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A nomogram to predict lymph node metastasis before resection in intrahepatic cholangiocarcinoma

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ARTICLE INFO

Article history:
Received 1 November 2017
Received in revised form
16 December 2017
Accepted 12 January 2018
Available online xxx

Keywords:
Intrahepatic cholangiocarcinoma
Lymph node metastasis
Predictors
Nomogram

ABSTRACT

Background: In this study, we developed and validated a nomogram to predict lymph node metastasis before surgery in patients with intrahepatic cholangiocarcinoma (ICC).

Methods: Using the data from January 2006 to January 2015, we enrolled a total of 218 eligible patients with clinicopathologically confirmed ICC as a primary cohort to develop the nomogram. After various variables before surgery were analyzed by multivariable logistic regression, we combined the preoperative carbohydrate antigen 19-9, primary site of tumor, lymphonodus size on computed tomography imaging, tumor growth pattern, and (if applicable) histologic grade to make two different predictive nomograms. Then, the results were validated in 62 consecutive ICC patients from February 2015 to December 2016. We also compared the performance of the different nomograms via calibration, discrimination, and clinical use.

Results: The nomogram displayed fine discrimination (the concordance index, 0.761) and fine calibration in the primary cohort. When applied to the validation cohort, the nomogram also showed fine discrimination (concordance index, 0.794) and fine calibration. After adding the histologic grade to the nomogram, the integrated discrimination for predictive performance improved significantly. Finally, the clinical usefulness of predictive nomogram was proven via the decision curve analysis.

Conclusions: The proposed nomograms can be selectively used to achieve more accurate lymph node metastasis predictions before surgery in patients with ICC, and this information can help with clinical management.

Introduction

The incidence rate of intrahepatic cholangiocarcinoma (ICC) has increased over the past several decades, both in the United States of America and worldwide.[1] ICC made up approximately 5%-30% of all primary liver cancer cases.[2,3] ICC is the second most common liver cancer. It is highly malignant and has an extremely poor prognosis.[4] Correct judgment of lymph node metastasis (LNM) is important for prognosis analysis and treatment selection in ICC patients.[5-8] Many

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0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2018.01.024

histopathologic variables were reported as predictive factors of LNM, but they are unknown until after surgery.[5,8] A recent study, using only multivariate analysis, revealed that tumor size, distinct tumor boundary, and histologic differentiation were useful for preoperative detection of LNM in ICC.[9] Preoperative individualized prediction of LNM is very important for surgical planning. According to National Comprehensive Cancer Network guidelines of ICC,[10] the portal lymphadenectomy is reasonable as this provides relevant staging information. But gross LNM to the porta hepatis portends a poor prognosis, and resection should only be considered in highly selective cases.[10] Therefore, preoperative individualized prediction of LNM through clinicopathologic factors in ICC has effective clinical significance for considered resection.

For the prognostic prediction of ICC, a few nomograms have been developed.[11-14] The use of nomograms was shown to be more effective for the prognostic prediction of ICC and proposed as the new criterion.[12-14] We found no existing study that has developed and validated a nomogram to preoperatively predict LNM in ICC. In our study, we developed and validated a nomogram for predicting individual LNM probabilities in ICC patients before surgery. It was possible to predict the individual patients with LNM through the predictive nomogram using preoperative factors. This information helped with surgical planning and clinical management.

Materials and methods

Patients

This study was approved by the Ethics Committee of the Medical Faculty of Fujian Medical University in China. Oral informed consent was obtained from all patients before surgery. The primary cohort was selected based on retrospective data of patients who underwent radical resection and regional lymphadenectomy for ICC from January 2006 to January 2015 at Fujian Medical University Union Hospital (Fujian, China). Enrolled patients had diagnosed ICC by clinical imaging and histopathology. We excluded patients with history of other malignancies, preoperative anticancer therapy, mixed type primary liver cancer, metastatic liver tumors, and tumors of uncertain origin. Finally, 218 patients were enrolled into the primary cohort.

An independent validation cohort was formed with 62 patients enrolled from February 2015 to December 2016 prospectively. The following variables were extracted: gender, age (≤60 y and >60 y), hepatitis B status, hepatolithiasis, preoperative carcinoembryonic antigen (CEA) (≤5 ng/mL and >5 ng/mL), preoperative carbohydrate antigen 19-9 (CA19-9; ≤37 U/mL and >37 U/mL), tumor size (≤5 cm and >5 cm), primary site of tumor (left lobe and right lobe), tumor number (single and multiple), lymphonodus size on computed tomography (CT) imaging (<1 cm and ≥1 cm), tumor growth pattern, histologic grade, and histopathologically confirmed LNM. The tumor size was measured as the largest diameter of the tumor. The primary site of tumor was defined as the location of live lobe in single tumors and the location of the biggest tumor when multiple tumors are present. Lymphonodus size for the largest diameter was stratified as ≥1 cm and <1 cm on CT imaging. Tumor growth patterns were classified as intraductal growth (IG) type, mass-forming (MF) type, and periductal infiltrating (PI) type via examination of preoperative CT-imaging appearance. In the present study, all 14 patients with IG-type tumors were found to be free of LNM. A previous study also revealed that all 22 patients with IG-type tumors in 341 ICC patients who underwent surgery were found to be free of LNM.[15] These data indicated that the IG type of ICC has hardly any metastasis of lymph node (LN). Therefore, it was picked out and enrolled into another management. Histologic grades were known from tissue specimen section after surgery and classified as grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated).

Statistical analysis

Statistical analysis was conducted with R software (R software, version 3.4.1, http://www.r-project.org). All P values were based on two-sided statistical analysis, and $P < 0.05$ was considered statistically significant.

Development of the predictive nomogram

We evaluated age, gender, hepatitis B status, hepatolithiasis, preoperative CEA, CT imaging, tumor growth pattern, and histologic grade as possible clinical candidate predictors for LNM. Based on the multivariable logistic analysis, we established the nomogram to predict individual ratios for LNM of ICC in the primary cohort. The calibration curve, combined with the Hosmer–Lemeshow test, was applied to evaluate the consistency between actual outcomes and predictions using the predictive nomogram.[16] The relative discriminative abilities of the nomogram were assessed using the Harrell concordance index (C-index). The relatively correctional C-index of the nomogram was calculated through bootstraps with 1000 resamples.

Validation of the predictive nomogram

The C-index and calibration curve were derived based on the validation cohort by the regression analysis. The performance of the predictive nomogram was validated in the validation cohort. In this study, the histologic grade was obtained from the surgical specimen instead of the preoperative biopsy, which was not obtained for all patients before surgery. Therefore, we calculated the C-index, calibration curve, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) for evaluating the added value of histologic grade. The NRI was used to evaluate reclassification nomograms and quantifies the improvement in risk prediction.[17,18] The IDI was used to measure the IDIs in risk prediction, which is independent of class limits.[19]

Clinical usefulness

We presented the decision curve to estimate the net benefits of different threshold probabilities for individuals to confirm clinical usefulness of the predictive nomogram.[20] The