

Chemoembolization for Hepatocellular Carcinoma in Patients with Extrahepatic Spread: Prognostic Determinants and Appropriate Candidates

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ABSTRACT

Purpose: To investigate treatment outcome, prognostic factors for overall survival, and appropriate candidates for transarterial chemoembolization among patients with hepatocellular carcinoma (HCC) and extrahepatic spread (EHS).

Materials and Methods: From January 2010 to June 2014, 111 consecutive patients with HCC and EHS treated by transarterial chemoembolization alone were evaluated. Factors associated with overall survival were evaluated using Cox regression analysis, and a scoring equation was established to subgroup patients with EHS.

Results: Median follow-up was 3.8 months, and median overall survival was 3.8 months (95% confidence interval [CI], 2.9–4.7 months). Multivariate analysis demonstrated maximum tumor size ≥ 10 cm (hazard ratio [HR] 1.58; 95% CI, 1.02–2.46; $P = .041$), multifocal intrahepatic tumors (HR 1.55; 95% CI, 1.03–2.33; $P = .037$), and portal vein tumor thrombosis (PVTT) (HR 1.81; 95% CI, 1.12–2.91; $P = .015$) as significant predictors of overall survival. Based on these factors, a scoring equation was developed to predict treatment outcome of transarterial chemoembolization, with an area under the receiver operating characteristic curve of 0.76 in predicting 6-month survival. Using a cutoff score of 5.5, patients with HCC and EHS were divided into 2 groups with significantly different overall survival (8.1 months for EHS1 and 2.4 months for EHS2; $P < .001$). The described method of subgrouping remained discriminatory regardless of baseline characteristics.

Conclusions: Maximum tumor size, intrahepatic tumor distribution, and presence of PVTT were significant determinants of overall survival for patients with HCC and EHS. Transarterial chemoembolization may be appropriate for patients with EHS but lower intrahepatic tumor burden.

ABBREVIATIONS

AFP = alpha fetoprotein, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, EHS = extrahepatic spread, HCC = hepatocellular carcinoma, HR = hazard ratio, PVTT = portal vein tumor thrombosis

According to the Barcelona Clinic Liver Cancer staging system, advanced hepatocellular carcinoma (HCC) is characterized by the development of cancer-related symptoms, portal vein tumor thrombosis (PVTT), or extrahepatic spread (EHS) (1). The guidelines of the European

Association for the Study of Liver Disease and the American Association for the Study of Liver Disease recommend sorafenib as first-line treatment in patients with advanced HCC (2,3). Although 2 randomized clinical trials (Sorafenib Hepatocellular Carcinoma Assessment Randomized

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J Vasc Interv Radiol 2017; ■:1–7

<http://dx.doi.org/10.1016/j.jvir.2017.02.016>

None of the authors have identified a conflict of interest.

Protocol [SHARP] trial and Asia-Pacific trial) have confirmed the efficacy of sorafenib in patients with advanced HCC, it was not shown in the subgroup analyses of these 2 trials that sorafenib has a beneficial effect compared with placebo in improving overall survival of patients with EHS (4–7).

In a recent study, Sohn et al (8) demonstrated that intrahepatic tumor remains a poor prognostic factor for both disease progression and overall survival in patients with HCC and EHS treated with sorafenib; moreover, it has been reported that intrahepatic tumor progression is the principal cause of death in patients with EHS (9,10). Consequently, control of intrahepatic tumors may be beneficial for patients with HCC and EHS (11). Transarterial chemoembolization, as the most commonly used palliative treatment, mainly targets intrahepatic lesions and significantly benefits patients with unresectable HCC (12–14). Considering the limited survival benefit and locoregional efficacy of sorafenib, it was hypothesized that better control of intrahepatic tumors using transarterial chemoembolization would increase survival benefit in patients with HCC and EHS (15). The aims of the present study were to (i) investigate the treatment outcomes of transarterial chemoembolization in patients with HCC and EHS, (ii) evaluate prognostic factors associated with overall survival, and (iii) select the appropriate candidates for transarterial chemoembolization.

