (n = 220)	*P* value	Reoperative hepatectomy or thermoablation (611 [87.2%])	Sorafenib (37 [5.2%])	Chemoembolization (53 [7.6%])	*P* value
Actual treatment								
Reoperative hepatectomy or thermoablation	NA	NA	NA	NA	247 (40.4)	16 (43.2)	30 (56.6)	.01
Sorafenib	NA	NA	NA		171 (28.0)	13 (35.1)	4 (7.5)	
Chemoembolization	NA	NA	NA		193 (31.6)	8 (21.6)	19 (35.8)	
Age at recurrence, median (IQR), y	72.90 (66.93-76.59)	71.26 (63.32-76.97)	72.82 (66.56-77.16)	.10	71.59 (64.76-76.06)	78.52 (75.28-83.38)	77.02 (73.89-80.46)	<.001
Female	65 (22.2)	45 (23.9)	41 (18.6)	.41	124 (20.3)	13 (35.1)	14 (26.4)	.07
Male	228 (77.8)	143 (76.1)	179 (81.4)		487 (79.7)	24 (64.9)	39 (73.6)	
Cirrhosis	194 (67.4)	123 (65.8)	140 (63.6)	.68	412 (67.4)	31 (83.8)	18 (34.0)	<.001
Child-Pugh class B	11 (6.0)	7 (5.7)	10 (7.4)	.84	NA	NA	NA	NA
No. of recurrence nodules								
>1	70 (24.5)	120 (74.1)	123 (67.2)	<.001	340 (55.6)	18 (48.6)	24 (45.3)	.27
Median (IQR)	1 (1-1)	2 (1-5)	2 (1-4)	<.001	2.00 (1.00-3.00)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	.03
Bilobar recurrence	31 (13.2)	49 (49.5)	68 (42.2)	<.001	165 (27.0)	21 (56.8)	36 (67.9)	<.001
Size, cm								
≥5	21 (7.9)	36 (23.4)	26 (15.0)	<.001	95 (15.5)	3 (8.1)	2 (3.8)	.03
Median (IQR)	2 (1.5-2.5)	2.5 (1.5-4.4)	2 (1.5-3.4)	<.001	2.00 (1.50-3.30)	2.40 (1.60-3.30)	1.50 (1.00-2.00)	<.001
MVI	98 (39.2)	78 (47.0)	75 (41.2)	.28	258 (42.2)	19 (51.4)	19 (35.8)	.34
Extrahepatic recurrence	28 (9.6)	61 (33.9)	11 (5.2)	<.001	89 (14.6)	16 (43.2)	0	<.001
TTR, median (IQR), months	17.87 (7.93-34.46)	10.46 (5.05-30.08)	13.26 (6.79-23.34)	.001	15.11 (6.57-28.98)	6.79 (2.43-17.64)	21.90 (10.98-41.41)	<.001

Abbreviations: MVI, microvascular invasion; NA, not applicable; SAR, survival after recurrence; TTR, time to recurrence (from first surgery).

[a] The treatment leading to the highest SAR for each patient.

Figure 1. Comparison of the Association of Treatments With Survival After Recurrence Evaluated Using Cox Univariate Models in the Subgroups Defined by Each Feature Selected by Least Absolute Shrinkage and Selection Operator Penalization

