Research Article

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Prediction of aggressiveness in early-stage hepatocellular carcinoma for selection of surgical resection

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Background & Aims: In early-stage hepatocellular carcinoma (eHCC), radiofrequency ablation (RFA) has comparable outcomes to surgical resection (SR); however, micrometastases may be present, resulting in tumor recurrence after local ablation. Therefore, we investigated predictors of aggressiveness in eHCC to select patients at high risk of recurrence after RFA who would benefit from SR.

Methods: First, we analyzed 128 patients with newly diagnosed eHCC (single tumor with a diameter <3 cm) who underwent SR between January 2006 and December 2011. Risk factors for micrometastasis (representative of tumor aggressiveness) such as microvascular invasion or poor histologic grade were investigated. We then analyzed 201 eHCC patients who underwent RFA between July 2007 and December 2011. Identified risk factors were validated to determine their influence on tumor recurrence.

Results: The only significant risk factor for tumor aggressiveness in the SR group was the product of serum levels of α-fetoprotein (AFP) and prothrombin induced by vitamin K absence-II (PIVKA-II) ($A*P \geqslant 1600$; hazard ratio [HR] 4.764; 95% confidence interval [CI], 1.867–12.161; $p = 0.001$). This product also showed statistical significance for predicting recurrence in the RFA group (HR 2.296; 95% CI, 1.237–4.262; $p = 0.008$). Patients with RFA and $A*P \geqslant 1600$ had significant early tumor recurrence ($p = 0.008$) and poor late survival outcomes ($p = 0.001$) compared with other patients.

Conclusions: The product of AFP and PIVKA-II levels is a useful predictor of aggressiveness in eHCC, which predicts tumor recurrence after RFA. Therefore, it should be considered when selecting SR as first-line treatment.

Keywords: Prediction; Aggressiveness; Early-stage hepatocellular carcinoma; Radio frequency ablation; Surgical resection.

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Abbreviations: HCC, hepatocellular carcinoma; eHCC, early-stage hepatocellular carcinoma; RFA, radiofrequency ablation; SR, surgical resection; HBV, hepatitis B virus; HCV, hepatitis C virus; TB, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; AFP, α-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II; CT, computed tomography; MRI, magnetic resonance imaging.

Introduction

Hepatocellular carcinoma (HCC) surveillance in high-risk populations, such as cirrhotic patients, has led to an increase in detection of early-stage HCC (eHCC) that is eligible for curative therapies [1]. The use of locoregional therapies, including percutaneous ethanol injection and thermal ablation (i.e., microwave coagulation therapy, radiofrequency ablation [RFA], and cryotherapy) for eHCC has increased [2,3]. RFA is performed most frequently among these locoregional therapies, and has shown comparable survival outcomes and low complication rates as compared with surgical resection (SR) for eHCC [4]. Accordingly, RFA has been recommended as a treatment option for eHCC since the issue of the 2005 Practice Guidelines published by the American Association for the Study of Liver Diseases [5].

It is well known that HCC undergoes multi-step carcinogenesis. If the tumor progresses, arterial blood inflow can exceed blood outflow, causing a decrease in drainage into the hepatic vein. Consequently, portal backflow develops and can replace all venous outflow. If portal backflow develops, this can result in the presence of tumor micrometastases, which derive from the main tumor via the portal system and can be one of the major causes of HCC recurrence [6]. Micrometastases, which cannot often be detected by various imaging modalities, are not the direct targets of local ablation therapy, so there is a strong possibility of local recurrence after RFA [7]. However, in SR, the main vessels are ligated and the tumor is widely excised such that micrometastases would simultaneously be removed with the tumor, even if they were not recognized on preoperative imaging, and the possibility of residual micrometastases can be greatly reduced [8].

Therefore, we hypothesized that even in eHCC, if the patient has risk factors related to the presence of micrometastases, such

