**Name of Journal: *World Journal of Clinical Cases***

**Manuscript NO: 39532**

**Manuscript Type: ORIGINAL ARTICLE**

***Retrospective Study***

**Prognostic role of alpha-fetoprotein response after hepatocellular carcinoma resection**

Rungsakulkij N *et al.* Prognostic role of AFP in HCC

Narongsak Rungsakulkij, Wikran Suragul, Somkit Mingphruedhi, Pongsatorn Tangtawee, Paramin Muangkaew, Suraida Aeesoa

**Narongsak Rungsakulkij, Wikran Suragul, Somkit Mingphruedhi, Pongsatorn Tangtawee, Paramin Muangkaew, Suraida Aeesoa,** Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

**ORCID numbers:** Narongsak Rungsakulkij (0000-0003-3522-5800); Wikran Suragul (0000-0002-9933-9279); Somkit Mingphruedhi (0000-0002-1404-1968); Pongsatorn Tangtawee (0000-0001-9598-5479); Paramin Muangkaew (0000-0002-2470-8164); Suraida Aeesoa (0000-0002-4137-3861).

**Author contributions:** Rungsakulkij N designed the study, collected and interpreted the data, and wrote the paper; Suragul W collected the data and wrote the paper; Mingphruedhi S collected and analyzed the data; Tangtawee P collected and analyzed the data; Muangkaew P collected the data; Aeesoa S analyzed the data.

**Institutional review board statement:** This study was reviewed and approved by the Ramathibodi Hospital Institutional Review Board Committee on Human Rights Related to Research Involving Human Subjects (protocol number ID 03-61-25).

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** All authors declare no conflicts-of-interest related to this article.

**Data sharing statement:** No additional data are available.

**Open Access:** This article is an open access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creative commons.org/licenses/by-nc/4.0

**Manuscript source:** Invited manuscript

**Correspondence to: Wikran Suragul, FRCS (Gen Surg), MD, Doctor, Surgeon,** Department of Surgery, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Praram VI Road, Ratchathewi, Bangkok 10400, Thailand. wikran.sur@mahidol.ac.th

**Telephone:** +66-2-2011527

**Fax:** +66-2-2012471

**Received:** April 26, 2018

**Peer-review started:** April 27, 2018

**First decision:** May 9, 2018

**Revised:** May 11, 2018

**Accepted:** May 30, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To investigate whether the change in pre-/post-operation serum alpha-fetoprotein (AFP) levels is a predictive factor for hepatocellular carcinoma (HCC) outcomes.

***METHODS***

We retrospectively analyzed 334 HCC patients who underwent hepatic resection at our hospital between January 2006 and December 2016. The patients were classified into three groups according to their change in serum AFP levels: (1) the normal group, pre-AFP ≤ 20 ng/mL and post-AFP ≤ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP decrease of ≥ 50% of pre-AFP; and (3) the non-response group, pre-AFP level > 20 ng/mL and post-AFP decrease of < 50% or higher than pre-AFP level, or any pre-AFP level < 20 ng/mL but post-AFP >20 ng/mL

***RESULTS***

Univariate and multivariate analyses revealed that multiple tumors [hazard ratio (HR): 1.646, 95%CI: 1.15-2.35, *P* < 0.05], microvascular invasion (mVI) (HR: 1.573, 95% CI: 1.05-2.35, *P <* 0.05), and the non-response group (HR: 2.425, 95% CI: 1.42-4.13, *P <* 0.05) were significant independent risk factors for recurrence-free survival. Similarly, multiple tumors (HR: 1.99, 95% CI: 1.12-3.52, *P <* 0.05), mVI (HR: 3.24, 95%CI: 1.77-5.90, *P <* 0.05), and the non-response group (HR: 3.62, 95%CI: 1.59-8.21, *P <* 0.05) were also significant independent risk factors for overall survival. The non-response group had significantly lower overall survival rates and recurrence-free survival rates than both the normal group and the response group (*P <* 0.05). Thus, patients with no response regarding post-surgery AFP levels were associated with poor outcomes.

***CONCLUSION***

Serum AFP responses are significant prognostic factors for the surgical outcomes of HCC patients, suggesting post-resection AFP levels can direct the management of HCC patients.

**Key words:** Alpha-fetoprotein; Hepatocellular carcinoma; Risk factors; Prognosis; Liver neoplasms

**© The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Alpha-fetoprotein (AFP) is a widely used tumor marker for both pre- and post-treatment hepatocellular carcinoma (HCC) patients. To investigate whether changes in pre- and post-operation serum AFP levels were a predictive prognostic factor in HCC patients, we retrospectively analyzed 334 HCC patients who underwent hepatic resection at our hospital. Serum AFP responses were found to be a significant prognostic factor for surgical outcomes in patients with high pre-operative AFP levels. The non-response group, which was classified as having a < 50% decrease from preoperative AFP levels that were > 20 ng/mL, was associated with poor outcomes. In summary, post-surgery AFP levels are valuable for properly managing HCC patients.

Rungsakulkij N, Suragul W, Mingphruedhi S, Tangtawee P, Muangkaew P, Aeesoa S. Prognostic role of alpha-fetoprotein response after hepatocellular carcinoma resection. *World J Clin Cases* 2018; In press

**INTRODUCTION**

Worldwide, the most common type of primary liver cancer is hepatocellular carcinoma (HCC)[1]. Hepatic resection is potentially curative for early-stage HCC if adequate reserve liver function is present[2]; however, the death rate from HCC remains high due to the high recurrence rate following hepatectomy[3-5]. Recently, a screening program for detecting early-stage disease in high-risk patients was found to improve surgical outcomes[6]. Alpha-fetoprotein (AFP) has been used as a classical marker for HCC[7]. Historically, AFP levels were used to diagnose HCC[8]; however, the current guidelines for the surveillance of high-risk patients includes ultrasonography every 3-6 months without AFP[9,10]. Although AFP does not currently play a diagnostic role in HCC, it is still a useful marker for estimating the post-surgery follow-up period according to current guidelines[11].

AFP is a large glycoprotein produced by the yolk sac and fetal liver that is present in large quantities during gestation and is generally repressed in healthy adults; however, it is re-expressed in a variety of tumors[12,13]. In Thailand, the only available tumor marker associated with HCC is serum AFP[14]. AFP levels are widely used as a tumor marker for HCC in both pre- and post-treatment cases[15]. Several studies have reported that pre-operative serum AFP levels are a significant prognostic factor for post-treatment survival[16-19]. However, other studies have reported that AFP was not useful for predicting the poor prognosis group among HCC patients[20-22]. Finally, a third set of studies reported that changes in serum AFP better predict prognosis[23-25]; however, we lack a definition of what constitutes a significant change in serum AFP (a response signature) after hepatic resection. The aim of this study is to investigate whether the change in serum AFP levels between pre- and post-operation samples is a predictive factor for the prognosis of HCC patients following hepatic resection.