Source	HR (95% CI)
Age >75 y	
Sorafenib vs reoperative hepatectomy or thermoablation	2.01 (1.16-3.46)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.62 (0.94-2.82)
Age 75 y	
Sorafenib vs reoperative hepatectomy or thermoablation	5.03 (3.36-7.54)
Chemoembolization vs reoperative hepatectomy or thermoablation	2.23 (1.47-3.39)
Cirrhosis	
Sorafenib vs reoperative hepatectomy or thermoablation	4.50 (2.47-8.21)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.63 (0.83-3.21)
No cirrhosis	
Sorafenib vs reoperative hepatectomy or thermoablation	3.36 (2.28-4.95)
Chemoembolization vs reoperative hepatectomy or thermoablation	2.14 (1.46-3.14)
1 Recurrent nodule	
Sorafenib vs reoperative hepatectomy or thermoablation	3.33 (1.94-5.71)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.65 (0.95-2.88)
>1 Recurrent nodule	
Sorafenib vs reoperative hepatectomy or thermoablation	2.93 (1.83-4.70)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.63 (1.01-2.64)
Size of recurrent nodules = 5 cm	
Sorafenib vs reoperative hepatectomy or thermoablation	3.45 (2.41-4.95)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.92 (1.33-2.77)
Size of recurrent nodules >5 cm	
Sorafenib vs reoperative hepatectomy or thermoablation	3.09 (1.43-6.67)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.79 (0.80-4.03)
Recurrence not bilobar	
Sorafenib vs reoperative hepatectomy or thermoablation	4.63 (3.14-6.84)
Chemoembolization vs reoperative hepatectomy or thermoablation	2.10 (1.37-3.20)
Bilobar recurrence	
Sorafenib vs reoperative hepatectomy or thermoablation	1.49 (0.82-2.69)
Chemoembolization vs reoperative hepatectomy or thermoablation	1.02 (0.57-1.83)
Hepatic recurrence	
Sorafenib vs reoperative hepatectomy or thermoablation	3.18 (2.16-4.68)
Chemoembolization vs reoperative hepatectomy or thermoablation	2.07 (1.45-2.96)
Extrahepatic recurrence	
Sorafenib vs reoperative hepatectomy or thermoablation	2.74 (1.37-5.46)
Chemoembolization vs reoperative hepatectomy or thermoablation	2.85 (1.07-7.58)



HR indicates hazard ratio.

nodules and size included more than 1 coefficient because they were modeled flexibly using fractional polynomials. Thus, the model included all second-order interactions of treatment with each feature. The area under the ROC curve of the model's ROC was high (80.5% [95% CI, 74.8%-86.2%] at 36 months and 78.5% [95% CI, 71.7%-85.3%] at 60 months) and remained satisfactory even after correcting for overoptimism using bootstrap resampling (74.3% [95% CI, 69.9%-79.5%] at 36 months and 72.1% [95% CI, 64.9%-79.1%] at 60 months; **Figure 2**A and B). A good level of calibration was reached as observed and the predicted SAR were in strong agreement (Figure 2C and D). The performance of the model was also tested on 2 external validation sets, the ITA.LI.CA cohort and the cohort from Tokyo University, including patients with recurrence after surgery. The model provided again a good discrimination level: in the ITA.LI.CA cohort, area under the ROC curve was 71.4% (95% CI, 64.6%-78.3%) at 36 months and 76.8% (95% CI, 69.1%-84.5%) at 60 months (eFigure 3 in Supplement 1) and in the cohort from Tokyo University, area under the ROC curve was 69.7% (95% CI, 63.8%-75.6%) at 36 months and 70.9% (95% CI, 64.3%-77.4%) at 60 months (eFigure 4 in Supplement 1). A description of the characteristics of patients of the 2 validation sets is shown in eTable 3 (ITA.LI.CA. cohort) and eTable 4 (Tokyo University) in Supplement 1, while a comparison among these cohorts and the derivation set is available in eTables 5 and 6 in Supplement 1.

For each patient, we estimated the potential SAR predicted by the model at 36 and 60 months under the 3 treatments and compared the distributions (eFigure 5 in Supplement 1). According to our model, the potential SAR would tend

to be higher if all were treated with a curative approach (median [IQR] at 60 months: 0.63 [0.48-0.75]) and lower if all were treated with sorafenib (0.31 [0.20-0.47]) or chemoembolization (0.44 [0.19-0.61]).

