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Published in:
Annals of Surgical Oncology

Publication status and date:
Published: 01/11/2022

DOI (link to publisher):
10.1245/s10434-022-12156-1
10.1245/s10434-022-12156-1

Document Version
Publisher's PDF, also known as Version of record

Document License/Available under:
Unspecified

Citation for the published version (APA):
Spolverato, G., Capelli, G., Lorenzoni, G., Gregori, D., He, J., Popescu, I., Marques, H. P., Aldrighetti, L., Maithel, S. K., Pulitano, C., Bauer, T. W., Shen, F., Poultsides, G. A., Soubrane, O., Martel, G., Koerkamp, B. G., Itaru, E., Lv, Y., & Pawlik, T. M. (2022). Dynamic Prediction of Survival After Curative Resection of Intrahepatic Cholangiocarcinoma: A Landmarking-Based Analysis. *Annals of Surgical Oncology*, *29*(12), 7634-7641. https://doi.org/10.1245/s10434-022-12156-1, https://doi.org/10.1245/s10434-022-12156-1

Ann Surg Oncol
https://doi.org/10.1245/s10434-022-12156-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Dynamic Prediction of Survival After Curative Resection of Intrahepatic Cholangiocarcinoma: A Landmarking-Based Analysis

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ABSTRACT

Background. The current study aimed to develop a dynamic prognostic model for patients undergoing curative-intent resection for intrahepatic cholangiocarcinoma (ICC) using landmark analysis.

Methods. Patients who underwent curative-intent surgery for ICC from 1999 to 2017 were selected from a multi-institutional international database. A landmark analysis to undertake dynamic overall survival (OS) prediction was performed. A multivariate Cox proportional hazard model was applied to measure the interaction of selected variables with time. The performance of the model was internally cross-validated via bootstrap resampling procedure. Discrimination was evaluated using the Harrell's Concordance Index. Accuracy was evaluated with calibration plots.

Results. Variables retained in the multivariable Cox regression OS model included age, tumor size, margin status, morphologic type, histologic grade, T and N category, and tumor recurrence. The effect of several variables on OS changed over time. Results were provided as a survival plot and the predicted probability of OS at the desired time in the future. For example, a 65-year-old patient with an intraductal, T1, grade 3 or 4 ICC measuring 3 cm who underwent an R0 resection had a calculated estimated 3-year OS of 76%. The OS estimate increased if the patient had already survived 1 year (79%). The discrimination ability of the final model was very good (C-index: 0.80).

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First Received: 7 March 2022
Accepted: 16 June 2022

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Published online: 24 July 2022

Conclusion. The long-term outcome for patients undergoing curative-intent surgery for ICC should be adjusted based on follow-up time and intervening events. The model in this study showed excellent discriminative ability and performed well in the validation process.

Intrahepatic cholangiocarcinoma (ICC) is a rare, biologically aggressive tumor that accounts for roughly 10–15% of all primary liver cancers, making it the second most common primary hepatic malignancy after hepatocellular carcinoma.[1] Although surgical resection represents the best chance for curative-intent treatment, only 10–20% of patients with HCC present with resectable disease. Among the patients who do undergo resection, the postoperative prognosis can vary significantly. In fact, the overall probability of cure may be only 10–15%, yet survival varies significantly based on patient-, tumor-, and hospital-specific factors.[2] In particular, a subset of patients will experience very early recurrence (i.e., within 6 months after surgery), whereas other patients will enjoy a long-term survival benefit from resection.[3,4]

Survival estimation after surgical intervention is critical for patients and providers to inform treatment, surveillance, and life planning. A multitude of statistical methods are available to examine survival, and the most commonly used methods are the Kaplan–Meier estimator, the log-rank test, and the Cox proportional hazards regression model.[5–7] However, these survival estimates have several shortcomings. Traditionally based solely on factors obtained at the time of diagnosis/surgery, standard survival estimates rely on static rather than dynamic measures of long-term survival.[8,9] In addition, survival estimates often aggregate data into prognostic groups, which may be helpful for the general prediction of survival, but may not be as applicable to determine the prognosis of an individual patient.[10] In particular, although they are a powerful tool, survival analyses also are vulnerable to a number of biases, which can lead to biased conclusions.[11]