**MATERIALS and METHODS**

***Patients and samples***

A total of 334 consecutive patients who underwent hepatic resection and had pathologically proven HCC at the Department of Surgery, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand between January 2006 and December 2016 were enrolled in this study. The inclusion criteria are as follows: (1) patients were ≥15-years-old when they underwent hepatic resection; (2) a pathologically confirmed HCC diagnosis was made; and (3) pre- and post-operative AFP data were complete. All patients underwent preoperative cross-sectional dynamic imaging using either triple-phase computed tomography (CT) or magnetic resonance imaging (MRI). Routine blood examinations included complete blood count, coagulogram, liver and kidney function tests, and pre-operative serum AFP levels. A pre-operative indocyanine green retention test at 15 min (ICG-R15) was also performed. The Makuuchi criteria were used to select patients for curative resection[26]. The extent of liver resection was based on the patients’ reserve liver function as assessed mainly by the Makuuchi criteria, including pre-operative ascites volume, Child-Pugh score, ICG-R15 value, and occasionally, volumetric CT analysis. Liver cirrhosis was intraoperatively defined by the macro- or micro-nodular surface of the liver.

The pre-operative serum AFP level (pre-AFP) was defined as the serum AFP level before hepatic resection. The post-operative serum AFP level (post-AFP) was defined as the serum AFP level 1-180 d following resection. For patients who had more than one postoperative serum AFP measurement, the lowest level was used for analyses. Patients whose post-AFP data were missing were excluded from the study. Patients were classified into three groups according to pre- and post-AFP levels: (1) the normal group, pre-AFP ≤ 20 ng/mL and post-AFP ≤ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP a decrease of ≥ 50% of pre-AFP; and (3) the non-response group, pre-AFP > 20 ng/mL and post-AFP a decrease of < 50% or higher than pre-AFP level, or any pre-AFP level < 20 ng/mL but post-AFP > 20 ng/mL.

Pathological specimens were reviewed by a pathologist to confirm HCC diagnoses. Patients with combined cholangiocarcinoma and other malignancies were excluded from this study. Microvascular invasion (mVI) was defined as the presence of tumor cells in the microvasculature. Clinical and pathological staging were performed according to the American Joint Committee on Cancer staging manual, 7th edition[27]. Patients were followed up in outpatient clinics every 3-6 mo after surgery and routinely underwent imaging (ultrasonography, CT, MRI) and blood tests. Recurrent disease was defined as the presence of new tumors found by imaging (CT or MRI) during the follow-up period.

***Statistical analysis***

Patient characteristics with continuous variables were compared using the Student’s *t*-test, while categorical variables were compared with *χ*2 or Fisher’s exact tests. A *P-*value < 0.05 was considered statistically significant. Potential risk factors were analyzed by univariate and multivariate methods using the Cox regression model. Independent risk factors were expressed as hazard ratios (HRs) with 95%CIs. Survival analyses were performed using the Kaplan-Meier method and evaluated with the log-rank test.

**RESULTS**

***Patient demographics***

In total 334 patients were analyzed; their mean age at the time of surgery was 50.56 ± 4.03 years, and there were 155 male (46.4%) and 179 female patients. Hepatitis B virus infections were found in 186 patients (55.7%), and hepatitis C virus infections were found in 60 patients (17.96%). The median tumor size was 4.3 cm (range: 0.5-26.5 cm). A single tumor was found in 262 patients (78.4%). Stage I tumors were found in 204 patients (61.1%), and positive margins were found in 18 patients (6.38%; Table 1). When comparing the clinicopathological parameters between the three groups, there were no significant differences regarding age, gender, hepatitis B or C infection, platelet count, median tumor size, number of tumors, mVI, stage, resection margin, or anti-viral treatment.

***Risk factors associated with disease recurrence***

Next, univariate and multivariate analyses were used to identify risk factors for recurrence-free survival (Table 2); the recurrence rate was 45.81% (153/334 patients). Univariate analyses of the 153 patients with recurrent disease revealed that the following factors were associated with recurrence-free survival: tumor size (HR: 1.05, 95%CI: 1.02-1.10, *P <* 0.05), multiple tumors (HR: 1.79, 95%CI: 1.26-2.54, *P <* 0.05), mVI (HR: 1.88, 95%CI: 1.30-2.73, *P <* 0.05), stage II disease or higher (HR: 1.53, 95%CI: 1.10-2.12, *P <* 0.05), and the non-response group (HR: 2.438, 95%CI: 1.45-4.08, *P <* 0.05). Multivariate analyses revealed that multiple tumors (HR: 1.646, 95%CI: 1.15-2.35, *P <* 0.05), mVI (HR: 1.573, 95%CI: 1.05-2.35, *P <* 0.05), and the non-response group (HR: 2.425, 95%CI: 1.42-4.13, *P <* 0.05) were associated with recurrence-free survival.

***Prognostic factors associated with mortality***

Univariate and multivariate analyses were also used to identify risk factors for overall survival (Table 3); the overall mortality rate was 15.57% (52/334 patients). Univariate analyses of the 52 patients revealed the following factors were associated with overall survival: multiple tumors (HR: 2.24, 95%CI: 1.27-3.94, *P <* 0.05), mVI (HR: 3.32, 95%CI: 1.85-5.95), *P <* 0.05), and the non-response group (HR: 3.63, 95%CI: 1.61-8.18, *P <* 0.05). Multivariate analyses confirmed these results, showing that multiple tumors (HR: 1.99, 95%CI: 1.12-3.52, *P <* 0.05), mVI (HR: 3.24, 95%CI: 1.77-5.90, *P <* 0.05), and the non-response group (HR: 3.62, 95%CI: 1.59-8.21, *P <* 0.05) were associated with overall survival.

***Analysis of disease-free and overall survival rates with regard to responses in serum AFP levels***

Kaplan-Meier survival analyses showed that recurrence-free survival rates according to changes in serum AFP levels in the non-response group were significantly lower than those in the normal and response groups (*P <* 0.05; Figure 1A). The overall survival rate of the non-response group was also significantly lower than the normal and response groups (*P <* 0.05; Figure 1B).