Characteristics of the Patients After Identification of Their Best Potential Treatments

According to our model, patients were subgrouped again according to the treatment that may guarantee the potential best SAR individually. This stratification was used to understand the profiles of the patients who may benefit the more from 1 of the 3 treatments, according to our model. Reoperative hepatectomy or thermoablation was the best potential treatment for 611 patients (87.2%), while it was sorafenib for 37 (5.2%) and chemoembolization for 53 (7.6%). However, in the observed cohort only 40.4% (n = 247) of those in whom reoperative hepatectomy or thermoablation was the best potential treatment were actually treated by curative approaches; 35.1% (n = 13) were actually treated by sorafenib in which sorafenib was considered the best potential treatment by our model. In the case of chemoembolization, 35.8% (n = 19) of those who may benefit more from that approach were treated accordingly.

The characteristics of the best potential treatment cohorts are reported in Table 1, while a comparison among best potential treatment and the treatment actually received are summarized in eTable 7 in Supplement 1. Briefly, patients for whom the best potential treatment was reoperative hepatectomy or thermoablation were more frequently younger (median [IQR] age, 71.6 [64.6-76.1] years), often had cirrhosis (412 [67.4%]), frequently had larger tumors (95 individuals [15.5%] with size >5 cm), and occasionally presented with a concomitant extrahepatic spread (89 [14.6%]). Older patients (median [IQR] age, 78.5 [75.3-83.4] years), had cirrhosis (31 [83.8%]), frequently with a bilobar disease (21 [56.8%]), and with a high rate of extrahepatic spread (16 [43.2%]) were the best candidates for sorafenib. Finally, patients for whom chemoembolization was the best potential treatment had a similar median age with the sorafenib group (median [IQR] age, 77.0 [73.9-80.5] years), had a low incidence of cirrhosis (18 [34.0%]), but never had extrahepatic involvement. Median (IQR) time to recurrence was 15.11 (6.6-28.9), 6.79 (2.4-17.6), and 21.9 (10.9-41.4) months for reoperative hepatectomy or thermoablation, sorafenib, and chemoembolization, respectively, as the best potential treatment. Those risk profiles were depicted in an alluvial plot in eFigure 6 in Supplement 1.

The prediction model with the best treatment identification was also embedded in an online application, which is freely available.[13] Users must select the value of each feature to create a certain patient profile and check the potential SAR under each treatment predicted by the model (eFigure 7 in Supplement 1).

To graphically simulate how the algorithm thinks, age, size, and time to recurrence were dichotomized and predicted SAR curves for 32 risk profiles, according to the combination of 5 varying features (age, cirrhosis, number of nodules, recurrence localization, and bilobar recurrence) were then evaluated, after fixing 2 features (size of recurrent nodule, <5 cm; time to recurrence, 15 months). The curves were reported in eFigure 8 in Supplement 1 (intrahepatic recurrence) and in eFigure 9 in Supplement 1 (extrahepatic recurrence). This model's approximation was used to build up graphical decision trees, which are available in **Figure 3**A (SAR at 60 months in cases of intrahepatic recurrence), Figure 3B (extrahepatic recurrence), and eFigures 10 and 11 in Supplement 1.

Table 2. Coefficients and Standard Errors of the Cox Prediction Model[a]

