Prognostic Accuracy of 12 Liver Staging Systems in Patients with Unresectable Hepatocellular Carcinoma Treated with Transarterial Chemoembolization

Christos S. Georgiades, MD, PhD, Eleni Liapi, MD, Constantine Frangakis, PhD, Ju-un Park, BS, Hyung Woo Kim, BS, Kelvin Hong, MD, and Jean-Francois H. Geschwind, MD

PURPOSE: The objective of the present study was to rank the most common liver staging systems according to prognostic accuracy in patients with unresectable hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE).

MATERIALS AND METHODS: Survival of 172 consecutive patients with unresectable HCC treated with TACE was correlated with the pretreatment Child-Pugh (categoric and nominal), Okuda, Cancer of the Liver Italian Program, Barcelona Clinic Liver Cancer, Model for End-stage Liver Disease, Chinese University Prognostic Index (CUPI), Japanese Integrated Staging, Tumor/Node/Metastasis, Group d'Etude de Traitement du Carcinoma Hepatocellulaire, Liver Cancer Study Group of Japan, and Tokyo staging systems. The systems were ranked according to error reduction in predicting median survival (Kaplan-Meier survival curve and Cox regression analysis). The error reduction was normalized to the error in predicting survival in the absence of a staging system.

RESULTS: Median survival was 80 weeks. The error in predicting survival of an unstaged population was 51 weeks. The Child-Pugh nominal, CUPI, and Tokyo scores yielded the largest reduction in survival prediction error, at 20.8%, 21.6%, and 19.6%, respectively. Their actual error measurements in predicting survival were 40.4, 40.0, and 41.0 weeks, respectively.

CONCLUSIONS: Child-Pugh nominal, CUPI, and Tokyo scores provide the best prognostic accuracy among the systems studied. However, those of the Tokyo and CUPI methods are artificially enhanced because of their greater number of staging levels. The Child-Pugh nominal liver staging system is the most accurate in predicting survival of patients with unresectable HCC treated with TACE, and it is recommended that it be adopted as the standard for HCC staging in such patients.

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Abbreviations: BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of the Liver Italian Program, CUPI = Chinese University Prognostic Index, HCC = hepatocellular carcinoma, MELD = Model for End-stage Liver Disease, TACE = transarterial chemoembolization

RECENT studies (1–3) have shown a survival benefit in selected patients with unresectable hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE). However, despite the widespread use of TACE, lack of standardization affects all aspects of patient treatment, including patient selection, disease staging, embolization technique, follow-up, and repeat treatment. One of the nonstandardized issues facing interventional radiologists today in planning TACE treatment for their patients is which liver staging system to use. Standardizing the staging system would optimize patient selection by eliminating unnecessary procedures, allow for more valid comparisons among studies, and provide more accurate survival prediction for patients and their families.

Results of limited comparisons between two or three liver staging systems have been published; however, these comparisons do not answer the question which system provides the best survival predictive accuracy (4–7). Grieco et al (4) have reported better prognostic accuracy with use of the Barcelona Clinic Liver Cancer (BCLC) system as opposed to the Okuda sys-

From the Departments of Vascular and Interventional Radiology (C.S.G., E.L., J.U.P., H.W.K., K.H.) and Biostatistics (C.F.), Johns Hopkins University; 600 North Wolfe Street, Blalock 545, Baltimore, Maryland 21287. Received April 4, 2006; and accepted July 3. **Address correspondence to** J.F.H.G.; E-mail: jfg@jhmi.edu

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tem or the Cancer of the Liver Italian Program (CLIP) system for patients with unresectable HCC treated with TACE. Brown et al (5) have reported that the Child-Pugh system is superior to the Model for End-stage Liver Disease (MELD) system in predicting patient survival after TACE for unresectable HCC. The Okuda system was reported by Testa et al (6) as being inferior to the CLIP and MELD systems in predicting survival of patients with viral hepatitis and unresectable HCC treated with TACE. Other authors use different staging systems in the same study interchangeably (ie, Okuda and Child-Pugh), assuming that their similar stratification levels (there are three) offer the same prognostic accuracy (7). Finally, the CLIP system was reported to be superior to the Okuda system in correlating with survival of patients with unresectable HCC treated with TACE (8).

In general, authors who look for possible benefits of TACE for unresectable HCC will select the staging system they believe is more accurate, even without strong scientific support for their specific choice. Such studies cannot be compared with one another because of lack of standardization of the liver staging system, among other factors. Therefore, the question which liver staging system is best in predicting the survival of patients with unresectable HCC treated with TACE is important to address. To this end, we attempted to rank the 12 most commonly used liver staging systems (see Appendix) according to their prognostic accuracy for patients with unresectable HCC treated with TACE.

