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ORIGINAL ARTICLE

Combined resection and radiofrequency ablation versus transarterial embolization for intermediate-stage hepatocellular carcinoma: A propensity score matching study

Wendell Espinosa ^{a,b}, Yueh-Wei Liu ^c, Chih-Chi Wang ^c,
Chih-Che Lin ^c, Jing-Houng Wang ^b, Sheng-Nan Lu ^b,
Chao-Hung Hung ^{b,*}

^a Department of Internal Medicine, Dr. Pablo O. Torre Memorial Hospital, Bacolod City, Philippines

^b Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

^c Department of Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

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KEYWORDS

Hepatocellular carcinoma;
Resection plus radiofrequency ablation;
Transarterial embolization;
Survival;
Time to progression

Abstract *Background/purpose:* This study aimed to compare the outcomes of combined hepatic resection (HR) plus intraoperative radiofrequency ablation (RFA) and transarterial embolization (TAE) for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC) in case-controlled patient groups using the propensity score.

Methods: A total of 179 patients with multifocal HCC treated with HR plus RFA ($n = 26$) or TAE ($n = 153$) were retrospectively studied. All patients were classified as BCLC stage B and Child–Pugh class A. Analyses were performed over all participants as well as for propensity score-matched (1:3) patients to adjust for baseline differences. Cumulative overall survival (OS) and time to progression (TTP) were compared between the two groups using the Kaplan–Meier method, and independent predictors were identified by multivariate Cox regression analysis.

Results: Patients treated with HR plus RFA had better OS and longer TTP than those with TAE ($p = 0.011$ and $p < 0.001$, respectively). Multivariate Cox regression analysis showed that combined therapy (hazard ratio 0.31; 95% confidence interval (CI), 0.12–0.78; $p = 0.013$), BCLC substage B2 (hazard ratio 1.82; 95% CI, 1.13–2.92; $p = 0.013$) and alpha-

* Corresponding author. Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung 833, Kaohsiung, Taiwan. Fax: +886 7 7322402.
E-mail address: chh4366@yahoo.com.tw (C.-H. Hung).

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fetoprotein ≥ 400 ng/ml (hazard ratio 1.85; 95% CI, 1.12-3.05; $p = 0.016$) were independent factors associated with OS. After propensity score matching, combined therapy was the significant factor associated with OS and TTP by univariate and multivariate analyses.

Conclusion: Combined HR plus RFA may provide survival advantage compared to TAE in patients with BCLC stage B HCC.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies, and the third leading cause of cancer-related death in the world.¹ In Taiwan, HCC is the second leading cause of cancer mortality with an estimated 7000 deaths per year.² The dismal prognosis of HCC is largely caused by the late diagnosis, and potentially curative treatments are feasible only at early tumor stages. Hepatic resection (HR) offers a potential cure and a long survival rate, but is limited by inadequate functional hepatic reserve, unfavorable anatomical location, and multifocal involvement.^{3–5}

The management of HCC is multi-disciplinary with a wide range of treatment options. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most commonly used HCC management guideline.⁶ HR, orthotopic liver transplantation and percutaneous local ablation such as radiofrequency ablation (RFA) are recommended as curative therapies in patients with very early (BCLC 0) and early stage (BCLC A) tumors providing a 5-year survival rate of 50–75%.^{6–9} In patients with BCLC stage B (intermediate HCC), transarterial chemoembolization (TACE) or transarterial embolization (TAE) are the standard treatments with clinical benefits (median survival from 16 to 22 months).^{6,7}

Recently, HR in combination with intraoperative RFA for multifocal hepatic tumors has been introduced.^{10–13} The addition of ablation therapy offers the possibility of increasing the cure rate of surgery, and more patients might become candidates for HR among patients with multinodular tumors.^{10–13} In this study, we aimed to evaluate if combined HR plus RFA could improve the prognosis of patients with BCLC stage B HCC compare to TAE by using a statistically valid propensity scores matching model.

Methods

Patients

From January 2009 to April 2015, 26 patients who underwent HR and intraoperative RFA and 153 patients who received TAE for BCLC stage B HCC were retrospectively enrolled. Data were collected from an electronic database of Kaohsiung Chang Gung Memorial Hospital. Baseline data included age, gender, body mass index (BMI), presence of diabetes mellitus (DM), hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), BCLC stage, tumor size and number, alpha-fetoprotein (AFP), Child–Pugh score, aspartate aminotransferase (AST), alanine transaminase (ALT) and platelet count. All patients were

classified as Child–Pugh class A. This study was approved by the ethical committee of Chang Gung Memorial Hospital with the IRB No. 201600143B0.

HCC treatment

The diagnosis of HCC was compatible with the guidelines of the American Association for the Study of Liver Disease.⁶ The extent of resection was assessed by Child–Pugh score, indocyanine green (ICG) clearance, and computed tomography (CT) volumetry. All cases were discussed in a multi-disciplinary meeting for the management of HCC in our hospital. Informed consent was obtained from each patient before treatment. These patients with multifocal hepatic tumors who were deemed unresectable by classic standards or difficult to completely ablate due to either the location involved or the tumor numbers were treated surgically with both resection and RFA during one operation. In general, these patients met the following conditions: (1) Bilobar disease; (2) dominant lesion could be resected *en bloc*, whereas minor lesion(s) in the contralateral lobe could also be ablated; (3) the ICG retention rate at 15 min $< 20\%$; (4) the estimated mass volume of the residual liver after resection more than 30% of the original liver.

The Cool-tip radiofrequency system (Radionics, Burlington, MA, USA) was used in patients under real-time ultrasonographic guidance using a 17-gauge, 2 or 3-cm, cooled-tip electrode connected to a generator. The radiofrequency energy was initially delivered at 60 watts, then, gradually increased until the first cycle rolled off. For large tumors, the electrode was repeatedly inserted into different sites, such that the entire tumor could be enveloped with the ablation zone extending 0.5 cm beyond the tumor margin. After each ablation in the tumor, the electrode was stepwise pulled out with ablation from the insertion site under the tip temperature more than 80 °C to reduce the risk of bleeding and tumor seeding.

TAE with lipiodol-ethanol was offered to patients with acceptable liver function (bilirubin < 3 mg/dl, absence of biliary infection, AST and ALT < 300 U/L, no large artery-portal and artery-venous shunt, and no main portal vein thrombosis) and the tumors were deemed unresectable, or resectable but with $< 30\%$ predicted remnant liver volume, or did not consent for resection. The TAE procedure was described elsewhere.¹⁴ An informed consent from patients was obtained prior to any procedure.

Surveillance was recommended for all patients to detect recurrence of HCC. A dynamic CT scan or magnetic resonance imaging (MRI) was performed one month after any treatment, subsequently, every 6–12 months or when the sonography

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