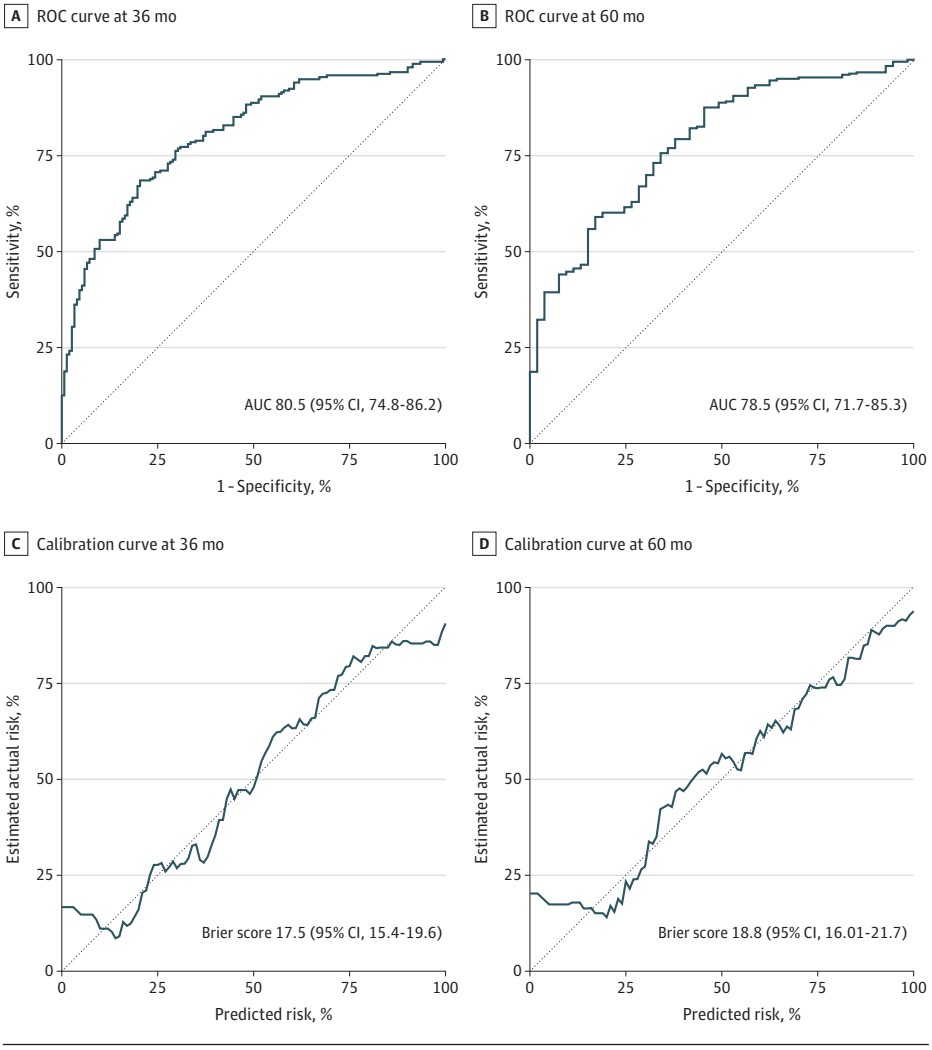
Factor	Estimated coefficient (SE)
Treatment sorafenib vs reoperative hepatectomy or thermoablation	6.59 (1.91)
Treatment chemoembolization vs reoperative hepatectomy or thermoablation	3.65 (2.03)
Female (age)	0.04 (0.02)
Cirrhosis: yes vs no	0.15 (0.29)
Female (No. of recurrence nodules): 1	−0.04 (0.65)
Female (No. of recurrence nodules): 2	7.80 (5.69)
Female (size recurrence nodules): 1	0.32 (0.17)
Female (size recurrence nodules): 2	0.85 (0.38)
Bilobar recurrence: yes vs no	0.63 (0.39)
Extrahepatic recurrence: yes vs no	1.02 (0.35)
Female (time to recurrence)	0.68 (0.24)
Sorafenib × female (age)	−0.05 (0.02)
Chemoembolization × female (age)	−0.02 (0.02)
Sorafenib × cirrhosis	−0.30 (0.37)
Chemoembolization × cirrhosis	0.31 (0.40)
Sorafenib × female (No. of recurrence nodules): 1	−1.27 (0.89)
Chemoembolization × female (No. of recurrence nodules): 1	−0.86 (0.85)
Sorafenib × female (No. of recurrence nodules): 2	−4.89 (6.51)
Chemoembolization × female (No. of recurrence nodules): 2	−5.47 (6.68)
Female (No. of recurrence nodules): 1 × female (No. of recurrence nodules): 2	−0.15 (0.13)
Sorafenib × female (size recurrence nodules): 1	0.14 (0.12)
Chemoembolization × female (size recurrence nodules): 1	−0.06 (0.17)
Sorafenib × female (size recurrence nodules): 2	0.45 (0.39)
Chemoembolization × female (size recurrence nodules): 2	0.09 (0.61)
Female (size recurrence nodules): 1 × female (size recurrence nodules): 2	0.08 (0.04)
Sorafenib × bilobar recurrence	−0.88 (0.51)
Chemoembolization × bilobar recurrence	−0.87 (0.47)
Sorafenib × extrahepatic recurrence	−0.62 (0.42)
Chemoembolization × extrahepatic recurrence	0.90 (0.57)
Sorafenib × female (time to recurrence)	−0.38 (0.31)
Chemoembolization × female (time to recurrence)	0.16 (0.33)