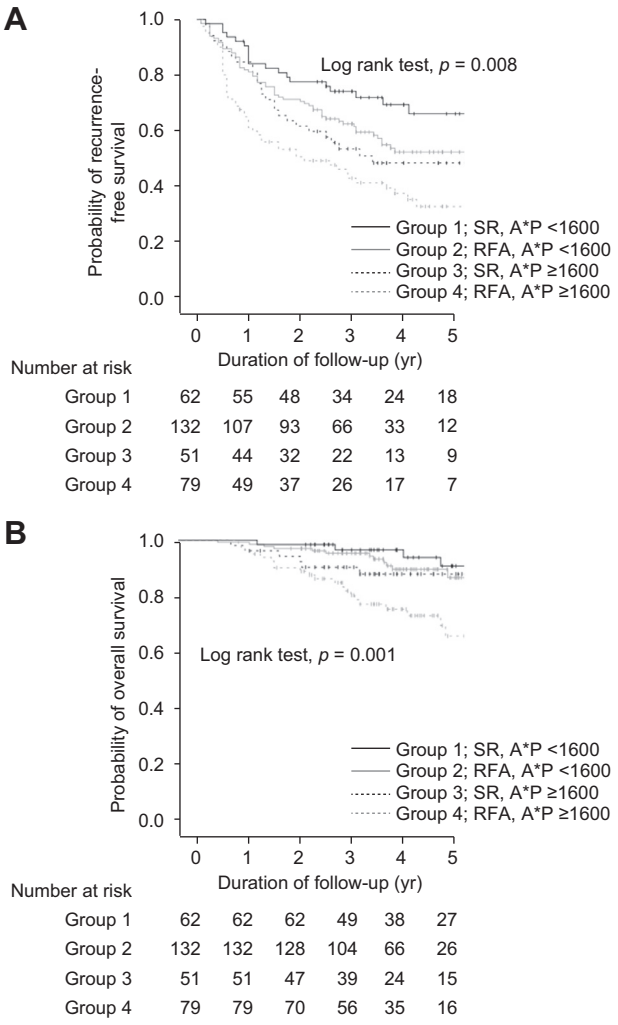

Fig. 1. Recurrence-free survival and overall survival in patient subsets. (A) Cumulative probability of tumor recurrence. The frequency of recurrence was significantly higher recurrence in Group 4. ($p = 0.008$), especially during the first year (1-year recurrence-free survival: Group 1, 90.4%; Group 2, 81.1%; Group 3, 84.6%; Group 4, 64.9%). The curves continued to diverge during 2 years of follow-up, but then continued parallel, and the cumulative probability of recurrence after 2 years was not significantly different ($p = 0.418$). (B) The cumulative probability of overall survival. Significant difference was found in overall survival according to the type of procedure and combined levels of AFP and PIVKA-II ($p = 0.001$). The curve of Group 4 significantly diverged from that of the other groups (HR 2.159; 95% CI, 1.154–4.042; $p = 0.016$).

as microvascular invasion or poor histologic differentiation [7], there may be a greater chance of tumor recurrence after RFA, and SR may be the better treatment option. Second, if we determine the significant preoperative risk factors for aggressiveness in patients with eHCC, we can more accurately predict the risk of tumor recurrence after RFA, and SR can be recommended in such cases.

The aim of this study was first, to identify preoperative risk factors for tumor aggressiveness in eHCC patients undergoing SR, and second, in a group of patients undergoing RFA, to validate these identified risk factors in terms of HCC recurrence.

Patients and methods

This retrospective cohort study was approved by the institutional review board of the Seoul National University Hospital (Seoul, Korea) and was exempted from the requirement to obtain informed consent. The first step of this study was to identify preoperative risk factors through the analysis of patients who underwent SR. Between January 2006 and December 2011, 128 patients with newly diagnosed eHCC at Seoul National University Hospital, which was defined as a single tumor less than 3 cm, were analyzed. Patients with advanced-stage HCC, previous treatment history of HCC, or insufficient clinical data were excluded from the analysis. The risk for micrometastases, which represents tumor aggressiveness, was defined as the presence of at least 1 of the following factors: Edmonson and Steiner histologic grade 3 or 4 and/or microvascular invasion. The following data were collected on all patients to determine the risk factors for tumor aggressiveness: age, sex, body mass index, presence of hepatitis B virus (HBV) and hepatitis C virus (HCV), preoperative laboratory results (levels of total bilirubin [TB], albumin, and the international normalized ratio [INR]), tumor marker levels (α-fetoprotein [AFP] and prothrombin induced by vitamin K absence-II [PIVKA-II]), and tumor characteristics (tumor size, histologic grade, and presence of microvascular invasion).

The second step of the study was the validation of risk factors in patients treated with RFA. We validated the identified risk factors after adjusting for several parameters as demographics, laboratory results, radiologic findings that might have influenced tumor recurrence in the RFA group. Between July, 2007 and December 2011, 201 newly diagnosed eHCC patients who underwent RFA for initial treatment were investigated. Clinical variables were the same as those outlined for the first step of the analysis, except that pathologic results were also collected and the risk factors for tumor recurrence after RFA were identified. The cumulative probability of tumor recurrence and overall survival according to the type of treatment and identified risk factors were also compared.

All patients were followed-up at 1, 3, and 6 months, and then every 3 to 6 months when necessary. At every visit, imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography, and serologic tests such as tumor marker analyses and biochemical liver function tests were performed.

Procedure

RFA was performed by 2 specialized intervention radiologists using a 200 W RF generator (Radionics, Burlington, MA), with a 17-gauge single cooled-tip needle electrode for HCC less than 2 cm, or a triple-cluster needle electrode for HCC 2 cm or larger. Under ultrasound guidance, the radiofrequency electrode was placed at the deep margin of the tumor and RF energy delivery to target tumors was maintained for 12–18 min depending on tumor size. The ablation was performed repeatedly until the entire lesion was enveloped by assumed necrotic areas which was presented as echogenic bubble clouds. The completeness of the ablation was evaluated using dynamic CT immediately after the procedure, and a repeat RFA was performed for any incomplete ablation.

SR was performed by 3 surgeons experienced in hepatobiliary surgery. The surgery was performed under low central venous pressure at less than 5 mmHg. Anatomic partial hepatectomy was performed in a standardized manner; however, if the patients had poor liver function, non-anatomic partial hepatectomy was also performed. All SRs were performed by ligating the feeding vessels, and margins of at least 2 cm were secured.

Statistical analysis

For intergroup comparisons, the distribution of the data was first evaluated for normality using the Shapiro–Wilk test. Normally distributed data are presented herein as means ± standard deviation, and groups were compared using the Student's t test. Descriptive variables were subjected to χ^2 analysis or Fisher's exact test, as appropriate. The optimal cut-off value for the level of AFP, PIVKA-II, and the product of AFP and PIVKA-II (A*P) were determined by the area under the receiver operating characteristic analysis. Multivariate analysis using an ordinary logistic regression model was performed to investigate the risk factors for tumor aggressiveness in SR patients in the first step, and the influence of these factors on tumor recurrence after RFA was evaluated in the second step. Survival and recurrence according to the type of procedure and presence of the identified risk factors were plotted using the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis using the Cox proportional hazard regression method was performed to investigate the risk factors for recurrence-free survival and overall survival. p values of <0.05 were regarded as statistically significant. Statistical analysis was conducted using SPSS ver. 19.0 (SPSS Inc., Chicago, IL).