Landmark analysis splits the follow-up time at a common, prespecified time point, the so-called "landmark."[12] In turn, landmark analysis allows for a more dynamic prediction of survival that accounts for the time elapsed since the initial surgery, as well as the occurrence of intervening events such as recurrence. The current study aimed to develop a dynamic prognostic model for patients undergoing curative-intent resection for ICC using landmark analysis. Such a tool may assist patients and providers in predicting prognosis and tailoring both treatment and follow-up strategy for ICC patients.

METHODS

Patient Population and Data Collection

The study identified patients who underwent curative-intent surgery for ICC between 1999 and 2017 at institutions included in the International Cholangiocarcinoma Consortium (The Ohio State University Wexner Medical Center, Columbus, Ohio; Johns Hopkins Hospital, Baltimore, Maryland; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; Hopitaux Universitaires De Genève, Geneva, Switzerland; Ospedale San Raffaele, Milan, Italy; Medical College of Wisconsin, Milwaukee; Stanford University, Palo Alto, California; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; University of Virginia, Charlottesville; Emory University, Atlanta, Georgia; and University of Sydney, Sydney, Australia).

The study excluded patients who died within 90 days after surgery, individuals who underwent resection with remaining macroscopic disease (R2), patients with metastatic disease at the time of diagnosis (stage 4), and patients who underwent palliative surgery.

Overall, 1220 patients with histologically proven ICC met the inclusion criteria and were enrolled as the analytic cohort. Most of the included patients were Caucasian. Nevertheless, not all the involved centers collected data on race/ethnicity. The study was approved by the Institutional Review Board at each participating institution.

Standard demographic and clinicopathologic data were collected, including sex, age, and primary tumor characteristics. Pathologic data such as tumor size and number, morphologic subtype, presence of vascular invasion, and histologic grade were obtained. Tumor size was defined as the largest diameter. In the case of multiple tumors, the largest lesion was used as the index lesion. Histologic grade was categorized as well-differentiated, moderately differentiated, or poorly differentiated.[13] If the tumor grade varied, the worst grade was used as the index tumor grade.

Disease was staged according to the American Joint Committee on Cancer (AJCC) staging manual.[13] Among treatment-related variables, information regarding the type of liver resection, number of lymph nodes harvested, and receipt of adjuvant therapy was obtained. Major hepatectomy was defined as the removal of three or more segments.

Postoperative complications were noted and graded according to the Clavien-Dindo classification.[14] Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up visit. Recurrence-free survival (RFS) was defined as the time from the date of surgery to tumor recurrence. Recurrence was defined as

suspicious or confirmed lesions on imaging or histologic examination.

Statistical Methods

Descriptive statistics were reported as median (interquartile range, [IQR]) for continuous variables and as percentages (absolute numbers) for categorical variables. A landmark analysis was performed to make dynamic OS and DFS predictions. In landmark analyses, different datasets, including only the patients at risk at a specific time point, are created, and the final dataset is obtained by stacking all the datasets.[15] Landmark time points were chosen every 3 months between 0 and 9 years from surgery.

Multivariable Cox proportional hazard models were used to assess the effect that the variables of interest and their interaction with landmark time had on mortality and disease relapse. These variables included age, sex, comorbidities, margin, size, number of lesions, AJCC 8th-ed N stage, AJCC 8th-ed T stage, morphologic type, histologic grade, direct invasion of adjacent organs, intrahepatic metastasis, postoperative complications, and recurrence.