[a] All second-order interactions of the features with treatment are included.

Discussion

The recognition of the best potential SAR allowed the identification that up to 87% of patients who were treated with surgery for HCC and then experienced a recurrence may find an advantage from a repetitive curative strategy. However, according to our data, almost 40% received a curative approach for their recurrence. Chemoembolization or sorafenib were

Figure 2. Performance of the Algorithm in Predicting Survival After Recurrence



AUC indicates area under the receiver operating characteristic curve; ROC, receiver operating characteristic.

frequently chosen, but they were the best potential treatment in less than 7% and 5% of participants, respectively. In other words, according to our prediction model, it seems that a large number of the cohort did not receive the best potential treatment according to the underlying characteristics. Our results, together with the model prediction accuracy, were confirmed also in cohorts different from ours, as another large Italian cohort, but also in an Eastern series as the one derived from the University of Tokyo. This suggests the urgent need for the implementation of a standardized, evidence-based treatment allocation protocol, because it seems that there is still a tendency to consider relapse after surgery as a failure of the curative intent. Although the superiority of repeated curative therapies is not surprising,[14-17] different approaches could be available in the daily practice,[18-20] as a result of the availability of multidisciplinary strategies, the high tumor heterogeneity, and the frequent coexistence of cirrhosis, which render clinical decisions more challenging.[16,21] Deciding among them may be intricate: our algorithm provides a way to simulate different strategies according to the patient's oncological characteristics. The classical stage-driven algorithms, per the Barcelona Clinic Liver Cancer,[22] have already been criticized for their rigidity in allocating patients at their first diagnosis,[4,23] and their role in the allocation of patients in cases of relapse has not even been recommended by the associations that have supported this system. Our methodological approach allowed us to create a highly patient-tailored algorithm, which accounted for the heterogeneity of the cases as the concomitant sum of several elements averaged by their impact on survival.

The variables selected for our model were all risk factors for mortality after recurrence, but they were also features that may change the treatment allocation. Some of them are well described as determinants of the prognosis, as in the case of a recurrent number of nodules and their sizes.[14-17] The localization of the recurrence, intra- or extrahepatic, plays a very important role not only in affecting the long-term outcomes, but also in determining the best potential treatment. The extrahepatic spread was long considered, in the stage-driven algorithms, an absolute contraindication for curative intent.[24]

