

# Combined hepatectomy and radiofrequency ablation versus TACE in improving survival of patients with unresectable BCLC stage B HCC

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**BACKGROUND:** Combined hepatectomy and radiofrequency ablation (RFA) provides an additional treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC) who are conventionally deemed unresectable. This study aimed to analyze the outcome of this combination therapy by comparing it with transarterial chemoembolization (TACE).

**METHODS:** We retrospectively reviewed 51 patients with unresectable BCLC stage B HCC who had received the combination therapy. We compared the survival of these patients with that of 102 patients in the TACE group (control). Prognostic factors associated with worse survival in the combination group were analyzed.

**RESULTS:** No differences in tumor status and liver function were observed between the TACE group and combination group. The median survival time for the combination group and TACE group was 38 (6-54) and 17 (3-48) months, respectively ( $P < 0.001$ ). The combination group required longer hospitalization than the TACE group [8 (5-14) days vs 4 (2-9) days,  $P < 0.001$ ]. More than two ablations decreased the survival rate in the combination group.

**CONCLUSIONS:** Combined hepatectomy and RFA yielded a better long-term outcome than TACE in patients with unresectable BCLC stage B HCC. Patients with a limited ablated size ( $\leq 2$  cm), a limited number of ablations ( $\leq 2$ ), and adequate surgical margin should be considered candidates for combination therapy.

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**KEY WORDS:** hepatocellular carcinoma; hepatectomy; radiofrequency ablation; transarterial chemoembolization; Barcelona Clinic Liver Cancer system

## Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatoma in the world.<sup>[1]</sup> In Asia, hepatitis B virus (HBV) infection is the major risk factor of HCC.<sup>[2]</sup> According to recent data, there are 400 million people infected with HBV worldwide.<sup>[3]</sup> Liver resection and liver transplantation are the curative treatments for early-stage HCC.<sup>[4-6]</sup> However, the treatment for multifocal HCC is controversial. According to the Barcelona Clinic Liver Cancer (BCLC) system, liver resection is no longer suitable for multifocal HCC exceeding the Milan criteria (stage B), and transarterial chemoembolization (TACE) is recommended.<sup>[3]</sup> However, tumor status in stage B HCC varies substantially, and researchers believe that some patients can still benefit from an aggressive surgical approach. Retrospective studies<sup>[7-9]</sup> have demonstrated that curative resection provides better survival than TACE and recently, a randomized clinical trial<sup>[10]</sup> showed consistent results that resection improves survival compared with TACE.

Nevertheless, a considerable number of patients with BCLC stage B HCC do not have the option of hepatectomy.<sup>[11, 12]</sup> For these patients, the non-curative therapeutic TACE is the only option. To increase curative chances for patients with multifocal HCC who on one hand can potentially benefit from surgery but on the other hand, resection is not feasible, the combination of radiofrequency ablation (RFA) and partial hepatectomy (PH) was introduced.<sup>[13]</sup> These patients presented with a resectable dominant tumor along with some other HCC nodules. RFA is a common locoregional therapy, and ac-

## Combined PH and RFA in unresectable stage B HCC

According to previous studies, RFA can achieve complete necrosis of HCC lesions less than 2 cm in diameter.<sup>[3]</sup> The combination of PH and RFA may possibly eradicate all HCC lesions and preserve more hepatic tissue without injury to the major vessels.<sup>[14,15]</sup>

This study was undertaken to compare the survival of patients treated with combined PH and RFA with that of those treated with conventional TACE in patients with unresectable BCLC stage B HCC. Furthermore, we analyzed the prognostic factors related to the survival of patients with HCC receiving the combination therapy and attempted to choose the suitable candidates for the treatment.