Variables were retained using a backward selection based on the Bayesian information criterion (BIC). Because patients could be included more than once in the final dataset, with different landmark time points, a Huber robust covariance estimation was performed to examine the correlation within repeated measurements. In addition, a robust sandwich variance estimator was used to account for correlation within repeated measurements.[16,17] The effect of selected variables was reported as hazard ratios (HRs) and 95% two-sided confidence intervals (CIs) at baseline, then 1 and 3 years after surgery. The p values associated with analysis of variance for the global effect of the variable and for the interaction with landmark time were provided.

To evaluate the concordance between observed and estimated survival probabilities at 3 years, a calibration plot was used. Performance analysis of the model was internally cross-validated via a bootstrap resampling procedure, with 150 replicates accounting for overfitting. The discrimination ability of the model was evaluated using Harrell's Concordance Index (C-index),[18] a measure of models' goodness of fit. Variables identified in the multivariable Cox models were incorporated into a dynamic nomogram. A p value lower than 0.05 was considered statistically significant, and the tests considered were two-sided. The statistical analyses were conducted using the open-source R software (version 4.1.2 available from https://www.R-project.org) with the package rms (available from https://CRAN.R-project.org/package=rms).

RESULTS

Demographic and Clinicopathologic Characteristics

The median age of the 1220 patients who underwent curative-intent liver resection for histology-confirmed ICC was 60 years (IQR, 51–68 years), and slightly less than one half of the patients were women (n = 550, 45.1%). A small subset of patients had cirrhosis (n = 123, 10.1%; Table S1). Most of the patients had a solitary tumor (n = 1027, 84.3 %), with a median tumor size of 6 cm (IQR, 4.0–8.5 cm).

At the time of surgery, a majority of the patients underwent a major hepatic resection (n = 663, 54.3%). Lymphadenectomy was performed for 570 (46.7%) of the patients.

The final pathology showed that most of the patients had mass-forming tumors (n = 988, 85.2%) with a moderate (G1–G2) tumor grade (n = 912, 79.4%). Vascular invasion was present in approximately one third of the patients (n = 403, 37.2%), whereas the patients less commonly had perineural (n = 211, 21%) or biliary (n = 140, 18.3%) invasion. Most tumors were AJCC T1 (n = 536, 44.6%) or T2 (n = 417, 34.2%) lesions. The median number of nodes examined was 1 (IQR, 0–4), with 826 (73%) patients having lymph node metastasis.

The overwhelming majority of the patients underwent an R0 resection (n = 1046, 85.7%). Overall, 449 patients (40.1%) experienced some type of complication within 90 days after surgery (Clavien-Dindo grade $\geq$3: n = 201, 39.8%). Approximately one half of the patients (n = 444, 48.3%) received adjuvant chemotherapy.

During a median follow-up period of 25.5 months (IQR, 12.0–49.1 months), 598 (49%) patient died and 687 (55.2%) experienced tumor recurrence. Overall, 333 (61.1%) patients had intrahepatic recurrence, whereas 99 (17.8%) patients had extrahepatic recurrence. The remaining 117 (21.4%) patients had both intra- and extrahepatic recurrence.

The median OS was 25.5 months (IQR, 12.0–49.1 months), and the median RFS was 8.4 months (IQR, 4.6–16.1 months). The OS rate was 78% (95% CI 76.0–80.8%) at 1 year, 49.1% (95% CI 46.0–52.5%) at 3 years, and 37.5% (95% CI 34.1–41.3%) at 5 years, whereas the RFS was 57.8% (95% CI 39.2–45.3%) at 1 year, 35.7% (95% CI 61.2–67.6%) at 3 years, and 32% (95% CI 64.7–71.3%) at 5 years.

Model Specifications and Predictors of OSl

The variables retained in the multivariable Cox regression OS model after the backward selection process included age, tumor size, margin status, morphologic type, histologic grade, T and N categories, and tumor recurrence.