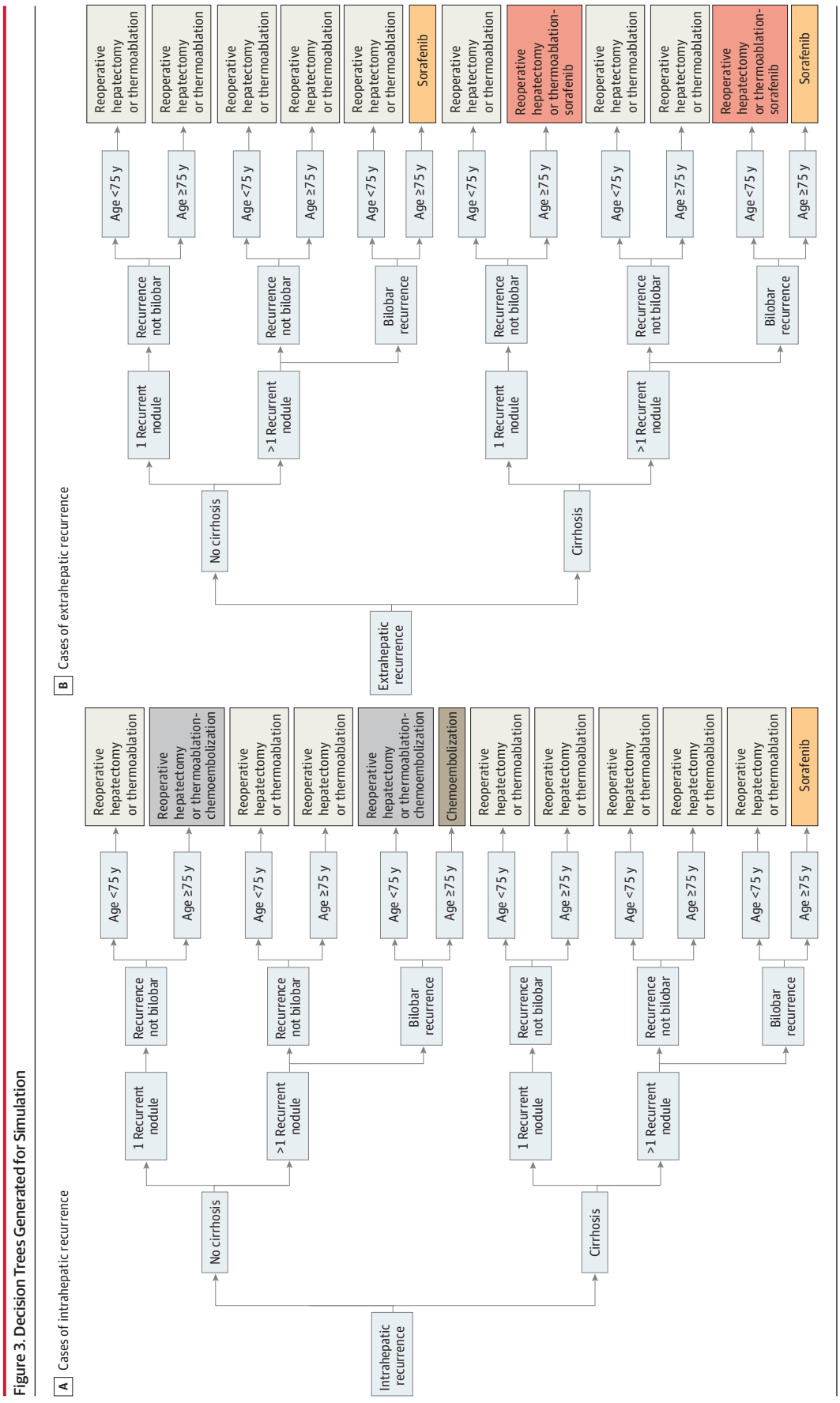


Figure 3. Decision Trees Generated for Simulation

However, different authors recently demonstrated that, in selected cases, there may also be a space for a cure in this advanced setting[25]: our results confirmed and take into account this indication.

The time to recurrence has been largely highlighted as a biological surrogate factor: an early relapse has been correlated with an intrahepatic metastatization, while a late recurrence was considered the expression of a de novo origin driven by the underlying liver damage, which is not fixed during the tumor resection.[16,26] Furthermore, the underlying liver function (here represented by the presence of cirrhosis) at the initial liver resection is strongly associated with the implementation of repeat curative therapies.[16,27] Thus, while the role of age in treatment allocation is clinically evident, its role in affecting survival has recently been discussed.[28,29] However, our model did not provide the tumor-specific risk of death, but the overall SAR, which is inevitably connected to aging, as evident in case of simulations among patients older than 80 years, where the survival tends to be similar and low among treatments.

