Value of alpha-foetoprotein for screening of recurrence in hepatocellular carcinoma post resection

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INTRODUCTION The aim of this study was to establish the value of alpha-foetoprotein (AFP) for the screening of recurrences in hepatocellular carcinoma (HCC) in patients who have undergone curative hepatic resection.

METHODS 72 HCC patients who had curative resection/liver transplant in 2000–2006 were monitored for recurrence by evaluating the three- or six-monthly AFP and computed tomography images. Patients without recurrence were followed up for a mean duration of 7.27 years.

RESULTS Out of the 72 patients, 34 (47.2%) suffered from HCC recurrence. 65.4% of recurrent cases had AFP values showing an upward trend. Patients with recurrence had higher AFP values than those without at last follow-up (119.45 µg/L vs. 3.1 µg/L, $p < 0.001$). AFP at recurrence was independent of gender, race, history of alcohol consumption and hepatitis C or cirrhosis status. Patient with hepatitis B or those with tumours larger than 5 cm had higher AFP values. The best cut-off AFP indicative of HCC recurrence was 5.45 µg/L (sensitivity 84.4%; specificity 77.1%). High preoperative AFP was associated with high AFP at recurrence (correlation coefficient 0.553, $p = 0.01$).

CONCLUSION AFP alone is an inadequate screening test for HCC recurrence since only about two-thirds of patients showed upward AFP trend on recurrence. Our study found a relatively low cut-off point for detection of recurrence (5.54 µg/L). Patients with high preoperative AFP tended to have high AFP on recurrence. Imaging is recommended for patients with AFP levels > 5.45 µg/L, especially when AFP shows a rising trend.

Keywords: alpha-foetoprotein, hepatocellular carcinoma, recurrence, screening
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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality in the world,[1] with the highest incidence rates in East Asia.[2] In Singapore, it is the fourth most common cancer in male Singaporeans.[3] To date, tumour resection remains the first choice of treatment for these patients as a definitive curative modality.[4] Early detection of HCC is important for its effective treatment, as large tumours are associated with a higher risk of recurrence and may even preclude surgery.[5]

While alpha-foetoprotein (AFP) has been used as a diagnostic test for HCC since the 1970s,[6] its usefulness as an effective screening or diagnostic tool remains controversial for surgically treatable HCC. Many conflicting conclusions pertaining to the reliability and importance of AFP as a screening or diagnostic tool for HCC and its recurrence have been reported.[5,7-14] With advances in imaging modalities such as ultrasonography (US), computed tomography (CT) and magnetic resonance (MR) imaging, the importance of AFP as a diagnostic test has been greatly reduced. Despite that, AFP measurement is still commonly used for surveillance in patients at risk for HCC.[15] A screening programme, comprising six-monthly liver US and serum AFP testing for certain high-risk patients (hepatitis B carriers), is the recommended screening modality,[16] and has been the current practice in our institution. There is, however, no screening guideline for the monitoring of recurrences. In this study, we aimed to establish the value of AFP in the screening of HCC recurrence.

METHODS

A retrospective review of our liver surgery database was conducted to identify patients who had curative resection/liver transplant for HCC at the National University Hospital Singapore from year 2000 to 2006. Histopathological results of resected specimen were analysed in order to confirm the diagnosis. The patients were monitored for recurrence of HCC using AFP and CT every three months for the first two years, then six-monthly for three years and yearly thereafter. Recurrence is defined as newly developed lesions on CT that showed hyperattenuation in the arterial phase, with washout in the delayed phase. The patients were followed up from the time of resection to detection of tumour recurrence, death or the last examination until March 31, 2010, whichever came first. The duration (mean ± 2 standard deviation [SD]) of follow-up for patients without recurrence was 7.27 ± 4.88 years.

Statistical analysis was carried out using PASW Statistics version 18 (IBM Corporation, New York, NY, USA). Disease-free survival, overall survival and time to recurrence were analysed. AFP values were compared across gender, race, alcohol consumption, tumour size and hepatitis B, hepatitis C and cirrhosis statuses. As AFP values have a skewed distribution,

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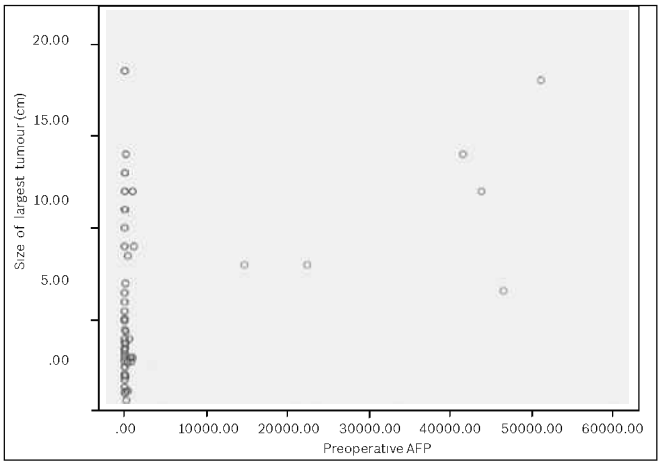

Fig. 1 Graph shows the size of the largest tumour plotted against the preoperative AFP values.

non-parametric tests (Mann-Whitney U and Kruskal-Wallis tests) were used.