MATERIALS AND METHODS

Patients

From January 2010 to June 2014, HCC and EHS were diagnosed in 243 consecutive patients in a single center. HCC was diagnosed according to the criteria of the European Association for the Study of Liver Disease and American Association for the Study of Liver Disease guidelines (2,3); EHS was confirmed pathologically or diagnosed by imaging, such as chest radiograph, computed tomography (CT), magnetic resonance (MR) imaging, or bone scintigraphy. Of the 243 patients, 117 received transarterial chemoembolization alone instead of sorafenib as a palliative treatment for economic or other reasons. After excluding 4 patients with Child-Pugh class > B score 8 and 2 patients with Eastern Cooperative Oncology Group (ECOG) performance status score > 2, 111 consecutive patients with presumed EHS, treated by transarterial chemoembolization alone were retrospectively evaluated. This study was approved by the institutional review board and written informed consent was obtained from all the patients before the initiation of treatment.

The baseline demographic and clinical characteristics of the patients are summarized in Table 1. The mean age of patients was 52.0 years; 92 patients (82.9%) were men; and hepatitis B virus was the most common underlying cause of liver disease (99; 89.2%). Of patients, 94 (84.7%) were Child-Pugh class A, and 17 (15.3%) were Child-Pugh class B. None of the 17 patients classified as Child-Pugh B had clinically overt jaundice or hepatic

Table 1. Baseline Demographics and Clinical Characteristics of Patients (N = 111)

Characteristics	Values
Sex, male/female	92 (82.9)/19 (17.1)
Age, y	52.0 ± 9.7
Etiology, HBV/HCV/others	99 (89.2)/4 (3.6)/8 (7.2)
Child-Pugh class, A/B	94 (84.7)/17 (15.3)
ECOG performance status, 0/1/2	26 (23.4)/82 (73.9)/3 (2.7)
Previous treatments	8 (7.2)
AFP, ng/mL	432.5 [27.8–20,135.5]
Intrahepatic tumor	
Tumor size, cm	10.2 ± 4.2
Tumor number, unifocal/multifocal	44 (39.6)/67 (60.4)
Portal vein tumor thrombosis	45 (40.5)
Site of extrahepatic metastasis	
Lymph node	77 (69.4)
Lung	30 (27.0)
Bone	7 (6.3)
Adrenal gland	5 (4.5)
Others	5 (4.5)
Baseline laboratory values	
Leukocyte, × 10 ⁹ /L	5.6 ± 2.0
Hemoglobin, g/L	126.8 ± 19.0
Platelets, × 10 ⁹ /L	152.7 ± 91.9
International normalized ratio	1.13 ± 0.15
Alanine aminotransferase, U/L	50.5 ± 38.7
Aspartate aminotransferase, U/L	73.4 ± 48.4
Albumin (g/L)	37.4 ± 4.9
Total bilirubin (μmol/L)	19.4 ± 12.1
Urea nitrogen (mmol/L)	5.0 ± 1.5
Serum creatinine (μmol/L)	79.0 ± 20.9

Note—Values are presented as number (%), mean ± SD, or median (interquartile range).

AFP = Alpha fetoprotein; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus.

encephalopathy. Most patients (108; 97.3%) had no or mild cancer-related symptoms, with an ECOG performance status score of 0 or 1. The median alpha fetoprotein (AFP) level was 432.5 ng/mL (interquartile range, 27.8–20,135.5 ng/mL). The mean diameter of the largest measurable lesion was 10.2 cm. There were 44 patients (39.6%) with a single intrahepatic lesion, and 45 patients (40.5%) had PVTT. The most frequent sites of EHS were the lymph nodes (77; 69.4%), lung (30; 27.0%), bone (7; 6.3%), adrenal gland (5; 4.5%), and other sites (5; 4.5%). Among the 66 patients without PVTT, 41 (62.1%) had extrahepatic metastases in lymph nodes, 23 (34.8%) had metastases in lung, 7 (10.6%) had metastases in bone, 3 (4.5%) had metastases in adrenal gland, and 2 (3.0%) had metastases in other sites. Of the patients in the study, 103 (92.8%) did not receive any other therapy before transarterial chemoembolization, and no patient was treated with sorafenib after embolization. Over the course of the study, most patients (83; 74.8%) had 1 session of transarterial chemoembolization;

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