PATIENTS AND METHODS

Patient Selection

This was a prospective study that was exempted by our institution's institutional review board. From June 1996 to June 2004, 207 consecutive patients with unresectable HCC who received treatment according to the Johns Hopkins TACE protocol (see Technique section) and had none of the exclusion criteria listed later were entered into the study. Patients whose disease reverted to being operable after TACE and underwent resection or transplantation were excluded from the study. Also excluded were patients who had multimodality treatment such as thermal or chemical ablation, external radiation treatment, or experimental chemotherapy in addition to TACE. Additional exclusion criteria were significant encephalopathy, uncorrectable bleeding diathesis, and total bilirubin level greater than 4 mg/dL. Of the initial 207 patients who met the inclusion criteria, an additional 35 patients were removed from the study because they failed to complete the treatment protocol as planned. The remaining 172 were monitored from the date of diagnosis to the date of death or of data collection if they were alive, and if enough data were available to enable calculation of their liver disease stage according to all 12 studied systems just before the first TACE procedure. All patients were reviewed at a multidisciplinary liver conference that included interventional and diagnostic radiologists, gastrointestinal surgeons, hepatologists, oncologists, and radiation treatment physicians. This liver conference group concluded in each case that TACE was the appropriate treatment option for the patients

Technique

Patients were seen in clinic, and the procedure, related risks, benefits, and alternatives were explained. Relevant laboratory data and dual-phase liver computed tomography (CT) and/or magnetic resonance (MR) imaging were reviewed. After 8 hours without food or water, patients were medicated with cefotetan 2 g intravenously (AstraZeneca, Wilmington, DE) or Zosyn (piperacillin and tazobactam; Wyeth, Philadelphia, PA) just before the procedure. Penicillin-allergic patients received clindamycin (Pharmacia & Upjohn, Kalamazoo, MI) 600 mg intravenously. On initial TACE, a superior mesenteric arteriogram with portal venous phase was obtained to document portal vein thrombosis and to show possible variant hepatic arterial supply. The celiac axis was selected with a 0.035-inch Terumo guide wire (Terumo, Somerset, NJ) and a Simmons-1 catheter, and the desired hepatic artery branch was subselected depending on tumor location. Occasionally, because of unfavorable anatomy, we could not advance the 5-F catheter into the left or right hepatic artery. In these cases, a 3-F Renegade High-Flo catheter (Boston Scientific, Natick, MA) was introduced coaxially over a 0.014-inch Transend wire (Boston Scientific). A 7- to 10-mL chemotherapy solution was infused (cisplatin 100 mg [Bristol Myers Squibb, Princeton, NJ], doxorubicin 50 mg [Adriamycin; Pharmacia & Upjohn], and mitomycin C 10 mg [Bedford Laboratories, Bedford, OH]) in a 1:1 volume ratio with Ethiodol (Savage Laboratories, Melville, NY) or a 2:1 ratio with twice as much chemotherapeutic agent as Ethiodol, depending on flow characteristics, to avoid complete stasis within the selected hepatic artery. If we noted during chemoembolization that the flow in the treated artery became sluggish too quickly to allow the entire amount of chemotherapeutic agent to be infused, we further diluted the chemotherapeutic agent and Lipiodol mixture with more chemotherapeutic agent. This was followed by infusion of 1–2 mL of Embosphere particles (Biosphere Medical, Boston, MA) 300–500 μm in size to slow down arterial inflow and prevent washout of the chemotherapeutic agents. The particles were diluted with the addition of the same volume of iodinated contrast medium. The endpoint of the procedure was achieved when the entire amount of chemotherapeutic agent was delivered and the infused Embospheres resulted in slowed arterial flow compared with initial flow. Extreme care was used to insure that forward flow in the hepatic artery was maintained at all times during the procedure to preserve patency of the artery, allow for repeat treatment, and minimize the theoretical risk of liver ischemia or infarction. Nonbuffered lidocaine (10–20 mL at 1:100) was also given intraarterially after chemoembolization for pain control. After TACE, patients were admitted overnight, and a noncontrast CT scan of the liver was obtained before discharge to document Ethiodol deposition. Technical success was defined by completion of the procedure and documentation of distribution of Lipiodol in the targeted lobe on follow-up CT.

Follow-up

Patients were monitored with dual-phase CT and/or MR imaging 4–6 weeks after TACE (with perfusion and