***Analysis of disease-free and overall survival rates with regard to responses in serum AFP levels regardless of pre-AFP values***

To analyze the effect of a 50% decrease from pre-AFP as a measure of responsiveness to treatment alone, patients were classified into the following groups: (1) post-AFP decrease of ≥ 50%; and (2) post-AFP decrease of <50%. Kaplan-Meier survival analyses of recurrence-free and overall survival between the two groups revealed no significant differences (Figure 2).

**DISCUSSION**

AFP was one of the first discovered tumor protein markers and belongs to the family of serum albumins. There are three major families of AFP glycoforms: AFP-L1, AFP-L2 and AFP-L3, which differ in their affinity for the lectin *lens culinaris agglutinin* and are produced in varying amounts depending on physiological/pathological conditions[28]. Previously, serum AFP levels in combination with abdominal ultrasonography were used to diagnose HCC[7]; however, recent studies have consistently shown that the low sensitivity of serum AFP and its high false-negative rate, resulting in impaired HCC diagnoses[29,30]. Currently, AFP levels are not considered a tumor marker for diagnosing HCC in guidelines[10,11,31]. Current guideline reported the data available show that the biomarkers tests are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC[10]. However, the National Comprehensive Cancer Network and the Liver Cancer Study Group of Japan guidelines still recommended that serum AFP in combination with abdominal ultrasonography be used for HCC screening[31,32].

The HCC serum tumor markers that are currently used to evaluate disease prognosis are AFP, protein induced by vitamin K absence-II and AFP-L3[33]. However, in Thailand, the only available serum tumor marker is AFP[15]. Serum AFP level is one of the serum markers previously studied in HCC patients following hepatic resection[23,34,35]. Many studies have reported that high pre-AFP was a poor predictive factor in HCC patients following hepatic resection, liver transplantation, and local ablation[16,36,37]. However, the most recent studies have reported that the change in AFP values between pre- and post-treatment samples better predicted surgical outcomes[23,24,37]. However, there are studies that reported negative results regarding associations between serum AFP levels and the prognosis of HCC patients following hepatic resection[20-22,38]. Our univariate and multivariate analyses showed that being in the non-response group was an independent factor for poor overall and recurrence-free survival. Additionally, these analyses revealed two other independent risk factors for poor overall and recurrence-free survival: multiple tumors and mVI. These factors were previously reported to be histologic features associated with poor surgical outcomes in HCC patients[39-44].

In our study, the non-response group was defined as pre-AFP > 20 ng/mL and post-AFP a decrease of < 50% or greater than pre-AFP and patients who had pre-AFP < 20 ng/mL and post-AFP > 20 ng/mL. Bjerner *et al*[45] reported the AFP reference intervals in 498 healthy individuals from the Nordic region reference interval project and found that the normal range of the serum AFP was not greater than 20 ng/mL. Zhou *et al*[46] reported that the pre-AFP cut-off value of 20 ng/mL had significant prognostic impact for both overall and tumor-free survival, whereas < 400 ng/mL did not. Silva *et al*[47] reported the prognostic utility of baseline AFP for 41,107 HCC patients, and baseline AFP < 20 ng/mL showed the highest median overall survival compared with the higher AFP groups. From these, we classified our patients using the pre-operative cut-off value of 20 ng/mL. For the post-AFP level, there are many previous studies that have reported various post-operative cut-off or response values[20,23,24,48,49]. Some studies have consistently reported that a treatment response is indicated by a post-AFP decrease of > 50%[23,50,51]. Riaz *et al*[50]reported that HCC patients who had baseline AFP >200 ng/mL and underwent locoregional therapy and those who had a > 50% decrease from baseline after treatment had better outcomes. Memon *et al*[51] investigated 629 HCC patients who underwent transarterial locoregional therapies and found that the AFP response group could be defined as those with serum AFP decreases of > 50% compared with baseline had favorable outcomes that correlated with the European Association for the Study of the Liver and World Health Organization response criteria. According to these studies, we used the definition of response as a ≥ 50% decrease of pre-AFP levels.

Survival analysis between the three groups showed that the non-response group had significantly poorer prognoses compared with the normal and response groups. Moreover, the normal group, which still had normal AFP levels after hepatic resection, and the group with post-AFP decreases of < 50% had better prognoses than the high pre-AFP group, which is consistent with previous studies. Shen *et al*[23] reported a study of HCC patients beyond the Milan criteria and also stratified patients by pre-AFP > 20 ng/mL following hepatectomy; they found that the group who had decreased AFP by < 50% following hepatectomy had a poorer prognosis compared with the normal or decrease >50% groups[23]. Toyoda *et al*[49]reported a study of serum tumor marker changes in HCC patients after hepatectomy and found that patients who had elevated pre-AFP and post-AFP following hepectomy had significantly lower survival rates than the other groups. Kao *et al*[52] reported AFP responses in HCC patients who had pre-AFP levels ≥ 100 ng/mL and underwent radiofrequency ablation, finding that patients who had post-AFP decreases of < 20% had significantly lower overall rates.

High AFP levels are strongly associated with the disease burden and aggressiveness due to extrahepatic metastasis, advanced stage, large tumors, portal vein thrombosis and poorly differentiated cells[18,47,53]. Recently, patients with high post-AFP levels were called “non-responders”, indicating that either surgical resection was incomplete or that there were either intra- or extra-hepatic occult metastases[17,37,54]. Recently, Lu *et al*[55] reported that the molecular mechanism underlying how AFP promotes HCC metastasis was *via* activating PI3K/AKT signaling. They concluded that AFP overexpression in HCC cells was related to metastatic characteristics in human HCC patients and plays a critical role in promoting the invasion and distant metastasis of HCC cells by up-regulating the expression of metastasis-related proteins[55]. In viral hepatitis-related HCC patients, the chronic hepatitis background is associated with high serum AFP levels. Ogden *et al*[56] and Sung *et al*[57] reported that the hepatitis B protein HBx dysregulates p53-mediated AFP expression *via* directly binding to p53, and that high hepatitis B virus integration into the host genome was correlated with high serum AFP levels. These data highlight the importance of AFP as a factor that promotes carcinogenesis by the following pathways: (1) stimulating cell proliferation, silencing AFP causes the accumulation of HCC cells at the G1-S transition; (2) promoting cell motility and the invasive growth of some HCC cell lines *in vitro*, and promoting metastases in a xenograft tumor model; and (3) acting as a growth factor that is secreted into the medium by cancer cells[28].

