CLINICAL STUDY

# A Patient-Based Nomogram for Predicting Overall Survival after Radiofrequency Ablation for Hepatocellular Carcinoma

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## ABSTRACT

**Purpose:** To develop a prognostic nomogram based on specific patient and tumor factors capable of estimating individual survival outcomes after radiofrequency (RF) ablation as a primary therapy for hepatocellular carcinoma (HCC).

**Materials and Methods:** This retrospective study included 893 patients who were initially treated with curative RF ablation for HCC; patients were temporally divided into derivation (n = 607) and validation (n = 286) cohorts. A multivariate Cox proportional hazards model for overall survival was developed and validated. The discriminatory accuracy of the model was compared with the preexisting Cancer of the Liver Italian Program (CLIP) system and the Tokyo score previously proposed for percutaneous therapy for HCC by analyzing receiver operating characteristic (ROC) curves.

**Results:** A nomogram was generated for 3-year survival, incorporating largest tumor diameter and number of tumors, serum albumin and creatinine, platelet count, prothrombin time, and serum α-fetoprotein on a logarithmic scale. It had good calibration and discrimination abilities with a C-index of 0.74. The validation results also showed that the nomogram performed well in terms of goodness-of-fit and discrimination (C-index, 0.72). Analysis of ROC curves in the validation cohort indicated that the model had better predictive power than CLIP and Tokyo scores (C-indexes, 0.54 and 0.66, respectively).

**Conclusions:** This prognostic tool quantifying per-patient expected survival after RF ablation can be used in daily clinical decision making with regard to patients with HCC deemed suitable for radical ablation and is probably more reliable than existing guidelines.

## ABBREVIATIONS

AFP = α-fetoprotein, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IQR = interquartile range, PEIT = percutaneous ethanol injection therapy, RF = radiofrequency, ROC = receiver operating characteristic

Local ablation techniques are considered the optimal treatment option for patients with nonresectable and nontransplantable small hepatocellular carcinoma (HCC) (1). Of these techniques, thermocoagulation radiofrequency (RF) ablation has been the most widely implemented, and RF ablation is currently recommended as a first-line treatment for Barcelona Clinic Liver Cancer (BCLC) stage A HCC (2).

In several studies, RF ablation consistently yielded better results than other percutaneous modalities including percutaneous ethanol injection therapy (PEIT) (3,4). Because of the high complete response rate to RF ablation and the low rate of complications including seeding

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of nodules specifically for tumors 2 cm or smaller (2), an update of the BCLC decision-making algorithm was proposed in which RF ablation is the first-line therapy in patients with BCLC 0 stage HCC who are not available for liver transplantation, leaving resection as a secondary or rescue option (5). This latest therapeutic trend in the treatment of very early HCC has led to the practical application of RF ablation and the optimal candidates for it to be clinically highlighted. Nevertheless, comprehensive data on robust clinical parameters related to the prognosis of patients after ablation are still scarce, specifically on an individual basis, with the exception of target lesion diameter, although several studies reported that liver function factors and serum levels of biomarkers including α-fetoprotein (AFP) at baseline are relevant prognostic indicators for patients with HCC treated by RF ablation (6–8). The purpose of this study was to develop a prognostic nomogram based on specific patient and tumor factors capable of estimating individual survival outcomes after RF ablation as primary therapy for HCC.

## MATERIALS AND METHODS

This study was approved by the institutional review board of our institution.

### Study Population

The development cohorts and their relevant baseline and outcome data were retrospectively collected using a single-institution database of 924 patients of good performance status who underwent percutaneous RF ablation as first HCC treatment at our institution between March 2000 and December 2009 and were followed for at least 1 year. All patients either were not suitable for or refused curative resection or liver transplantation. The diagnosis of HCC was confirmed based on current American and European practice guidelines (1,2).

The final study analysis included 893 patients after excluding 31 patients as follows: (*a*) seven patients who had advanced stage HCC accompanying gross vascular invasion or distant metastasis; (*b*) one patient who had Child-Pugh C liver function, which is not an optimal indication for RF ablation according to current guidelines (2); and (*c*) 23 patients in whom technique effectiveness was not initially achieved, regardless of the number and size of nodules. Technical effectiveness was defined as complete ablation of the target tumor or tumors as shown on computed tomography (CT) images obtained 1 month after the procedure and based on the standardization of terminology and reporting criteria by the International Working Group on Image-Guided Tumor Ablation (9). None of the enrolled patients had severe comorbidities or secondary malignancies that might affect survival time. Of 893 patients with a mean age of 57.1 years ± 9.7, 74.1% were men, 71.2% had liver disease related to hepatitis B virus (HBV), and 92.3% had liver function corresponding to Child-Pugh class A (**Table 1**). Mean serum levels of AFP, aspartate aminotransferase (AST), alanine aminotransferase, platelet count, and international normalized ratio for prothrombin time were 192.9 ng/mL ± 775.4, 52.7 IU/L ± 38.7, 43.9 IU/L ± 39.5, 111.6 × $10^3$/$mm^3$ ± 56.1, and 1.2 ± 0.2. With respect to tumor factors, 881 patients (98.7%) fulfilled the Milan criteria; mean size of the largest nodule on a per-patient basis was 2.0 cm ± 0.7; 37 patients had tumors greater than or equal to 3 cm; and 804 (90%) had single tumor, and the rest had two to four tumors (**Table 1**). Cancer of the Liver Italian Program (CLIP) scores of 0, 1, 2, 3, and 4 or greater were recorded in 747, 144, 2, 0, and 0 patients, and Tokyo scores of 0, 1, 2, 3, 4, and 5 were recorded in 122, 283, 233, 147, 78, and 30 patients (10,11). For temporal external validation, the development data were divided into two parts: one part (the derivation set) involving 607 patients treated in an earlier period (March 2000 to December 2007) while gaining experience of the model and the other part (the validation set) involving 286 patients treated more recently to assess its performance (January 2008 to December 2009) (12).

### Workup before Procedure and Evaluation after Procedure

In our center, the staging workup protocol of HCC included liver dynamic CT or magnetic resonance imaging or both for assessing intrahepatic and extrahepatic tumor status in the abdominal cavity and chest CT and bone scan for assessing common metastatic sites of HCC. In addition, blood tests for liver function, cause of liver disease, and AFP level were always checked. Before RF ablation treatment, a planning ultrasound examination was routinely performed to assess the technical feasibility and applicability of RF ablation.

Immediately after each procedure, contrast-enhanced CT was performed to macroscopically confirm technical success (ie, whether the tumor had been treated according to a protocol defined for all patients) (9). Technical success was achieved after one session of RF ablation in 857 patients (96%) and after two or more sessions in 36 patients (4%). Subsequent imaging follow-up employed dynamic CT 1 month after treatment, the time at which technique effectiveness (9) was assessed on a routine basis, and thereafter mostly at 3-month intervals in the first 2 years and every 3–6 months in subsequent years if tumors did not recur. Dynamic CT images were obtained from 5-mm-thick contiguous slices employing a multiphasic liver protocol using spiral multidetector CT scanners (LightSpeed QX/i or LightSpeed Plus; GE Medical Systems, Milwaukee, Wisconsin, or Somatom Sensation 16; Siemens AG, Erlangen, Germany), which consisted of unenhanced scans as well as images during the arterial, portal venous, and equilibrium phases at 36