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ABOUT COVER

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AIM AND SCOPE

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ORIGINAL ARTICLE

Retrospective Study

Prognostic role of alpha-fetoprotein response after hepatocellular carcinoma resection

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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.

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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 $\leqslant$ 20 ng/mL and post-AFP $\leqslant$ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP decrease of $\geqslant$ 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: Risk factors; Prognosis; Alpha-fetoprotein; Hepatocellular carcinoma; Liver neoplasms

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.

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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 mo 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 $\leqslant$ 20 ng/mL and post-AFP $\leqslant$ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP a decrease of $\geqslant$ 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 $\geqslant$ 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).

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 × 10^3, 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.

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

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)	0.12		
Platelet × 10^3	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)	0.01		
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.

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 sig-

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 × 10^3	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	3.240 (1.77-5.90)	0
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)	0.05		
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		
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.

nificantly 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-

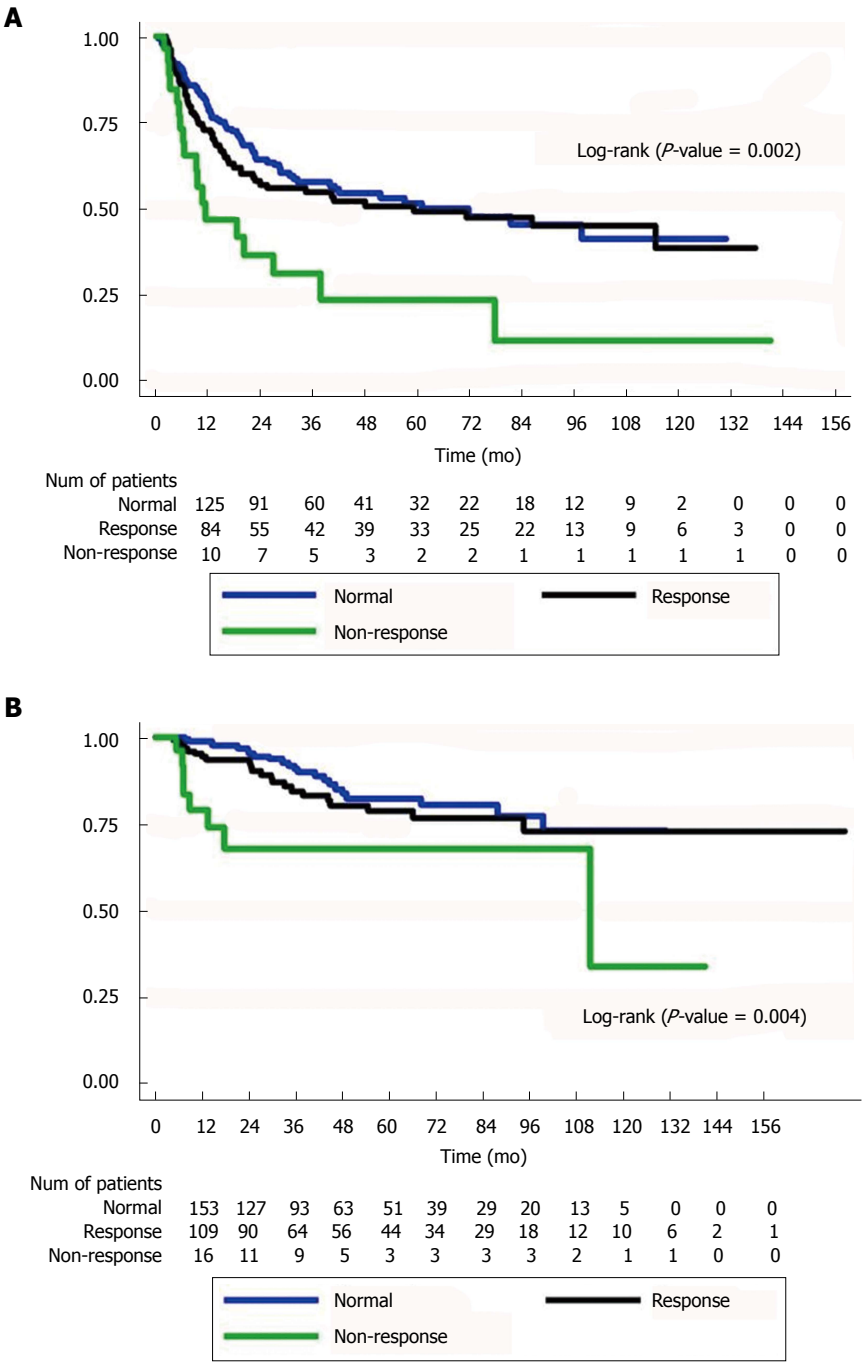

Figure 1 Recurrence-free-survival and overall survival rate of hepatocellular carcinoma patients after hepatic resection. A: Kaplan-Meier analysis of recurrence-free survival; B: Kaplan-Meier analysis of overall survival.