This study had several limitations. First, it was retrospective in nature. Second, the population studied was small. Some patients who underwent preoperative transarterial chemoembolization could interfere with the pre-AFP levels. Third, some patients, especially in the early period of the study, were not treated with anti-viral drugs for unknown reasons. Fourth, there is lack of consensus for timing the measurement of post-AFP levels. Fifth, a number of studies have indicated that biomarkers such as protein induced by vitamin K absence-II, des-gamma carboxyprothrombin and AFP-L3, may be more accurate prognostic biomarkers than AFP; however, these tumor markers are not currently measured in our hospital. Sixth, the post-AFP level period was 1-180 day following hepatic resection which represents a large period of time that could lead to some selection bias.

AFP is a multifaceted serum tumor marker in HCC. Serum AFP responsiveness was found to be a significant prognostic factor for surgical outcomes in the high pre-AFP group, and non-responsive patients were associated with poor outcomes. AFP levels following hepatic resection have important roles in managing HCC patients.

**ARTICLE HIGHLIGHTS**

***Research background***

Historically, alpha-fetoprotein (AFP) levels were used to diagnose hepatocellular carcinoma (HCC); however, the current guidelines for the surveillance of high-risk patients include ultrasonography every 3-6 mo without AFP. Although AFP does not currently play a diagnostic role in HCC, it is still a useful marker for estimating the post-surgery follow-up period according to current guidelines.

***Research motivation***

AFP levels are widely used as a tumor marker for HCC in both pre- and post-treatment cases. Several studies have reported that pre-operative serum AFP levels are a significant prognostic factor for post-treatment survival. However, other studies have reported that AFP was not useful for predicting the poor prognosis group among HCC patients. Finally, a third set of studies reported that changes in serum AFP better predict prognosis; however, we lack a definition of what constitutes a significant change in serum AFP (a response signature) after hepatic resection.

***Research objectives***

To investigate whether the change in pre-/post-operation AFP levels is a predictive factor for HCC outcomes.

***Research methods***

We retrospectively analyzed 334 HCC patients who underwent hepatic resection at Ramathibodi hospital, Thailand between January 2006 and December 2016. The patients were classified into three groups according to their change in serum AFP levels: (1) the normal group, pre-operative serum AFP level (pre-AFP) ≤ 20 ng/mL and post-operative serum AFP level (post-AFP) ≤ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP decrease of ≥ 50% of pre-AFP; and (3) the non-response group, pre-AFP level > 20 ng/mL and post-AFP decrease of < 50% or higher than pre-AFP level, or any pre-AFP level < 20 ng/mL but post-AFP > 20 ng/mL

***Research results***

Univariate and multivariate analyses revealed that multiple tumors [hazard ratio (HR): 1.646, 95%CI: 1.15-2.35, *P <* 0.05], microvascular invasion (mVI) (HR: 1.573, 95%CI: 1.05-2.35, *P <* 0.05), and the non-response group (HR: 2.425, 95%CI: 1.42-4.13, *P <* 0.05) were significant independent risk factors for recurrence-free survival. Similarly, multiple tumors (HR: 1.99, 95%CI: 1.12-3.52, *P <* 0.05), mVI (HR: 3.24, 95%CI: 1.77-5.90, *P <* 0.05), and the non-response group (HR: 3.62, 95%CI: 1.59-8.21, *P <* 0.05) were also significant independent risk factors for overall survival. The non-response group had significantly lower overall survival rates and recurrence-free survival rates than both the normal group and the response group (*P <* 0.05). Thus, patients with no response regarding post-surgery AFP levels were associated with poor outcomes.

***Research conclusions***

AFP is a multifaceted serum tumor marker in HCC. Serum AFP responsiveness was found to be a significant prognostic factor for surgical outcomes in the high pre-AFP group, and non-responsive patients were associated with poor outcomes. AFP levels following hepatic resection have important roles in managing HCC patients.

***Research perspectives***

In the future, the prospective cohort studies in the selected patients group should be conduct to confirmation this hypothesis and the usefulness of the post-operative serum AFP level in the clinical practice.

**Acknowledgements**

We thank Mr. Napaphat Poprom for reviewing the biostatistical analysis.

**References**

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

2 **Bruix J**, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; **53**: 1020-1022 [PMID: 21374666 DOI: 10.1002/hep.24199]

3 **Poon RT**, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer* 2000; **89**: 500-507 [PMID: 10931448 DOI: 10.1002/1097-0142(20000801)89:33.0.CO;2-O]

4 **Kaibori M**, Ishizaki M, Saito T, Matsui K, Kwon AH, Kamiyama Y. Risk factors and outcome of early recurrence after resection of small hepatocellular carcinomas. *Am J Surg* 2009; **198**: 39-45 [PMID: 19178896 DOI: 10.1016/j.amjsurg.2008.07.051]

5 **Lee EC**, Kim SH, Park H, Lee SD, Lee SA, Park SJ. Survival analysis after liver resection for hepatocellular carcinoma: A consecutive cohort of 1002 patients. *J Gastroenterol Hepatol* 2017; **32**: 1055-1063 [PMID: 27797420 DOI: 10.1111/jgh.13632]

6 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]

7 **Zhao YJ**, Ju Q, Li GC. Tumor markers for hepatocellular carcinoma. *Mol Clin Oncol* 2013; **1**: 593-598 [PMID: 24649215 DOI: 10.3892/mco.2013.119]

8 **Bruix J**, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]

9 **Sherman M**, Bruix J, Porayko M, Tran T; AASLD Practice Guidelines Committee. Screening for hepatocellular carcinoma: the rationale for the American Association for the Study of Liver Diseases recommendations. *Hepatology* 2012; **56**: 793-796 [PMID: 22689409 DOI: 10.1002/hep.25869]

10 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **pii**: S0168-8278(18)30215-0 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

11 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]

12 **Gillespie JR**, Uversky VN. Structure and function of alpha-fetoprotein: a biophysical overview. *Biochim Biophys Acta* 2000; **1480**: 41-56 [PMID: 11004554 DOI: 10.1016/S0167-4838(00)00104-7]

13 **Mizejewski GJ**. Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. *Exp Biol Med* (Maywood) 2001; **226**: 377-408 [PMID: 11393167 DOI: 10.1177/153537020122600503]

14 **Rungsakulkij N**, Keeratibharat N, Suragul W, Tangtawee P, Muangkaew P, Mingphruedhi S, Aeesoa S. Early recurrence risk factors for hepatocellular carcinoma after hepatic resection: Experience at a thai tertiary care center. *J Med Assoc Thai* 2018; **101**: 63-69