At baseline, decreased OS was associated with tumor size (HR 1.3; 95% CI 1.1–1.5), margin status (HR 1.8; 95% CI 1.1–3.1), periductal infiltrating morphology (reference mass-forming tumors: HR 2.1; 95% CI 1.2–3.3), tumor grades 3 and 4 (reference grades 1 and 2: HR 2.3; 95% CI 1.6–2.2), and AJCC T category (reference T1: T2 HR 1.5 [95% CI 1.0–2.2] vs T4 HR 2.5 [95% CI 1.5–4.3]). In contrast, better OS was associated with N0 stage (reference N1–2: N0 HR 0.5; 95% CI 0.3–0.6) at the time of surgery.

The effect of several variables on OS changed over time. For example, the effect of grade on OS was greatest at the time of surgery and decreased as patients remained alive for increasingly longer periods during the follow-up period (1-year HR 1.9 [95% CI 1.4–2.6] vs. 3-year HR 1.3 [95% CI 0.8–2.1]; interaction with time, $p = 0.03$). Similarly, morphologic subtype other than mass-forming ICC was associated with increasingly worse OS over time (interaction with time, $p = 0.0003$). Interestingly, the effect of recurrence decreased from year 1 (HR 3.2; 95% CI 2.6–3.9) to year 3 (HR 2.4; 95% CI 1.6–3.6) ($p < 0.001$) after surgery.

Prognostic Tool for OS Prediction

Based on the proposed dynamic models, a tool to predict the OS of patients undergoing curative-intent resection for ICC was developed (Fig. 1). Predictions were based on variables retained in the model following the backward stepwise selection process (Table 1). The results from the tool were provided as a survival plot and the predicted probability of OS at the desired time in the future. For example, a 65-year-old patient with an intraductal ICC, T1, grade 3 or 4 lesion measuring 3 cm who underwent an R0 resection had a calculated estimated 3-year OS of 76% (95% CI 72–81%). The OS estimate incrementally increased if the patient had already survived 1 year (79%; 95% CI 76–83%; Fig. 2).

In a different example, a patient who was the same age with an intraductal ICC, T4 lesion, grade 3 or 4 measuring 5 cm who underwent an R0 resection would have a 3-year OS of 45% (95% CI 37–54%). The OS estimate similarly increased in an incremental manner as the patient survived for an increasingly longer period after surgery (1-year survival, 55% [95% CI 49–61%] vs 3-year survival, 72% [95% CI 67–79%]; Fig. 3).

Model Performance

The performance of the final model was internally cross-validated via bootstrap resampling procedure with 150 replicates. Discrimination ability for OS based on the C-statistic was excellent (C-index, 0.80). Agreement between the observed and estimated 3-year OS was evaluated with calibration plots (Fig. 4) and showed good prediction with minimal evidence of overfitting.