### Methods

#### Patients

Patients who had been diagnosed with HCC in West China Hospital of Sichuan University from January 2008 to June 2012 were retrospectively reviewed. We enrolled HCC patients who had received the combination therapy. The inclusion criteria were: (1) adult male or female between the age of 18 and 70 years; (2) unresectable BCLC stage B HCC; (3) preoperative liver function corresponding to Child-Pugh A with normal total bilirubin (TB) levels; (4) no evidence of extrahepatic metastasis on preoperative 3-phase enhanced computed tomography (CT) or magnetic resonance imaging (MRI); (5) pathological confirmation of HCC; (6) indocyanine green (ICG) retention rate at 15 minutes  $\leq 15\%$  for major liver resection ( $\geq 3$  segmentectomy) and  $\leq 20\%$  for minor liver resection ( $< 3$  segmentectomy or non-anatomic resection); (7) a non-invasive diagnosis of HCC as per the American Association of the Study of Liver Disease (AASLD) criteria<sup>[16]</sup> in patients with a diagnosis of liver cirrhosis: two rounds of radical imaging showed typical features of HCC (contrast uptake in the arterial phase followed by rapid washout in venous phase) confirming the clinical diagnosis of HCC. Percutaneous liver biopsy was not performed in our center. For some cases of small HCC with atypical imaging features, we followed the patients and reevaluated them three months later according to the guidelines; (8) at least 1 cm of margin was required for hepatectomy. Our exclusion criteria were as follows: (1) recurrent HCC; (2) residual tumor tissue found on the cutting edge; (3) performance status (PS)  $> 0$ ; and (4) other locoregional or systemic treatment carried out simultaneously with hepatectomy and RFA.

In the TACE group, liver function and tumor status were similar to those in the combination group. Preoperative TB, albumin (ALB), ALT, and AST levels were used to match the liver function of the patients. Tumor status was classified into four subgroups. Group Ia: tumor num-

ber  $\leq 3$ , the dominant tumor  $> 3$  cm and  $\leq 5$  cm; group Ib: tumor number  $\leq 3$ , the dominant tumor  $> 5$  cm; group IIa: tumor number  $> 3$ , the dominant tumor  $\leq 5$  cm; and group IIb: tumor number  $> 3$ , the dominant tumor  $> 5$  cm. Matching up was performed according to the subgroup of tumor status. For patients in the TACE group, at least 2 sessions of TACE were required. In this study, the definition of unresectable HCC in BCLC stage B was based on collective decision-making. Five liver surgery experts and one experienced radiologist determined the surgical options by evaluating liver function, ICG results, remnant liver volume on preoperative imaging scans, and other accompanying diseases.

We compared baseline demographic data and data on hospitalization, postoperative complications and survival outcomes between the two groups. The primary endpoint was the overall survival rate (OS); the secondary endpoint was the postoperative complication rate. The study was approved by our institutional review board.

#### Surgical combination therapy

For all patients, open surgery was performed by a single surgical team. Liver resection involved one dominant tumor within two liver segments or one lobe. A Cavitron Ultrasonic Surgical Aspirator (CUSA) was used to dissect the parenchyma under ultrasound guidance. According to tumor location, discontinuous selective hepatic occlusion was applied to control surgical blood loss. RFA was also performed under ultrasound guidance after hepatic resection. Before ablation, we scanned every inch of the remnant liver to locate and evaluate residual tumors. Every detected lesion was ablated using an internally cooled system manufactured by Valleylab (Boulder, CO, USA). A single-needle electrode with an exposed tip was inserted to the tumor bottom under ultrasound guidance. The process of ablation required at least 2 cycles, each lasting 5 to 10 minutes. Afterward, we rescanned the lesion to find out whether the ablative region had already covered the whole tumor. Therefore, a second or a third ablation would be carried out until a satisfying ablative area was covered. A final ultrasound examination was performed to confirm the absence of residual tumor tissue and complete necrosis after resection and ablation. No specimens were taken during the operation; suspicious nodules detected by ultrasound were all ablated, but only those larger than 1 cm in diameter were recorded as additional tumors. When HCC recurrence occurred, re-resection, RFA, TACE, or sorafenib was recommended to the patients according to the location of recurrence and health conditions.<sup>[17]</sup>

#### TACE

TACE was carried out under local anesthesia using

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