A Novel Prognostic Nomogram Accurately Predicts Hepatocellular Carcinoma Recurrence after Liver Transplantation: Analysis of 865 Consecutive Liver Transplant Recipients

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BACKGROUND: Although radiologic size criteria (Milan/University of California, San Francisco [UCSF]) have led to improved outcomes after liver transplantation (LT) for hepatocellular carcinoma (HCC), recurrence remains a significant challenge. We analyzed our 30-year experience with LT for HCC to identify predictors of recurrence.

STUDY DESIGN: A novel clinicopathologic risk score and prognostic nomogram predicting post-transplant HCC recurrence was developed from a multivariate competing-risk Cox regression analysis of 865 LT recipients with HCC between 1984 and 2013.

RESULTS: Overall patient and recurrence-free survivals were 83%, 68%, 60% and 79%, 63%, and 56% at 1-, 3-, and 5-years, respectively. Hepatocellular carcinoma recurred in 117 recipients, with a median time to recurrence of 15 months, involving the lungs (59%), abdomen/pelvis (38%), liver (35%), bone (28%), pleura/mediastinum (12%), and brain (5%). Multivariate predictors of recurrence included tumor grade/differentiation (G4/poor diff hazard ratio [HR] 8.86; G2-3/mod-poor diff HR 2.56), macrovascular (HR 7.82) and microvascular (HR 2.42) invasion, nondownstaged tumors outside Milan criteria (HR 3.02), nonincidental tumors with radiographic maximum diameter $\geq$5 cm (HR 2.71) and <5 cm (HR 1.55), and pretransplant neutrophil-to-lymphocyte ratio (HR 1.77 per log unit), maximum alpha fetoprotein (HR 1.21 per log unit), and total cholesterol (HR 1.14 per SD). A pretransplantation model incorporating only known radiographic and laboratory parameters had improved accuracy in predicting HCC recurrence (C statistic 0.79) compared with both Milan (C statistic 0.64) and UCSF (C statistic 0.64) criteria alone. A novel clinicopathologic prognostic nomogram included explant pathology and had an excellent ability to predict post-transplant recurrence (C statistic 0.85).

CONCLUSIONS: In the largest single-institution experience with LT for HCC, excellent long-term survival was achieved. Incorporation of routine pretransplantation biomarkers to existing radiographic size criteria significantly improves the ability to predict post-transplant recurrence, and should be considered in recipient selection. A novel clinicopathologic prognostic nomogram accurately predicts HCC recurrence after LT and may guide frequency of post-transplantation surveillance and adjuvant therapy. (J Am Coll Surg 2015;220:416–427. © 2015 by the American College of Surgeons)

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Abbreviations and Acronyms

AFP = alpha fetoprotein
AJCC = American Joint Committee on Cancer
HCC = hepatocellular carcinoma
HR = hazard ratio
IQR = interquartile range
LT = liver transplantation
MC = Milan criteria
MELD = Model for End-Stage Liver Disease
NASH = nonalcoholic steatohepatitis
NLR = neutrophil-to-lymphocyte ratio
UCSF = University of California, San Francisco

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of cancer-related death.[1] In the United States, the incidence of HCC has nearly doubled over the last 2 decades.[2-4] Although the majority of patients present with locally advanced or metastatic disease, early stage patients may be candidates for potentially curative surgical therapy, including resection and liver transplantation (LT).[5] Liver transplantation provides a complete oncologic resection while simultaneously replacing the diseased liver, a predisposing factor in more than 90% of patients with HCC.

Despite the logic of this approach, the early results of LT for HCC were plagued with prohibitive tumor recurrence and mortality,[6-9] largely due to poor patient selection. The so-called Milan criteria (MC), introduced in 1996, limited LT to patients with a single tumor of 5 cm diameter or less or up to 3 tumors, none larger than 3 cm.[10] Application of MC resulted in excellent post-transplant recurrence-free survival and solidified LT as the gold-standard therapy for patients with underlying liver dysfunction and tumors meeting these specified size criteria. In an attempt to extend the life-saving benefit of LT, numerous subsequent criteria have been proposed, allowing for transplantation of a larger size and number of tumors and reporting survival comparable to that with the MC.[11-13]

With the introduction in 2002 of the Model for End-Stage Liver Disease (MELD) liver allocation system,[14] which allows for prioritization of HCC recipients with tumors meeting radiographic size criteria, the frequency of LT for HCC has nearly doubled.[15] Currently, HCC is the indication for LT in nearly one-quarter of adult liver recipients in the US. Despite nationwide adoption of the Milan/University of California, San Francisco (UCSF) radiographic size criteria, HCC recurrence after transplantation remains a significant cause of graft loss and mortality, affecting up to 8% to18% of recipients.[16,17] This is explained in part by the recognition that radiographic size is only a rough surrogate for the key pathologic characteristics that define tumor biology, including tumor grade/differentiation and vascular invasion.[16,17]

This study reports a large, single-center experience of LT for HCC spanning 3 decades. We sought to identify important multivariate predictors of HCC recurrence and to develop a novel clinicopathologic prognostic nomogram incorporating radiographic, laboratory, and pathologic characteristics that can be used to accurately predict the risk of post-transplantation HCC recurrence and guide adjuvant therapy.

METHODS

We performed a retrospective review of a prospectively maintained transplant database and identified all adult patients (aged 18 years and older) who underwent LT for HCC or were incidentally discovered to have HCC on explant pathology at the University of California, Los Angeles from 1984 to 2013. Multiple recipient variables (age, sex, primary end-stage liver disease diagnosis, diabetes, hypertension, hyperlipidemia, coronary artery disease), donor and operative characteristics (donor age, sex, heart-beating cadaveric, non-heart–beating cadaveric, split graft, cold ischemia time, warm ischemia time), laboratory variables (alpha fetoprotein [AFP], neutrophil-to-lymphocyte ratio [NLR], Model for End-Stage Liver Disease [MELD] score, total cholesterol) pretransplant radiographic data (number of lesions, maximal tumor diameter, cumulative tumor diameter), and pathologic variables (number of lesions, maximal tumor diameter, cumulative tumor diameter, T stage, grade, differentiation, and vascular invasion) were analyzed to determine predictors of HCC recurrence after orthotopic liver transplantation. This study was approved by the UCLA Institutional Review Board.

Pretransplantation disease extent was determined based on CT or magnetic resonance images. Patients with HCC were classified as having tumors within MC, beyond MC but within UCSF criteria, or exceeding UCSF criteria. Patients without a pretransplant radiographic diagnosis of HCC who had an incidental HCC discovered on explant were categorized as within radiographic MC. Pretransplantation adjuvant treatments including chemotherapy, thermal ablation (radiofrequency or microwave ablation), transarterial embolizations (bland transarterial embolization, chemoembolization, radioembolization), and liver resections were used in select patients. Patients beyond MC were further characterized based on the ability of adjuvant treatments to downstage them into MC before LT.