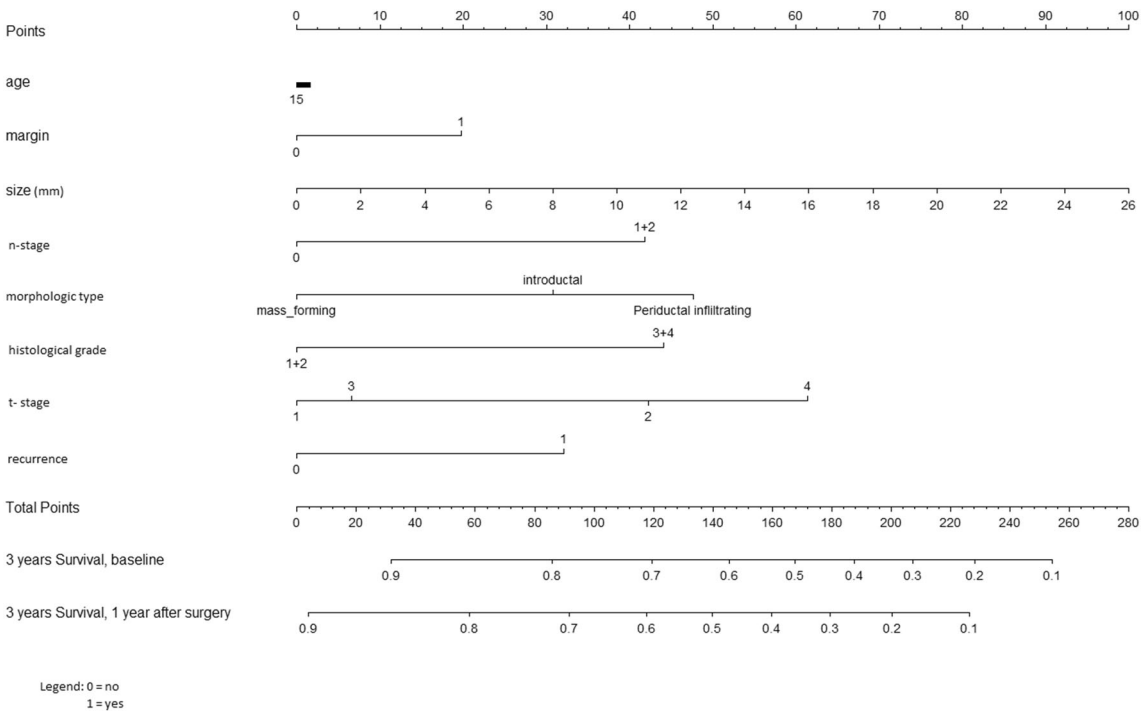

FIG. 1 Prognostic nomogram to predict overall survival (OS) after curative-intent surgery for intrahepatic cholangiocarcinoma (ICC)

TABLE 1 Results of the multivariable Cox regression analysis for overall survival (OS) estimation showing the hazard ratios for 1- and 3-year survival after surgery

Variable		Baseline		1 Year after surgery		3 Years after surgery		Global effect	Interaction with time
		HR	95% CI	HR	95% CI	HR	95% CI	*p* value	*p* value
Age	50:68	1.1	0.8–1.3	1.1	0.8 –1.3	1.1	0.8–1.4	0.7	0.894
Tumor size (mm)	3.9:8	1.3	1.0–1.5	1.2	1.0 –1.3	1.0	0.8–1.3	0.0	0.199
Margin	1:0	1.8	1.1–3.1	1.4	0.9 –2.2	0.8	0.2–2.6	0.1	0.278
Morphologic type	Intraductal: mass-forming	0.9	0.6–1.4	1.2	0.8–1.8	2.6	1.6–4.2	**<.0001**	**0.000**
	Periductal infiltrating: mass-forming	2.1	1.3–3.3	1.8	1.1–2.9	1.3	0.5–3.2		
Histologic grade	3+4:1+2	2.3	1.7–3.3	1.9	1.4–2.5	1.2	0.7–2.1	**<.0001**	0.032
AJCC 8th-ed	2:1	1.5	1.0–2.2	1.6	1.2–2.1	1.7	1.0–2.9	**0.001**	0.203
T stage	3:1	1.4	0.8–2.3	1.1	0.7–1.8	0.7	0.3–1.5		
	4:1	2.6	1.5–4.3	2.3	1.5–3.7	1.9	1.1–3.3		
AJCC 8th-ed	0:1+2	0.4	0.3–0.6	0.5	0.3–0.7	0.7	0.4–1.1	0.0	0.153
N stage									
Recurrence	Yes:no			3.2	2.6–3.9	2.4	1.6–3.6	**<0.001**	0.171
Harrell's C-index of the model: 0.8									

HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer

p Values for the global effect of the variable of interest and for its interaction with time are provided