The size of tumours (largest) was plotted against the preoperative AFP values, and the outlier points were identified (Fig. 1). All the outliers were found to have a tumour size > 5 cm. Therefore, 5 cm was chosen as a cut-off point, and the AFP values were dichotomised at a tumour size of 5 cm. The AFP values (post-resection to recurrence) of patients who had recurrence of their HCC were tabled and observed for signs of an upward trend. The distribution of AFP at recurrence was analysed across difference type of HCCs. Receiver operating characteristic (ROC) curve analysis was used to determine the best cut-off AFP value that was indicative of HCC recurrence. Sensitivities, specificities, positive and negative predictive values of the various AFP cut-off values were analysed using chi-square test; AFP values (at recurrence or at the last follow-up for non-recurrence) were categorised into two groups at the cut-off values (i.e. ≥ 5.45 μg/L and < 5.45 μg/L) and cross-tabulated with presence or absence of recurrence. The association between preoperative AFP and AFP at recurrence or last follow-up was analysed.

Table I. Patient demographics (n = 72).

Demographic	No. (%)
Gender	
Male	56 (78)
Female	16 (22)
Race	
Chinese	65 (90)
Malay	1 (1)
Indian	3 (4)
Others	3 (4)
History of alcohol consumption	
Yes	8 (11)
No	64 (89)
Hepatitis B	
Positive	45 (63)
Negative	27 (37)
Hepatitis C	
Positive	4 (6)
Negative	68 (64)
Cirrohosis	
Yes	28 (39)
No	44 (61)
Type of treatment for HCC	
Liver resection	64 (89)
Liver transplantation	8 (11)

HCC: hepatocellular carcinoma

Table II. Median AFP at recurrence, at the last follow-up for non-recurrence and with different types of recurrence.

	Median AFP; range (μg/L)	p-value
At recurrence	119.45; 1.2–200,001.0	< 0.001
At last follow-up for non-recurrence	3.1; 1.2–276.0	
Type of recurrence		
Intrahepatic recurrence only (n = 21)	14.2; 1.20–22,835.0	0.060
Intra- and extrahepatic recurrence (n = 11)	434.2; 3.4–200,001.0	
Extrahepatic recurrence only (n = 2)	2381.65; 3.3–4760.0	

AFP: alpha-foetoprotein

RESULTS

A total of 72 patients underwent curative resection or liver transplantation for HCC from 2000 to 2006. Eight (11%) patients underwent liver transplant, all of whom had orthotropic liver transplant. The demographics of the patients are presented in Table I. AFP values were followed up from the time of resection to tumour recurrence or death. Survival was followed up until March 31, 2010. Patients without recurrence were followed up for 7.27 ± 4.88 years (mean ± 2 SD). For patients with recurrence, the mean duration of time to recurrence was 0.73 ± 2.16 years (mean ± 2 SD). HCC recurrence occurred early in the disease process, and 40% of patients had disease recurrence by the first year (Fig. 2). An additional 7% of patients had tumour recurrence in the second year and another 10% in the third year. Overall survival (Fig. 3) was found to be 77% at one year, 73% at two years and 64% at three years.

Out of the 72 patients, 34 (47.2%) suffered from HCC recurrence, and an average of 2.5 AFP tests were performed for each patient from the time of curative surgery to recurrence. Out of these 34 patients, sufficient AFP information for the study of AFP trends to recurrence was available for 26 patients. At least three serial AFP measurements were required in order to study the upward trend. Therefore, only 26 out of the 34 patients had sufficient information for the study of AFP trend. It was found that 65.4% (n = 17) had AFP values on the upward trend. The AFP values at recurrence were available for 32 out of the 34 patients who suffered from HCC recurrence. The difference between the median AFP at recurrence (119.45 μg/L) and median AFP at last follow-up for patients with no recurrences (3.1 μg/L) was statistically significant ($p < 0.001$) (Table II). The median AFP values for the different types of HCC recurrence are depicted in Table II. No significant differences between the different recurrence groups were observed ($p = 0.060$).

The preoperative AFP values as well as the AFP at recurrence or last follow-up were independent of gender, race, history of

Table III. Difference in AFP values across gender, race, alcohol consumption, hepatitis C status and cirrhosis status.

