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Alpha fetoprotein changes predict hepatocellular carcinoma survival beyond the Milan criteria after hepatectomy

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ABSTRACT

Background: Assessing the outcomes of surgeries for hepatocellular carcinoma (HCC) patients who exceed the Milan criteria is necessary. Some studies have demonstrated that preoperative or postoperative alpha fetoprotein (AFP) can predict HCC patients' prognoses.
Methods: A total of 280 HCC patients who were positive for AFP and received curative resection were retrospectively analyzed. The patients were classified into three groups according to their preoperative and postoperative AFP levels (group A: normalized AFP; group B: AFP decreases >50%, but continued abnormality; and group C: AFP decreases <50%). Disease-free survival and overall survival rates were analyzed using the Kaplan–Meier method. The factors associated with AFP changes were evaluated by logistic regression.
Results: AFP dynamic changes were independently associated with disease-free survival and overall survival rates. Group A had better 3- and 5-y survivals than groups B or C (58.7% and 39.5% versus 31.3% and 14.9% versus 17.1% and 8.8%, $P < 0.001$). Preoperative AFP, tumor differentiation, tumor diameter, microvascular invasion, and satellite nodules remained significant risk factors that were associated with AFP changes. Furthermore, in group A, the disappearances of AFP within and beyond 8 wk resulted in similar overall survival rates ($P > 0.05$). Among those with HCC recurrence, the patients treated with resurgery or radiofrequency ablation achieved the best recurrence to death survivals. Those treated with transcatheter arterial chemoembolization achieved the next best survivals.
Conclusions: AFP changes predicted the prognoses of patients with HCC beyond the predictions of the Milan criteria. Preoperative AFP (>400 ng/mL), tumor differentiation, tumor diameter, and satellite nodules were the risk factors related to AFP normalization. The regular follow-up and early detection of recurrent HCCs that are suitable for curative therapies, such as resurgery and radiofrequency ablation, might improve the prognoses. Other therapies, such as transcatheter arterial chemoembolization, might also be effective.

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Introduction

Approximately 383,000 people die from liver cancer every year in China, and these patients account for up to 51% of the deaths from liver cancer worldwide. Among these patients, a large proportion are diagnosed in intermediate or advanced stages because of the lack of symptoms and an insufficient screening system.[1] Curative therapy for hepatocellular carcinoma (HCC) includes surgical resection and liver transplantation. Intermediate HCC has already surpassed the oncological criteria for transplantation, which are commonly known as the Milan criteria. Moreover, the American Association for the Study of Liver Diseases (AASLD)/European Association for the Study of the Liver (EASL) guidelines recommend against surgical resection for these patients because of high recurrence and postoperative mortality. However, cumulative evidence suggests that hepatectomy can result in survival benefits compared with local regional therapy and transcatheter arterial chemoembolization (TACE) for HCC patients with well-preserved liver function regardless of their Barcelona Clinic Liver Cancer stage.[2-4] Surgery might be considered for HCC patients who have exceeded the Milan criteria. However, we cannot neglect the fact that intermediate HCC patients might not achieve comparable long-term survival after surgery compared with early HCC patients. To improve long-term survival, it is important to assess surgical outcomes and subsequently apply effective treatments. Alpha fetoprotein (AFP) is often elevated in HCC patients depending on their pathologic characteristics, including the degree of differentiation of the tumor cells and the tumor size.[5,6] Although the diagnostic value of AFP in various HCC stages is limited because some HCCs that are identified by imaging do not secrete diagnostic levels of AFP, AFP can be followed up easily.[7-11] Cumulative evidence suggests that the preoperative or postoperative AFP levels can predict the prognosis of HCC after hepatectomy.[5,9,12-14] For example, Ma *et al.* reported that a serum AFP level >400 ng/mL is closely correlated with HCC postoperative survival rate after hepatectomy.[9] The AFP concentration in the serum might serve as a reflection of tumor burden. A fall in AFP concentration is thought to indicate a good response to treatment.[5,12] Therefore, dynamic changes between preoperative and postoperative AFP levels might more accurately predict prognoses than preoperative or postoperative AFP levels alone. Zhang *et al.* suggested that HCC patients with decreased AFP-L3 (i.e., the fraction of AFP) tests after surgery achieve better survival than those with high AFP-L3 levels.[15] However, the availability of this assay is still confined to a few laboratories. Liu *et al.* revealed that patients with decreases in AFP levels between the initial stage and recurrent stage achieved the best recurrence to death survival (RTDS) among HCC patients after hepatectomy.[16] These findings both suggest some degree of correlation between the fluctuating levels of AFP after treatment and outcomes. Compared with early stage HCC patients, patients with intermediate HCC commonly suffer a heavy tumor burden, which includes larger tumor sizes and multiple tumors.[17] These patients account for a high proportion of those with elevated AFP levels, and AFP monitoring thus might be of great value. Further treatment might be required according to AFP changes.

In this study, we sought to analyze the relationships of AFP changes with the prognoses of AFP-positive HCC patients beyond the Milan criteria and to reveal the factors that affect AFP changes after curative surgery.

Materials and methods

Patients

The study was approved by the Ethics Committee of the West China Hospital of Sichuan University. Written consent for participation was obtained from all patients. The patients who underwent liver resection in the Department of Liver Surgery & Liver Transplantation Center of West China Hospital between February 2009 and April 2014 were identified from our prospectively maintained database. The patients were diagnosed with HCC based either on two types of imaging examination that presented the typical features of HCC or positive findings on one imaging examination together with an AFP level >400 ng/mL. HCC was confirmed by postoperative histopathologic examination. Microvascular invasion (MVI) and satellite nodules were identified under a light microscope by pathologists. Clinical variables, including demographic data, complete blood counts, liver function tests, AFP, hepatitis B virus DNA (HBV-DNA), and tumor features, including tumor number, MVI, satellite nodules, tumor differentiation, and maximum diameter, were collected. Our inclusion criteria were the following: (1) HCC beyond the Milan criteria (i.e., a solitary tumor >5 cm in diameter, ≤3 nodules that were >3 cm in diameter, or more than three nodules of any size[4]); (2) positive preoperative AFP test (>20 ng/mL); (3) underwent liver resection as the initial treatment; (4) a Child–Pugh grade A/B; and (5) a negative surgical margin.

Follow-up

The measurements of the preoperative AFP were performed 1 wk before surgery, and the evaluations of postoperative serum AFP levels were performed within 12 wk after surgery. After liver resection, all patients were followed up at the first, third, and sixth months in the first half year after the operation, every 3 mo during the subsequent 3 y, and every 6 mo thereafter. Blood cell tests, liver function tests, AFP measurements, HBV-DNA tests, and visceral ultrasonography, computed tomography or magnetic resonance imaging, and chest radiography were performed in the follow-up examinations. Bone scintigraphy was performed whenever HCC recurrence was suspected. Postoperative recurrence was defined by positive imaging findings compared with the preoperative examination values or confirmation via biopsy or resection. Antiviral drugs such as nucleoside acid analogs were administered to the patients with positive HBV-DNA tests before and after the operation. Treatment methods, including repeat hepatectomy, radiofrequency ablation (RFA), TACE, chemotherapy, such as sorafenib, and best supportive care (BSC) for recurrence were administered according to the