15 **Tangkijvanich P**, Anukulkarnkusol N, Suwangool P, Lertmaharit S, Hanvivatvong O, Kullavanijaya P, Poovorawan Y. Clinical characteristics and prognosis of hepatocellular carcinoma: analysis based on serum alpha-fetoprotein levels. *J Clin Gastroenterol* 2000; **31**: 302-308 [PMID: 11129271 DOI: 10.1097/00004836-200012000-00007]

16 **Toyoda H**, Kumada T, Kaneoka Y, Osaki Y, Kimura T, Arimoto A, Oka H, Yamazaki O, Manabe T, Urano F, Chung H, Kudo M, Matsunaga T. Prognostic value of pretreatment levels of tumor markers for hepatocellular carcinoma on survival after curative treatment of patients with HCC. *J Hepatol* 2008; **49**: 223-232 [PMID: 18571271 DOI: 10.1016/j.jhep.2008.04.013]

17 **Kim HS**, Park JW, Jang JS, Kim HJ, Shin WG, Kim KH, Lee JH, Kim HY, Jang MK. Prognostic values of alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II in hepatitis B virus-related hepatocellular carcinoma: a prospective study. *J Clin Gastroenterol* 2009; **43**: 482-488 [PMID: 19197197 DOI: 10.1097/MCG.0b013e318182015a]

18 **Liu C**, Xiao GQ, Yan LN, Li B, Jiang L, Wen TF, Wang WT, Xu MQ, Yang JY. Value of α-fetoprotein in association with clinicopathological features of hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 1811-1819 [PMID: 23555170 DOI: 10.3748/wjg.v19.i11.1811]

19 **Yang SL**, Liu LP, Yang S, Liu L, Ren JW, Fang X, Chen GG, Lai PB. Preoperative serum α-fetoprotein and prognosis after hepatectomy for hepatocellular carcinoma. *Br J Surg* 2016; **103**: 716-724 [PMID: 26996727 DOI: 10.1002/bjs.10093]

20 **Nanashima A**, Taura N, Abo T, Ichikawa T, Sakamoto I, Nagayasu T, Nakao K. Tumor marker levels before and after curative treatment of hepatocellular carcinoma as predictors of patient survival. *Dig Dis Sci* 2011; **56**: 3086-3100 [PMID: 21706206 DOI: 10.1007/s10620-011-1796-6]

21 **Toro A**, Ardiri A, Mannino M, Arcerito MC, Mannino G, Palermo F, Bertino G, Di Carlo I. Effect of pre- and post-treatment α-fetoprotein levels and tumor size on survival of patients with hepatocellular carcinoma treated by resection, transarterial chemoembolization or radiofrequency ablation: a retrospective study. *BMC Surg* 2014; **14**: 40 [PMID: 24993566 DOI: 10.1186/1471-2482-14-40]

22 **Shim JH**, Yoon DL, Han S, Lee YJ, Lee SG, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Is serum alpha-fetoprotein useful for predicting recurrence and mortality specific to hepatocellular carcinoma after hepatectomy? A test based on propensity scores and competing risks analysis. *Ann Surg Oncol* 2012; **19**: 3687-3696 [PMID: 22644512 DOI: 10.1245/s10434-012-2416-1]

23 **Shen JY**, Li C, Wen TF, Yan LN, Li B, Wang WT, Yang JY, Xu MQ. Alpha fetoprotein changes predict hepatocellular carcinoma survival beyond the Milan criteria after hepatectomy. *J Surg Res* 2017; **209**: 102-111 [PMID: 28032546 DOI: 10.1016/j.jss.2016.10.005]

24 **Allard MA**, Sa Cunha A, Ruiz A, Vibert E, Sebagh M, Castaing D, Adam R. The postresection alpha-fetoprotein in cirrhotic patients with hepatocellular carcinoma. An independent predictor of outcome. *J Gastrointest Surg* 2014; **18**: 701-708 [PMID: 24402605 DOI: 10.1007/s11605-013-2433-9]

25 **Zhang XF**, Yin ZF, Wang K, Zhang ZQ, Qian HH, Shi LH. Changes of serum alpha-fetoprotein and alpha-fetoprotein-L3 after hepatectomy for hepatocellular carcinoma: prognostic significance. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 618-623 [PMID: 23232633 DOI: 10.1016/S1499-3872(12)60234-3]

26 **Miyagawa S**, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. *Am J Surg* 1995; **169**: 589-594 [PMID: 7771622 DOI: 10.1016/S0002-9610(99)80227-X]

27  [**Compton**](http://xueshu.baidu.com/s?wd=author%3A%28Carolyn%20C%20Compton%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) **CC**,  [Byrd](http://xueshu.baidu.com/s?wd=author%3A%28David%20R%20Byrd%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) DR,  [Garciaaguilar](http://xueshu.baidu.com/s?wd=author%3A%28Julio%20GarciaAguilar%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) J,  [Kurtzman](http://xueshu.baidu.com/s?wd=author%3A%28Scott%20H%20Kurtzman%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) SH,  [Olawaiye](http://xueshu.baidu.com/s?wd=author%3A%28Alexander%20Olawaiye%29%20&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_f_para=sc_hilight%3Dperson) A. AJCC Cancer Staging Atlas: A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook. 2nd ed. New York: American Joint Committee on Cancer and Springer, 2012

28 **Sauzay C**, Petit A, Bourgeois AM, Barbare JC, Chauffert B, Galmiche A, Houessinon A. Alpha-foetoprotein (AFP): A multi-purpose marker in hepatocellular carcinoma. *Clin Chim Acta* 2016; **463**: 39-44 [PMID: 27732875 DOI: 10.1016/j.cca.2016.10.006]

29 **Wong RJ**, Ahmed A, Gish RG. Elevated alpha-fetoprotein: differential diagnosis - hepatocellular carcinoma and other disorders. *Clin Liver Dis* 2015; **19**: 309-323 [PMID: 25921665 DOI: 10.1016/j.cld.2015.01.005]

30 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/s0140-6736(18)30010-2]

31 **Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11**: 317-370 [PMID: 28620797 DOI: 10.1007/s12072-017-9799-9]