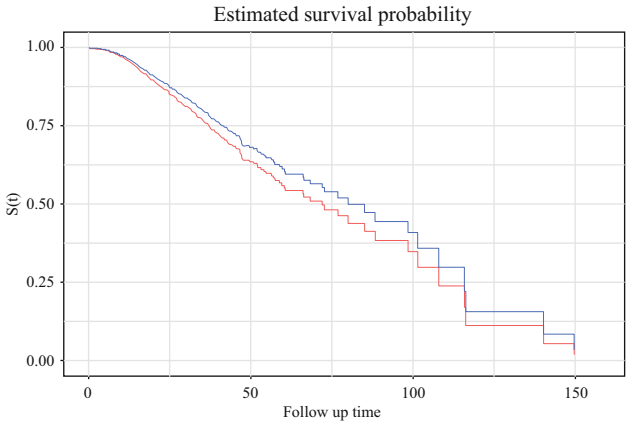

FIG. 2 Example of Kaplan-Meier curves obtained from the predictive model that show the overall survival (OS) of a 65-year-old patient with an intraductal T1 intrahepatic cholangiocarcinoma (ICC) grade 3 or 4 measuring 3 cm who underwent an R0 resection (*red line*) and the OS if the same patient has already survived 1 year after surgery (*blue line*)

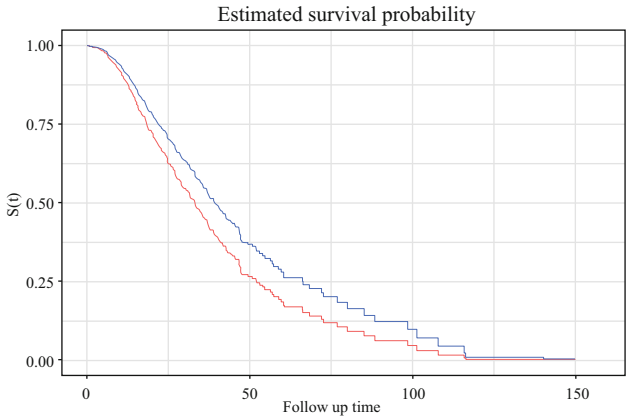

FIG. 3 Example of a Kaplan-Meier curve obtained from the predictive model that shows the overall survival (OS) of a 65-year-old patient with an intraductal T4 intrahepatic cholangiocarcinoma (ICC) grade 3 or 4 measuring 5 cm who underwent an R0 resection (*red line*) and the OS if the same patient has already survived 1 year after surgery (*blue line*)

DISCUSSION

Although ICC accounts for only 10–20% of all hepatic malignancies, the incidence has been increasing worldwide during the last several decades.[19] Many patients with ICC present with advanced disease given that the disease often is asymptomatic until later stages.[20] However, even among patients with earlier-stage disease, prognosis can be guarded, with long-term survival estimated to be only about 10–20%.[21]

For patients who present with disease amenable to surgery, resection is the treatment of choice.[22] Patient prognosis after curative-intent resection can, however, be varied, with a significant subset of patients having a high incidence of recurrence and poor long-term survival.[3,23,24]

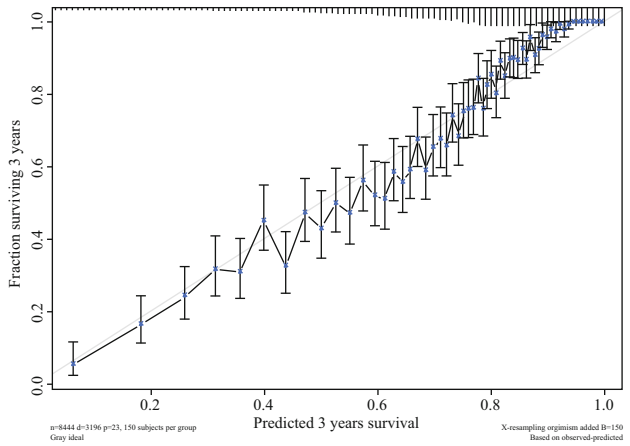

FIG. 4 Calibration plot showing the difference between predicted and actual 3-year overall survival (OS) of the model

To date, the AJCC eighth-edition staging system has demonstrated only modest-to-good overall discriminatory ability to define the prognosis for patients with ICC.[25] Estimating the prognosis for patients with a high-case fatality cancer diagnosis can be challenging.[26] In particular, traditional survival analysis methods may "overweigh" early deaths in population-based assessments of survival, discounting future survival probabilities among those who survive for a period of time.[8]