It is of interest that all of those factors were not under the control of the clinicians and were dependent on the underlying liver condition and the tumor biology. In this sense, the treatment choice is the only factor in which the physicians have the opportunity to influence the outcome. The era of multidisciplinary meetings has improved the ability to modify this factor appropriately: a novel algorithm, such as the one here proposed, which is found on the ability of machine learning approaches to greatly increase the prediction power,[30] may become a smart tool with which to simulate various scenarios under different treatments for the same patient. In other words, it systematically directs the choice toward the potentially most effective option on an individual basis. Our model provides a simulator to standardize the potential survival benefit according to some bio-oncological features; however, it cannot account for the feasibility of one treatment. The latter is a sum of factors as comorbidities, frailty considerations, patient will, but also surgeon's experience. Those elements cannot be foreseen or synthesized by a machine, and automatization in oncological decision-making should be considered as a chimera. Our model, in fact, is thought to help multidisciplinary meetings in making oncological simulations, as a support and not as a replacement of the physicians' professionalism and experience. Moreover, the parameters considered in the model reflected the tumor burden and the patients' conditions without considering factors that could diverge in different populations, like the etiology: this can permit a worldwide use of the model.

Limitations

The limits of the present study may be different. Although a large sample size, the most extreme cases are rare in our model (eg, young patients or extremely high number of nodules) and the forecasting ability in those settings may be poor. Although the underlying liver damage was a prognosis and treatment effect modifier, the severity of cirrhosis was not significant; this may be due to the good remnant liver functions of a cohort of patients that had been relatively recently treated by surgery. Special consideration is mandatory to discuss the absence of salvage liver transplant as a choice in our model. Although the well-known survival benefit of salvage liver transplant for recurrent HCC,[31] in the HE.RC.O.LE.S. database that approach has been chosen in only 48 patients (1.7%). The lack of data avoided any solid application in our analysis. However, the database depicts a 10-year real scenario among several hospitals (including those with a transplant program), suggesting that, at least in Italy, salvage liver transplant is still a rare indication. Nevertheless, the implementation of that treatment represents the room of growth for our model in the near future.

Conclusions

The herein presented algorithm should help in allocating patients with recurrent HCC to the best potential treatment according to their specific oncologic characteristics in a treatment hierarchy fashion.

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Invited Commentary

Can *The Matrix* Help Treat Recurrent Hepatocellular Carcinoma?

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In this issue of *JAMA Surgery*, Famularo et al[1] created a model for determining optimal treatment after postoperative recurrence of hepatocellular carcinoma (HCC) using data from 30 Italian centers, along with validation using international multicenter databases. We congratulate Famularo et al for their meticulous analysis and robust results.

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This research represents an innovative application of artificial intelligence (AI) in the field of surgery. AI has 4 main aspects: (1) machine learning, (2) natural language processing, (3) artificial neural networks, and (4) computer vision.[2] In their study, the authors used "supervised learning," a part of machine learning, to create an accurate algorithm for predicting prognosis of HCC recurrence after an initial surgical approach. They also created an intuitive web application that may help allocate patients to the best potential treatment for their specific clinical characteristics.

In clinical practice, we frequently see patients who develop recurrence after surgery for HCC. However, we need to be prudent when applying this study's model in the clinical setting for several reasons. First, HCC can have multiple recurrences, and with each recurrence the clinician must consider the best treatment modality/option for each individual patient. Second, the study's patient selection criteria are limited. Specifically, only patients who underwent hepatic resection as initial HCC treatment were included in the study cohort. For early HCC, ablation is comparable to hepatic resection.[3] Third, redo surgery, thermoablation, transarterial chemoembolization, and sorafenib are not the only treatment options after HCC recurrence. Additional local treatments, not included in the study model, include radiation therapy and radioembolization with yttrium-90.[4] Furthermore, systemic options such as molecular-targeted therapy or immunotherapy (an exclusion criterion in this study) are used increasingly in combination with other modalities.[5] Fourth, circulating tumor DNA has emerged as a potential tool to determine the optimal sequence of treatment in HCC.[6] Repeated evaluation of biological markers may improve the selection of treatment and better adjust the intensity of treatment to tumor burden. These novel approaches will require a significant amount of data, and the help of AI to analyze and pro-