32 **Benson AB 3rd**, Abrams TA, Ben-Josef E, Bloomston PM, Botha JF, Clary BM, Covey A, Curley SA, D'Angelica MI, Davila R, Ensminger WD, Gibbs JF, Laheru D, Malafa MP, Marrero J, Meranze SG, Mulvihill SJ, Park JO, Posey JA, Sachdev J, Salem R, Sigurdson ER, Sofocleous C, Vauthey JN, Venook AP, Goff LW, Yen Y, Zhu AX. NCCN clinical practice guidelines in oncology: hepatobiliary cancers. *J Natl Compr Canc Netw* 2009; **7**: 350-391 [PMID: 19406039 DOI: 10.6004/jnccn.2009.0027]

33 **Bertino G**, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellualar carcinoma serum markers. *Semin Oncol* 2012; **39**: 410-433 [PMID: 22846859 DOI: 10.1053/j.seminoncol.2012.05.001]

34 **An SL**, Xiao T, Wang LM, Rong WQ, Wu F, Feng L, Liu FQ, Tian F, Wu JX. Prognostic Significance of Preoperative Serum Alpha- fetoprotein in Hepatocellular Carcinoma and Correlation with Clinicopathological Factors: a Single-center Experience from China. *Asian Pac J Cancer Prev* 2015; **16**: 4421-4427 [PMID: 26028108 DOI: 10.7314/APJCP.2015.16.10.4421]

35 **Ma WJ**, Wang HY, Teng LS. Correlation analysis of preoperative serum alpha-fetoprotein (AFP) level and prognosis of hepatocellular carcinoma (HCC) after hepatectomy. *World J Surg Oncol* 2013; **11**: 212 [PMID: 23981851 DOI: 10.1186/1477-7819-11-212]

36 **Masuda T**, Beppu T, Horino K, Komori H, Hayashi H, Okabe H, Otao R, Horlad H, Ishiko T, Takamori H, Kikuchi K, Baba H. Preoperative tumor marker doubling time is a useful predictor of recurrence and prognosis after hepatic resection of hepatocellular carcinoma. *J Surg Oncol* 2010; **102**: 490-496 [PMID: 19937994 DOI: 10.1002/jso.21451]

37 **Zhang Q**, Shang L, Zang Y, Chen X, Zhang L, Wang Y, Wang L, Liu Y, Mao S, Shen Z. α-Fetoprotein is a potential survival predictor in hepatocellular carcinoma patients with hepatitis B selected for liver transplantation. *Eur J Gastroenterol Hepatol* 2014; **26**: 544-552 [PMID: 24614696 DOI: 10.1097/meg.0000000000000029]

38 **Giannini EG**, Marenco S, Borgonovo G, Savarino V, Farinati F, Del Poggio P, Rapaccini GL, Anna Di Nolfo M, Benvegnù L, Zoli M, Borzio F, Caturelli E, Chiaramonte M, Trevisani F; Italian Liver Cancer (ITA.LI.CA) group. Alpha-fetoprotein has no prognostic role in small hepatocellular carcinoma identified during surveillance in compensated cirrhosis. *Hepatology* 2012; **56**: 1371-1379 [PMID: 22535689 DOI: 10.1002/hep.25814]

39 **Hao S**, Fan P, Chen S, Tu C, Wan C. Distinct Recurrence Risk Factors for Intrahepatic Metastasis and Multicenter Occurrence After Surgery in Patients with Hepatocellular Carcinoma. *J Gastrointest Surg* 2017; **21**: 312-320 [PMID: 27815759 DOI: 10.1007/s11605-016-3311-z]

40 **Cucchetti A**, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanello M, Grazi GL, Golfieri R, Grigioni WF, Pinna AD. Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: a pilot study. *J Hepatol* 2010; **52**: 880-888 [PMID: 20409605 DOI: 10.1016/j.jhep.2009.12.037]

41 **Shah SA**, Greig PD, Gallinger S, Cattral MS, Dixon E, Kim RD, Taylor BR, Grant DR, Vollmer CM. Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. *J Am Coll Surg* 2006; **202**: 275-283 [PMID: 16427553 DOI: 10.1016/j.jamcollsurg.2005.10.005]

42 **Rodríguez-Perálvarez M**, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol* 2013; **20**: 325-339 [PMID: 23149850 DOI: 10.1245/s10434-012-2513-1]

43 **Huang G**, Lau WY, Zhou WP, Shen F, Pan ZY, Yuan SX, Wu MC. Prediction of Hepatocellular Carcinoma Recurrence in Patients With Low Hepatitis B Virus DNA Levels and High Preoperative Hepatitis B Surface Antigen Levels. *JAMA Surg* 2014; **149**: 519-527 [PMID: 24696192 DOI: 10.1001/jamasurg.2013.4648]

44 **Park JH**, Koh KC, Choi MS, Lee JH, Yoo BC, Paik SW, Rhee JC, Joh JW. Analysis of risk factors associated with early multinodular recurrences after hepatic resection for hepatocellular carcinoma. *Am J Surg* 2006; **192**: 29-33 [PMID: 16769271 DOI: 10.1016/j.amjsurg.2005.11.010]

45 **Bjerner J**, Høgetveit A, Wold Akselberg K, Vangsnes K, Paus E, Bjøro T, Børmer OP, Nustad K. Reference intervals for carcinoembryonic antigen (CEA), CA125, MUC1, Alfa-foeto-protein (AFP), neuron-specific enolase (NSE) and CA19.9 from the NORIP study. *Scand J Clin Lab Invest* 2008; **68**: 703-713 [PMID: 18609108 DOI: 10.1080/00365510802126836]

46 **Zhou L**, Rui JA, Wang SB, Chen SG, Qu Q. The significance of serum AFP cut-off values, 20 and 400 ng/mL in curatively resected patients with hepatocellular carcinoma and cirrhosis might be of difference. *Hepatogastroenterology* 2012; **59**: 840-843 [PMID: 22469729 DOI: 10.5754/hge10404]

47 **Silva JP**, Gorman RA, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, Gamblin TC. The prognostic utility of baseline alpha-fetoprotein for hepatocellular carcinoma patients. *J Surg Oncol* 2017; **116**: 831-840 [PMID: 28743160 DOI: 10.1002/jso.24742]

48 **Blank S**, Wang Q, Fiel MI, Luan W, Kim KW, Kadri H, Mandeli J, Hiotis SP. Assessing prognostic significance of preoperative alpha-fetoprotein in hepatitis B-associated hepatocellular carcinoma: normal is not the new normal. *Ann Surg Oncol* 2014; **21**: 986-994 [PMID: 24232510 DOI: 10.1245/s10434-013-3357-z]

