# Outcomes of Liver Transplantation in 490 Patients with Hepatocellular Carcinoma: Validation of a Uniform Staging after Surgical Treatment

Jean-Nicolas Vauthey, MD, FACS, Dario Ribero, MD, Eddie K Abdalla, MD, FACS, Sven Jonas, MD, Ankit Bharat, MD, Guido Schumacher, MD, Jan Lerut, MD, William C Chapman, MD, FACS, Alan W Hemming, MD, Peter Neuhaus, MD

**BACKGROUND:** The aim of this study was to compare the ability of staging systems (American Joint Committee on Cancer/Union Internationale contre le Cancer [AJCC/UICC], Japanese TNM, Pittsburgh, United Network for Organ Sharing [UNOS], Cancer of the Liver Italian Program [CLIP], Japan Integrated Staging [JIS], and Barcelona Clinic Liver Cancer [BCLC]) to predict survival after liver transplantation for hepatocellular carcinoma.

**STUDY DESIGN:** Four hundred ninety consecutive patients who underwent liver transplantation for hepatocellular carcinoma at 4 centers (1985 to 2005) were identified using a registry (US, Belgium, Germany). End points were overall (OS) and recurrence-free survival (RFS). Survival by stage was compared with the log-rank test. Sequential stage-wise discrimination of each system was evaluated using Cox regression.

**RESULTS:** Three- and 5-year overall survival rates were 71% and 64%, respectively; recurrence-free survival rates were 67% and 61%, respectively. Median followup among 327 living and 308 recurrence-free patients was 40 months. In only three systems—AJCC/UICC, Japanese TNM, and Pittsburgh—were overall and recurrence-free survivals longer for patients with low stage versus more advanced stage. For overall and recurrence-free survivals, sequential stages were different only for AJCC/UICC. In the Japanese TNM system, stages II and I were similar; for Pittsburgh, grades 3 and 2 were similar. For the United Network for Organ Sharing system, stages II and I and stages IVA1 and III were similar. All stages were similar for the Cancer of the Liver Italian Program. For the Japan Integrated Staging, scores 2 and 1 and scores 4 and 3 were similar. In the Barcelona Clinic Liver Cancer, stage D patients had significantly better survival than patients at stage C.

**CONCLUSIONS:** The AJCC/UICC staging system provides the best stratification of prognosis for patients undergoing liver transplantation for hepatocellular carcinoma. This confirms previous analyses in patients treated with hepatic resection. The AJCC/UICC staging system should be considered for uniform prediction of outcomes after surgery for hepatocellular carcinoma. (J Am Coll Surg 2007;204:1016–1028. © 2007 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm and the third most common cause of cancer-related deaths worldwide.[1,2] The role of liver transplantation (LT) as a curative option for HCC is expanding.[3,4] Several staging systems and schemes have been developed to stratify the outcomes of patients with HCC or have been structured in the form of treatment algorithms to guide clinical decision making.[5-11] Because a unique staging system encompassing the entire spectrum of patients with HCC is likely to suffer from scarce prognostic stratification

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From the Department of Surgical Oncology, the University of Texas MD Anderson Cancer Center, Houston, TX (Vauthey, Ribero, Abdalla); the Section of Transplantation, Washington University, St Louis, MO (Bharat, Chapman); the Abdominal Transplant Unit, Cliniques Universitaires Saint-Luc, Brussels, Belgium (Lerut); the Department of Surgery, University of Florida, Gainesville, FL (Hemming); and the Department of General and Transplantation Surgery, Charite-Campus Virchow Klinikum Humboldt University, Berlin, Germany (Jonas, Schumacher, Neuhaus).

Correspondence address: Jean-Nicolas Vauthey, MD, Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 444, Houston, TX 77030.





