CLINICAL STUDY

Comparative Study of Staging Systems for Hepatocellular Carcinoma in 428 Patients Treated with Radioembolization

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ABSTRACT

Purpose: To compare the utility of different staging systems and analyze independent predictors of survival in patients with hepatocellular carcinoma (HCC) treated with yttrium-90 (^{90}Y) radioembolization.

Materials and Methods: During the period 2004–2011, 428 patients with HCC were treated with ^{90}Y radioembolization. All patients were staged prospectively by the following staging systems: Child-Turcotte-Pugh (CTP), United Network for Organ Sharing, Barcelona Clinic Liver Cancer (BCLC), Okuda classification, Cancer of the Liver Italian Program (CLIP), Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire, Chinese University Prognostic Index, and Japan Integrated Staging. The ability of the staging systems to predict survival was assessed. The staging systems were compared using Cox proportional hazards regression model, linear regression, Akaike information criterion (AIC), and concordance index (C-index). Univariate and multivariate analyses were employed to assess independent predictors of survival.

Results: When tested independently, all staging systems exhibited significant ability to discriminate early (long survival) from advanced (worse survival) disease. CLIP provided the most accurate information in predicting survival outcomes (AIC = 2,993, C-index = 0.8503); CTP was least informative (AIC = 3,074, C-index = 0.6445). Independent predictors of survival included Eastern Cooperative Oncology Group performance status grade 0 (hazard ration [HR], 0.56; confidence interval [CI], 0.34–0.93), noninfiltrative tumors (HR, 0.62; CI, 0.44–0.89), absence of portal venous thrombosis (HR, 0.60; CI, 0.40–0.89), absence of ascites (HR, 0.56; CI, 0.40–0.76), albumin $\geq$ 2.8 g/dL (HR, 0.72; CI, 0.55–0.94), alkaline phosphatase $\leq$ 200 U/L (HR, 0.68; CI, 0.50–0.92), and α-fetoprotein $\leq$ 200 ng/mL (HR, 0.67; CI, 0.51–0.86).

Conclusions: CLIP was most accurate in predicting survival in patients with HCC. Given that not all patients receive the recommended BCLC treatment strategy, this information is relevant for clinical trial design and predicting long-term outcomes after ^{90}Y radioembolization.

ABBREVIATIONS

AFP = α-fetoprotein, AIC = Akaike information criterion, BCLC = Barcelona Clinic Liver Cancer, C-index = concordance index, CLIP = Cancer of the Liver Italian Program, CTP = Child-Turcotte-Pugh, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, JIS = Japan Integrated Staging, ^{90}Y = yttrium-90 radioembolization, PVT = portal vein thrombosis, UNOS = United Network for Organ Sharing

Hepatocellular carcinoma (HCC) is the sixth most common malignancy diagnosed worldwide. It is now the third most common cause of cancer-related mortality. Long-term outcomes remain dismal (1). Depending on

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R.S. is supported in part by NIH grant CA126809. None of the other authors have identified a conflict of interest.

http://dx.doi.org/10.1016/j.jvir.2014.01.010

tumor stage, patients may be offered surgical, locoregional, or systemic therapeutic options. The occurrence of HCC in patients with cirrhosis (influencing liver function, performance status, and treatment efficacy) has led to the development of multiple staging systems. Debate continues at the present time regarding the most appropriate and universally applicable HCC staging system (2).

Yttrium-90 (^{90}Y) radioembolization has assumed an important palliative role in the management of unresectable HCC by producing tumor necrosis and delaying progression (3–7). Although the utility of various staging systems in predicting prognosis of patients with unresectable HCC after chemoembolization has been investigated, this has never been investigated with radioembolization (8,9). Staging systems may exhibit different predictive power depending on the treatment applied. In a study including > 2,000 Taiwanese patients, the authors concluded that the applicability of HCC staging systems depended on treatment methods used (10,11). Incorporation of ^{90}Y radioembolization into the Barcelona Clinic Liver Cancer (BCLC) staging system has been suggested by single-center data (5,12,13). ^{90}Y radioembolization has been widely used in the setting of portal vein thrombosis (PVT) and has generated encouraging outcomes. Physicians using ^{90}Y radioembolization have shown trends toward using ^{90}Y radioembolization in more diffuse or advanced disease, while reserving chemoembolization for earlier disease treatable by selective catheterization. Intuitively, the reality of this selection bias may translate into different predictive abilities of staging systems based on the therapeutic efficacy of ^{90}Y radioembolization. A comparative effectiveness study concluded that ^{90}Y radioembolization leads to lower toxicity and longer time-to-progression compared with chemoembolization (5). Evidence-based personalized medicine (specific treatment tailored to each patient) has mandated the need for therapy-specific studies assessing the predictive ability of staging systems. This approach enables treating physicians to identify the staging system best fit for the intervention, simplify survival prediction, and permit comparison with other therapies. Finally, because ^{90}Y radioembolization has yet to be incorporated into BCLC staging, analyzing the prognostic ability of staging systems for patients treated with ^{90}Y radioembolization is clinically relevant.

A staging system should demonstrate similar outcomes for the same stage (homogeneity), significant survival differences when comparing the stages of a system (discriminatory ability), and longer survival in earlier stages (monotonicity of gradients). Given these criteria, a comprehensive analysis of the eight most widely used HCC staging systems was performed to investigate their prognostic utility in the setting of ^{90}Y radioembolization (Cox proportional regression model, linear regression, Akaike information criterion [AIC], and concordance index [C-index]) (10,14,15). Baseline variables independently affecting survival were also analyzed.

MATERIALS AND METHODS

Patient Cohort

From January 2004 to March 2011, 428 patients with HCC underwent 728 treatments with ^{90}Y radioembolization at our center. These patients (and baseline variables) were captured from a prospectively collected database, and all were included in this statistical analysis; no patient was excluded. The study was compliant with the Health Insurance Portability and Accountability Act and approved by the institutional review board.

Baseline Characteristics

Table 1 summarizes the baseline characteristics. Most patients were treatment-naïve (89%), ≥ 65 years old (52%), male (73%), white (70%), and Eastern Cooperative Oncology Group (ECOG) performance status grade 0 (55%). The mean and median number of ^{90}Y treatments/patient was 1.7 and 1, respectively.

Patient Evaluation and Staging

All patients provided informed written consent. History, physical examination, laboratory studies, and imaging studies were obtained. Patients underwent magnetic resonance imaging (institutional standard) or computed tomography (in the presence of a pacemaker or claustrophobia). Diagnostic criteria for HCC followed the criteria defined by the American Association for the Study of Liver Diseases and the National Comprehensive Cancer Networks guidelines (2,16,17). The criteria for treating patients with radioembolization included unresectable HCC as determined by surgery, ECOG grade ≤ 2, and bilirubin < 3.0 mg/dL (unless selective infusion was possible) (13).

Radioembolization Treatment

Mesenteric angiography and macroaggregated albumin scans were performed 1 week before treatment to assess vascular anatomy and lung shunt fraction (18). The device used was glass-based (Nordion, Ottawa, Ontario, Canada); this device has regulatory approval for HCC with or without PVT (United States) and liver neoplasia (worldwide). All procedures were performed on an outpatient basis (18,19). In brief, target dose was 120 Gy on a lobar (or segmental) basis in patients with HCC with bilirubin < 3.0 mg/dL with or without PVT. Retreatment was considered when there was persistent enhancement or recurrence.

Patient Follow-up

Assessments of toxicity and response were performed at 1 month after treatment and subsequently at intervals of 2–3 months, with future treatment decisions made at