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 d 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.

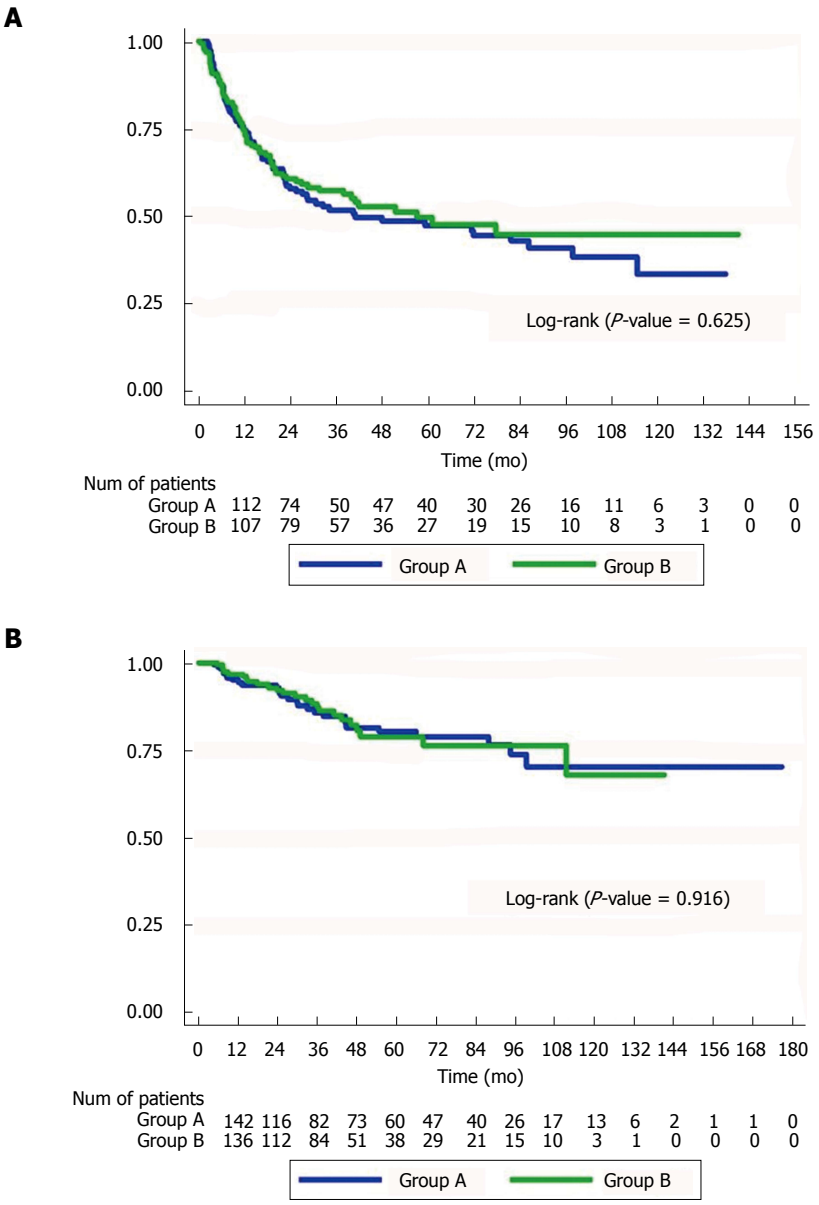

Figure 2 Recurrence-free-survival and overall survival rate of hepatocellular carcinoma patients after hepatic resection. A: Kaplan-Meier analysis of recurrence-free survival. The graph shows group A (AFP response > 50%) and group B (AFP response < 50%) regardless of pre-operative AFP levels; B: Kaplan-Meier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

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) $\leqslant$ 20 ng/mL and post-operative serum AFP level (post-AFP) $\leqslant$ 20 ng/mL; (2) the response group, pre-AFP > 20 ng/mL and post-AFP decrease of $\geqslant$ 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.

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