49 **Toyoda H**, Kumada T, Tada T, Ito T, Maeda A, Kaneoka Y, Kagebayashi C, Satomura S. Changes in highly sensitive alpha-fetoprotein for the prediction of the outcome in patients with hepatocellular carcinoma after hepatectomy. *Cancer Med* 2014; **3**: 643-651 [PMID: 24591342 DOI: 10.1002/cam4.218]

50 **Riaz A**, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, Ibrahim SM, Sato KT, Baker T, Miller FH, Newman S, Omary R, Abecassis M, Benson AB 3rd, Salem R. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol* 2009; **27**: 5734-5742 [PMID: 19805671 DOI: 10.1200/jco.2009.23.1282]

51 **Memon K**, Kulik L, Lewandowski RJ, Wang E, Ryu RK, Riaz A, Nikolaidis P, Miller FH, Yaghmai V, Baker T, Abecassis M, Benson AB 3rd, Mulcahy MF, Omary RA, Salem R. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. *J Hepatol* 2012; **56**: 1112-1120 [PMID: 22245905 DOI: 10.1016/j.jhep.2011.11.020]

52 **Kao WY**, Chiou YY, Hung HH, Su CW, Chou YH, Wu JC, Huo TI, Huang YH, Wu WC, Lin HC, Lee SD. Serum alpha-fetoprotein response can predict prognosis in hepatocellular carcinoma patients undergoing radiofrequency ablation therapy. *Clin Radiol* 2012; **67**: 429-436 [PMID: 22153231 DOI: 10.1016/j.crad.2011.10.009]

53 **Li P**, Wang SS, Liu H, Li N, McNutt MA, Li G, Ding HG. Elevated serum alpha fetoprotein levels promote pathological progression of hepatocellular carcinoma. *World J Gastroenterol* 2011; **17**: 4563-4571 [PMID: 22147961 DOI: 10.3748/wjg.v17.i41.4563]

54 **Cai ZQ**, Si SB, Chen C, Zhao Y, Ma YY, Wang L, Geng ZM. Analysis of prognostic factors for survival after hepatectomy for hepatocellular carcinoma based on a Bayesian network. *PLoS One* 2015; **10**: e0120805 [PMID: 25826337 DOI: 10.1371/journal.pone.0120805]

55 **Lu Y**, Zhu M, Li W, Lin B, Dong X, Chen Y, Xie X, Guo J, Li M. Alpha fetoprotein plays a critical role in promoting metastasis of hepatocellular carcinoma cells. *J Cell Mol Med* 2016; **20**: 549-558 [PMID: 26756858 DOI: 10.1111/jcmm.12745]

56 **Ogden SK**, Lee KC, Barton MC. Hepatitis B viral transactivator HBx alleviates p53-mediated repression of alpha-fetoprotein gene expression. *J Biol Chem* 2000; **275**: 27806-27814 [PMID: 10842185 DOI: 10.1074/jbc.M004449200]

57 **Sung WK**, Zheng H, Li S, Chen R, Liu X, Li Y, Lee NP, Lee WH, Ariyaratne PN, Tennakoon C, Mulawadi FH, Wong KF, Liu AM, Poon RT, Fan ST, Chan KL, Gong Z, Hu Y, Lin Z, Wang G, Zhang Q, Barber TD, Chou WC, Aggarwal A, Hao K, Zhou W, Zhang C, Hardwick J, Buser C, Xu J, Kan Z, Dai H, Mao M, Reinhard C, Wang J, Luk JM. Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma. *Nat Genet* 2012; **44**: 765-769 [PMID: 22634754 DOI: 10.1038/ng.2295]

**P-Reviewer:** Chedid MF, Dumitraşcu T, Mikulic D **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Specialty type:** Medicine, research and experimental

**Country of origin:** Thailand

**Peer-review report classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**Table 1 Clinicopathological features of patients in the three alpha-fetoprotein response groups *n* (%)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total****(*n* = 334)** | **Normal group** **(*n* = 178)** | **Response group** **(*n* = 129)** | **Non-response group** **(*n* = 27)** | ***P* value** |
| Gender |  |  |  |  |  |
| Male | 155 (46.41) | 86 (48.31) | 56 (43.41) | 13 (48.15) | 0.684 |
| Female | 179 (53.59) | 92 (51.69) | 73 (56.59) | 14 (51.85) |  |
| Age (mean ± SD, yr),  | 58.76 ± 10.09 | 59.94 ± 9.56 | 57.56 ± 10.43 | 56.70 ± 11.16 | 0.066 |
| HBV |  |  |  |  |  |
|  | No | 148 (44.31) | 81 (45.51) | 54 (41.86) | 13 (48.15) | 0.749 |
|  | Yes | 186 (55.69) | 97 (54.49) | 75 (58.14) | 14 (51.85) |  |
| HCV |  |  |  |  |  |
|  | No | 274 (82.04) | 151 (84.83) | 103 (79.84) | 20 (74.07) | 0.283 |
|  | Yes | 60 (17.96) | 27 (15.17) | 26 (20.16) | 7 (25.93) |  |
| Platelet × 103, median (range), *n* = 332 | 191 (14, 850) | 191 (49, 850) | 193 (14, 690) | 155 (36, 444) | 0.361 |
| Tumor size (cm), median (range), *n* =333 | 4.3 (0.5, 26.5) | 4 (0.5, 26.5) | 5.1 (0.8, 18) | 4.75 (1.3, 14) | 0.204 |
| No. of tumors |  |  |  |  |  |
|  | Single | 262 (78.44) | 143 (80.34) | 99 (76.74) | 20 (74.07) | 0.637 |
|  | Multiple | 72 (21.56) | 35 (19.66) | 30 (23.26) | 7 (25.93) |  |
| mVI |  |  |  |  |  |
|  | No | 254 (76.05) | 142 (79.78) | 95 (73.64) | 17 (62.96) | 0.116 |
|  | Yes | 80 (23.95) | 36 (20.22) | 34 (26.36) | 10 (37.04) |  |
| Stage |  |  |  |  |  |
|  | Stage I | 204 (61.08) | 114 (64.04) | 75 (58.14) | 15 (55.56) | 0.479 |
|  | Stage II or higher | 130 (38.92) | 64 (35.96) | 54 (41.86) | 12 (44.44) |  |
| Resection margin *n* = 282  |  |  |  |  |  |
|  | Free margin | 264 (93.62) | 141 (93.38) | 103 (94.50) | 20 (90.91) | 0.808 |
|  | Positive margin | 18 (6.38) | 10 (6.62) | 6 (5.50) | 2 (9.09) |  |
| Anti-viral treatment |  |  |  |  |  |
|  | No | 179 (53.59) | 92 (51.69) | 71 (55.04) | 16 (59.26) | 0.699 |
|  | Yes | 155 (46.41) | 86 (48.31) | 58 (44.96) | 11 (40.74) |  |
| Recurrence |  |  |  |  |  |
|  | No | 181 (54.19) | 103 (57.87) | 69 (53.49) | 9 (33.33) | 0.057 |
|  | Yes | 153 (45.81) | 75 (42.13) | 60 (46.51) | 18 (66.67) |  |
| Death |  |  |  |  |  |
|  | No | 282 (84.43) | 156 (87.64) | 107 (82.95) | 19 (70.37) | 0.059 |
|  | Yes | 52 (15.57) | 22 (12.36) | 22 (17.05) | 8 (29.63) |  |
| Time follow up (mo), median (range) | 35.63(0.56,176.6) | 37.96 (0.56,130.77) | 35.06(3.76,176.60) | 14.06(2.83,140.93) | 0.007 |

