Comparison of Transarterial Chemoembolization and Hepatic Resection for Large Solitary Hepatocellular Carcinoma: A Propensity Score Analysis

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ABSTRACT

Purpose: To compare long-term survival after hepatic resection and transarterial chemoembolization of large solitary hepatocellular carcinomas (HCCs).

Materials and Methods: Analysis of 91 and 68 consecutive patients with large ($\geq$ 5 cm) solitary HCCs who underwent hepatic resection and transarterial chemoembolization, respectively, was performed. Overall survival and time to progression (TTP) were estimated using the Kaplan-Meier method and compared using the Cox proportional hazards model. To control for treatment-selection bias, matched groups of patients were selected using a propensity score matching method, and survival analysis was repeated.

Results: During the follow-up period (median, 60.7 mo; range, 0.5–122.2 mo), 42 (46%) patients in the hepatic resection group and 35 (51%) patients in the transarterial chemoembolization group died. The 1-year, 3-year, and 5-year overall survival rates of the hepatic resection and transarterial chemoembolization groups were 91.1%, 80.0%, and 66.4% (hepatic resection group) and 89.8%, 72.8%, and 49.6% (transarterial chemoembolization group) ($P = .023$). TTP was significantly longer in patients who underwent hepatic resection ($P < .001$). Hepatitis B surface antigen positivity and the absence of portal hypertension were independent predictors for favorable overall survival. For patients with platelet counts $\leq$ 100,000/mm^3, Child-Pugh score of 6, smaller HCCs ($\leq$ 7 cm), or portal hypertension, hepatic resection and transarterial chemoembolization yielded similar overall survival rates. After propensity score matching, transarterial chemoembolization was comparable to hepatic resection in overall survival ($P = .293$), whereas TTP remained longer in patients who underwent hepatic resection ($P = .001$).

Conclusions: Transarterial chemoembolization can lead to results comparable to hepatic resection in the treatment of large solitary HCCs, particularly in patients with clinically presumed portal hypertension.

ABBREVIATIONS

AFP = alpha fetoprotein, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, TTP = time to progression

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide (1,2). Because HCC usually occurs in patients with underlying liver disease, candidates for treatment strategies should be selected based on tumor status and liver function (3). According to the Barcelona Clinic Liver Cancer staging system, which is widely used for treatment allocation, hepatic resection is considered the treatment of choice for solitary tumors without macrovascular invasion or extrahepatic spread (2–4). However, the Barcelona Clinic Liver Cancer system fails to allocate patients with large ($\geq$5 cm)

solitary HCCs and portal hypertension to optimal treatment, and the efficacy of treatment strategies for these patients has not been fully evaluated (5). These patients are beyond the Milan criteria; liver transplantation is not recommended as the first treatment choice because of the risk of recurrence and the scarcity of donors (6). Ablative therapies, such as percutaneous ethanol injection and radiofrequency ablation, rarely achieve complete necrosis in tumors $>$ 3 cm (7–9).

Consequently, hepatic resection is considered the only potentially curative treatment for these patients. Nevertheless, few patients are candidates for hepatic resection because of associated liver cirrhosis and the risk of inducing postoperative liver decompensation (10). Although perioperative mortality of hepatic resection in cirrhotic patients has decreased, candidates must be selected carefully to avoid life-threatening complications (11). The long-term outcome of hepatic resection remains poor, mainly because tumors often recur after resection (12). For these reasons, whether hepatic resection is the optimal treatment for large solitary HCCs is a matter of debate.

Transarterial chemoembolization is often performed because of the technical difficulty of hepatic resection, the risk of postoperative liver decompensation, and frequent tumor recurrence after resection. However, the outcomes of hepatic resection and transarterial chemoembolization for treatment of large solitary HCCs have not been well evaluated. This retrospective study was designed to compare the long-term survival of patients who underwent hepatic resection with survival of patients receiving transarterial chemoembolization as the initial treatment for large solitary HCCs.

MATERIALS AND METHODS

Study Patients

This study included data for 159 consecutive patients with a new diagnosis of large ($\geq$ 5 cm) solitary HCC from January 2003 through December 2007 at a tertiary referral center; clinical data were collected prospectively and retrieved retrospectively. This study was approved by the institutional review board and was exempted from the need for written informed consent because the data were analyzed anonymously.

The baseline information collected at the time of diagnosis included demographic characteristics, etiology of the liver disease, longest diameters of the tumors, laboratory findings, performance status, severity and complications of liver cirrhosis, and treatment modality. All patients were informed about the details of hepatic resection, which is standard treatment for large solitary HCCs, and transarterial chemoembolization was recommended to older patients or patients with clinically presumed portal hypertension. Treatment was selected based on the physician's advice and the patient's preference. Patients with the following conditions were excluded from the study: a) presence of vascular invasion or extrahepatic metastasis on imaging studies performed before the procedure, b) Child-Pugh class B or C liver cirrhosis, c) Eastern Cooperative Oncology Group performance scale score $\geq$ 2, or d) history of malignancies other than HCC within 5 years.

The diagnosis of HCC was based on the diagnostic criteria of the European Association for the Study of the Liver or the American Association for the Study of Liver Disease (13,14). The severity of liver dysfunction was estimated according to the Child-Pugh classification. The presence of portal hypertension was assumed when the platelet count was $<$ 100,000/mm^3 and associated splenomegaly or esophageal-gastric varices were detected. The Eastern Cooperative Oncology Group performance scale was used to assess performance status. The longest diameters of tumors and tumor responses were measured according to dynamic computed tomography (CT) or magnetic resonance (MR) imaging by an experienced liver radiologist independently without knowledge of the survival information of the study patients.

The baseline characteristics of the 159 consecutive patients are summarized in **Table 1**. Hepatic resection was performed in 91 patients, and transarterial chemoembolization was performed in 68 patients. In the transarterial chemoembolization group, patients were significantly older and had lower platelet counts, serum albumin levels, and serum bilirubin levels ($P = .037$, $P = .026$, $P = .004$, and $P = .024$). Patients in the hepatic resection group were more frequently positive for hepatitis B surface antigen (HBsAg) ($P = .023$). These two groups did not differ significantly in gender, serum transaminase levels, serum alkaline phosphatase levels, prothrombin time, Child-Pugh scores, alpha fetoprotein (AFP) levels, tumor size, performance status, and portal hypertension.

HCC Treatment

For anatomic resection, the hepatic parenchyma was transected at the intersegmental plane as described by Couinaud (15). Tumor number, size, and invasion of the major branches of the portal or hepatic veins were evaluated by intraoperative ultrasound. Negative resection margins, defined as absence of visible cancer cells at the margins of the remnant liver nearest to the tumor, were evaluated by frozen section investigation in every patient who underwent hepatic resection.

Transarterial chemoembolization was performed using techniques described previously (16). Transarterial chemoembolization was performed as selectively as possible through the tumor-feeding arteries using a microcatheter (Microferret [Cook, Inc, Bloomington, Indiana] or Progreat [Terumo, Tokyo, Japan]). First, iodized oil (Lipiodol; Andre Guerbe Lab, Aulnay-sous-Bios, France)