The current study was important because it was the first attempt to design a more dynamic prognostic model for ICC patients using landmark survival analysis. Unlike traditional survival analysis approaches (e.g., Kaplan Meier), landmark analysis accounts for the time elapsed since the initial surgery, as well as for the occurrence of intervening events such as recurrence.[12] As expected, several traditional factors (e.g., tumor size, margin status, tumor grade 3 or 4, AJCC T and N categories) were associated with prognosis, and the impact of these variables on survival were noted to vary over time. Thus, we developed a tool predicting the probability of OS at various times after resection accounting for intervening events. The probability of survival changed dramatically based not only on tumor factors, but also more importantly on survival time that had elapsed from surgical resection, as well as on the presence of recurrence. These data serve to highlight how long-term outcomes of patients undergoing curative-intent surgery for ICC need to be estimated and adjusted based on follow-up time and intervening events.

In this study, multiple tumor-specific factors were associated with long-term prognosis after curative-intent surgery. For example, tumor size and morphologic subtype both were linked to odds of overall survival. The impact of tumor size on the prognosis of patients undergoing resection of ICC has been debated. The initial AJCC staging of ICC in the seventh-edition staging manual did not include tumor size as a prognostic factor.[27] Rather, only the absence or presence of vascular invasion and uni-/multifocal disease were included in the T-category definition.

More recently, tumor size has been associated with the risk of microvascular invasion as well as lymph node metastasis.[28] In turn, tumor size has been linked to survival and subsequently incorporated into the latest version (8th edition) of the AJCC staging manual (T1a <5 cm vs T1b ≥5 cm).[25,27]

Similarly, ICC tumor morphology was found to affect long-term prognosis. To this point, Bagante et al.[29] reported that patients with periductal infiltrating morphology had a greater risk of death than patients who had a mass-forming ICC. The presence of nodal disease also was a strong predictor of survival. In fact, patients with node-negative disease had only half the chance of death in the long term (reference N1-2: N0 HR 0.5; 95% CI 0.3–0.6). For this reason, routine lymphadenectomy of at least six LNs is strongly recommended and should include examination beyond station 12 to have the greatest chance of accurate staging.[30]

Interestingly the effect of several prognostic factors changed over time. For example, although the effect of poor tumor grade on prognosis waned over time, the relative impact of morphologic status on survival was increasingly associated with worse prognosis as time elapsed. The varying impact of several prognostic factors may be due to the fact that some patients with prognostic factors defined as "adverse" at the time of surgery survived longer than expected. These patients were able "survive" to their initial prognosis, and the following probability of survival changed dramatically based on survival time that had elapsed from surgical resection.

Based on the proposed models, a dynamic tool to predict the OS of patients undergoing curative-intent resection for ICC was developed (Fig. 1). Using this model, clinicians can input patient- and tumor-specific factors, as well as the amount of time elapsed since surgery, allowing for a more accurate estimate of survival. The ability of the model to account for the changes in the prognostic impact of risk factors over time may explain the better performance of the proposed model (C-index, 0.80) versus "static" nomograms and the AJCC staging system.[31,32]

Several limitations should be considered when the results of this study are interpreted. Given the retrospective nature of the study, the analysis may have been subject to selection bias. Although the inclusion of multiple centers increased the sample size and the generalizability of the findings, the cohort was heterogeneous relative to treatment regimens. However, only major, high-volume tertiary hepatopancreatobiliary centers were included, which

contributed to standardization of care. Although the proposed prediction model performed well on internal validation, external validation in a separate cohort is needed.

In conclusion, the impact of several tumor- and patient-specific prognostic factors after curative-intent surgery for ICC varied over time. The landmark analysis was able to measure the effect of these variables over time and their dynamic impact on OS. The proposed dynamic model, designed to predict the OS of ICC patients after curative-intent resection, performed well at internal validation and could assist both patients and providers in predicting prognosis and in tailoring treatment and follow-up strategy for ICC patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-022-12156-1.

DISCLOSURE There are no conflicts of interest.

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