HBV: Hepatitis B virus; HCV: hepatitis C virus.

**Table 2 Univariate and multivariate analysis of factors associated with recurrence**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Univariate** |  | **Multivariate** |
| **HR (95%CI)** | ***P* value** | **HR (95%CI)** | ***P* value** |
| Gender |  |  |  |  |  |
|  | Male | 1 |  |  |  |  |
|  | Female | 0.882 (0.64-1.21) | 0.443 |  |  |  |
| Age (yr) | 0.997 (0.98-1.01) | 0.758 |  |  |  |
| HBV |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 1.079 (0.78-1.49) | 0.641 |  |  |  |
| HCV |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 1.373 (0.92-2.05) | 0.120 |  |  |  |
| Platelet × 103 | 1.002 (0.98-1.02) | 0.775 |  |  |  |
| Tumor size (cm) | 1.058 (1.02-1.10) | 0.003 |  | 1.040 (0.99-1.08) | 0.059 |
| No. of tumor |  |  |  |  |  |
|  | Single | 1 |  |  | 1 |  |
|  | Multiple | 1.793 (1.26-2.54) | **0.001** |  | 1.646 (1.15-2.35) | **0.006** |
| mVI |  |  |  |  |  |
|  | No | 1 |  |  | 1 |  |
|  | Yes | 1.889 (1.30-2.73) | **0.001** |  | 1.573 (1.05-2.35) | **0.026** |
| Stage |  |  |  |  |  |
|  | Stage I | 1 |  |  |  |  |
|  | Stage II or higher | 1.535 (1.10-2.12) | 0.010 |  |  |  |
| Resection margin |  |  |  |  |  |
|  | Free margin | 1 |  |  |  |  |
|  | Positive margin | 1.359 (0.69-2.67) | 0.375 |  |  |  |
| Anti-viral treatment |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 0.935 (0.68-1.28) | 0.682 |  |  |  |
| AFP |  |  |  |  |  |
|  | Normal group | 1 |  |  | 1 |  |
|  | Response group  | 1.137 (0.80-1.59) | 0.458 |  | 1.067 (0.75-1.50) | 0.711 |
|  | Non-response group  | 2.438 (1.45-4.08) | **0.001** |  | 2.425 (1.42-4.13) | **0.001** |

AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HCV: hepatitis C virus.

**Table 3 Univariate and multivariate analysis of factors associated with overall survival**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Univariate** |  | **Multivariate** |
| **HR (95%CI)** | ***P* value** | **HR (95%CI)** | ***P* value** |
| Gender |  |  |  |  |  |
|  | Male | 1 |  |  |  |  |
|  | Female | 1.083 (0.62-1.88) | 0.775 |  |  |  |
| Age (yr) | 0.998 (0.97-1.02) | 0.905 |  |  |  |
| HBV |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 1.032 (0.59-1.79) | 0.909 |  |  |  |
| HCV |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 1.154 (0.56-2.37) | 0.696 |  |  |  |
| Platelet × 103 | 1.002 (0.99-1.00) | 0.117 |  |  |  |
| Tumor size (cm) | 1.062 (0.99-1.13) | 0.066 |  |  |  |
| No. of tumor |  |  |  |  |  |
|  | Single | 1 |  |  | 1 |  |
|  | Multiple | 2.240 (1.27-3.94) | **0.005** |  | 1.991 (1.12-3.52) | **0.018** |
| mVI |  |  |  |  |  |
|  | No | 1 |  |  | 1 |  |
|  | Yes | 3.324 (1.85-5.95) | **0.000** |  | 3.240 (1.77-5.90) | **0.000** |
| Stage |  |  |  |  |  |
|  | Stage I | 1 |  |  |  |  |
|  | Stage II or higher | 1.941 (1.11-3.38) | 0.019 |  |  |  |
| Resection margin |  |  |  |  |  |
|  | Free margin | 1 |  |  |  |  |
|  | Positive margin | 2.544 (1.00-6.47) | 0.050 |  |  |  |
| Anti-viral treatment |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 0.786 (0.45-1.36) | 0.392 |  |  |  |
| Recurrence |  |  |  |  |  |
|  | No | 1 |  |  |  |  |
|  | Yes | 7.917 (3.56-17.56) | 0.000 |  |  |  |
| AFP |  |  |  |  |  |
|  | Normal group  | 1 |  |  | 1 |  |
|  | Response group  | 1.338 (0.74-2.41) | 0.334 |  | 1.168 (0.64-2.12) | 0.612 |
|  | Non-response group  | 3.635 (1.61-8.18) | **0.002** |  | 3.621 (1.59-8.21) | **0.002** |

AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HCV: hepatitis C virus.

A



B



**Figure 1 Recurrence-free-survival and overall survival rate of hepatocellular carcinoma patients after hepatic resection.** A: Kaplan-Meier analysis of recurrence-free survival; B: Kaplan-Meier analysis of overall survival.

A



B



**Figure 2 Recurrence-free-survival and overall survival rate of hepatocellular carcinoma patients after hepatic resection.** A: Kaplan-Meier analysis of recurrence-free survival. The graph shows group A (AFP response > 50%) and group B (AFP response < 50%) regardless of pre-operative AFP levels; B: Kaplan-Meier analysis of overall survival. The graph shows group A (AFP response > 50%) and group B (AFP response < 50%) regardless of pre-operative AFP levels. AFP: Alpha-fetoprotein.