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**Abbreviations and Acronyms**

AJCC/UICC = American Joint Committee on Cancer/ Union Internationale contre le Cancer
BCLC = Barcelona Clinic Liver Cancer
CLIP = Cancer of the Liver Italian Program
HCC = hepatocellular carcinoma
JIS = Japan Integrated Staging
LCSGJ = Liver Cancer Study Group of Japan
LT = liver transplantation
OS = overall survival
RFS = recurrence-free survival
UNOS = United Network for Organ Sharing

within each or some categories, several authors have advocated the need for different staging systems for different groups of patients.[12,13]

In 2003, the Consensus Conference on Staging of HCC, sponsored by the American-Hepato-Pancreato-Biliary Association (AHPBA) and the American Joint Committee on Cancer (AJCC), concluded that no single staging system fulfills the needs of all physicians treating HCC.[14] The AHPBA/AJCC Consensus Conference recommended the use of the Cancer of the Liver Italian Program (CLIP) staging system[9] to stratify the prognosis and to guide treatment recommendations in nonsurgical patients, and the sixth edition of the AJCC/UICC TNM for surgical patients after hepatic resection and LT.

Since its adoption, the current AJCC/UICC TNM staging system has been validated in different Asian[15,16] and European[17,18] studies of patients treated with hepatic resection. But its ability to stratify patients with respect to survival has not been specifically evaluated in a large cohort of patients undergoing LT for HCC. The primary objective of this analysis was to validate the AJCC/UICC staging system in a cohort of 490 patients who underwent LT for HCC and to compare, in this population, its prognostic ability to stratify recurrence-free and overall survivals with those of 6 commonly used HCC staging systems.

## METHODS

Four hundred ninety consecutive patients who underwent LT in the presence of HCC between August 1985 and October 2005, at 1 of 4 tertiary hepatobiliary centers (Humboldt University, Berlin, Germany; the University of Florida, Gainesville, FL; Washington University, St Louis, MO; and Cliniques Universitaires Saint-Luc, Brussels, Belgium), were entered into a multicenter liver transplant registry. Patients were identified from each institution's prospectively collected database. Patients with fibrolamellar variant of HCC and those who died postoperatively (within 30 days of transplantation, or during the same hospital stay, whenever death occurred) were considered ineligible for registration. The following data were collected for each patient: age, gender, etiology of the underlying liver disease, pretransplant Child-Pugh class, serum alpha-fetoprotein (AFP) concentration, and tumor characteristics. Tumor characteristics were assessed by means of histopathologic examination of the explanted specimen and included size (in patients with multiple HCCs, the largest tumor was used as the index lesion); number and location (uni- or bilateral); grade (defined according to the grading scheme proposed by Edmondson and Steiner);[19] presence of microscopic or major vascular invasion;[20] and regional lymph node and distant metastases.

Patients were classified separately according to the criteria of the following pathologic or clinical staging systems (Table 1): the AJCC/UICC tumor node metastasis (TNM) staging system (sixth edition),[5] the pathologic TNM classification system proposed by the Liver Cancer Study Group of Japan,[6] the prognostic scoring system proposed by Iwatsuki and colleagues[7] (hereafter referred to as Pittsburgh scoring system), the UNOS-modified TNM staging classification,[8] the Cancer of the Liver Italian Program (CLIP) score,[9] the Japan Integrated Staging Score (JIS score),[10] and the Barcelona Clinic Liver Cancer (BCLC) staging classification.[11]

The primary end points of this analysis used to measure the performance of the different staging systems were overall survival and recurrence-free survival. Overall survival was defined as the time from initial transplantation to patient death for any reason. Recurrence-free survival was defined as the time from initial transplantation to disease recurrence or death for any reason. Patients who were alive and without disease recurrence at the date of last followup were censored. Followup data were prospectively collected until March 31, 2006. At the time of analysis, 1 patient with incomplete survival data was excluded, leaving a final cohort of 489 patients.

Overall and recurrence-free survivals were estimated using the Kaplan-Meier method. Comparisons of survival distributions by stage were obtained using the log-rank test. The sequential stage-wise discrimination power of each system was evaluated using regression analysis. In detail, comparisons of the levels within staging systems were made using Cox proportional hazards regression with sequential parameterization. In this set of analyses, only stages containing at least 20 patients, a number that was considered the minimum informative sample size, were included. Statistical significance was defined as $p < 0.05$. The SAS (version 9.1; SAS Institute) and Splus (version 7; MathSoft Inc) software packages were used for the statistical analysis.