	Preoperative AFP (μg/L)*	p-value	AFP at recurrence/last follow-up (μg/L)*	p-value
Gender				
Male	21.35; 1.3–51,100.0	0.684	69.2; 1.2–200,001.0	0.579
Female	64.6; 1.5–46,500.0		454; 107–15400	
Race				
Chinese	21.35; 1.3–51,100.0	0.754	131; 1.2–200,001.0	0.431
Malay	8.6; 8.6–8.6		318; 318–318	
Indian	87.1; 26.2–148.0		8.3; 7.7–15.3	
Other	48.4; 27.9–384.0		147; 147–147	
Alcohol history				
Yes	79.7; 1.4–993.9	0.786	131; 1.2–200,001.0	0.568
No	26.2; 1.3–51,100.0		12; 8.3–2,690.0	
Hepatitis C				
Positive	8.8; 8.6–43,800.0	0.839	318; 3.3–22,835.0	0.341
Negative	26.2; 1.3–51,100.0		107.9; 1.2–200,001.0	
Cirrhosis				
Yes	13.5; 1.3–41,520.0	0.665	156.4; 6.5–8,015.0	0.753
No	31.9; 1.4–51,100.0		62.15; 1.2–200,001.0	

*Data is presented as median; range. AFP: alpha-foetoprotein

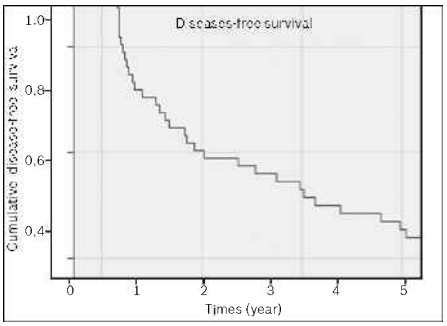

Fig. 2 Graph shows disease-free survival.

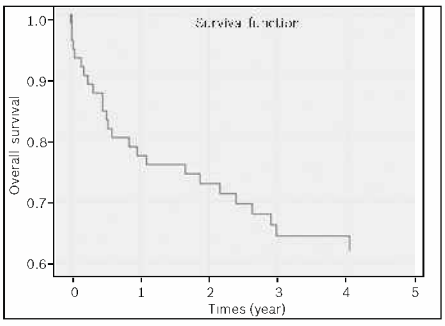

Fig. 3 Graph shows overall survival.

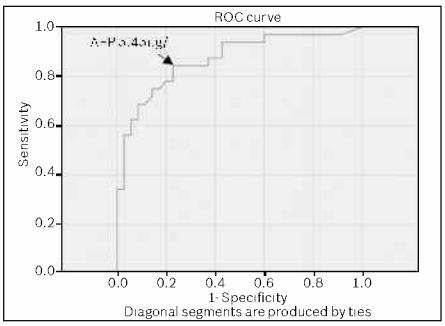

Fig. 4 Graph shows the Receiver Operating Characteristic (ROC) curve of AFP levels.

alcohol consumption, hepatitis C status and cirrhosis status (Table III). The difference in AFP values across hepatitis B and tumour size is shown in Table IV. Patients with hepatitis B tended to have higher preoperative AFP values, with statistical significance. Although these patients with hepatitis B also showed higher AFP values on follow-up, they were not statistically significant ($p = 0.167$). On the other hand, while large tumour size (≥ 5 cm) failed to show significantly higher preoperative AFP, AFP at recurrence or at follow-up was higher in patients with large tumours, and they were statistically significant. Therefore, preoperative large tumour size played a role in higher AFP even after the tumour had been resected.

The ROC curve (Fig. 4) analysis of AFP was performed to obtain the best cut-off value that was indicative of HCC recurrence, and we found that an AFP value of 5.45 μg/L maximised the sensitivity (84.4%) and specificity (77.1%) simultaneously (Table III). To determine the adequacy of the normal AFP range (0.00–15.00 μg/L) used at our institution, 15.00 μg/L was used as the cut-off point for predicting HCC recurrence. The sensitivity was reduced to 62.5%, but the specificity increased to 94.3% (Table V). When preoperative AFP was correlated with AFP at recurrence or at follow-up, a statistically significant moderate association was observed, with a correlation coeffiecient of 0.553 and a p-value of 0.01.

DISCUSSION

Currently, the recommendations for postoperative surveillance of HCC include imaging (CT/MR imaging) every 3–6 months for two years and annually thereafter. AFP monitoring is recommended every three months for the first two years and subsequently, every six-monthly after two years.[17] However, there is no recommended cut-off point for AFP for surveillance of recurrence. The normal AFP range of 0.00–15.00 μg/L used at our institution was found to have poor sensitivity for detection of HCC recurrence. Our study suggests that the AFP value in HCC recurrence after curative surgery is relatively low. We found that the cut-off point for diagnosis of HCC recurrence was 5.45 μg/L, which is relatively low and interposed with the AFP value in a normal person. Moreover, the sensitivity was only 84.4%; therefore, the AFP value alone should not be used for detection of HCC recurrence.

An upward trend of AFP was observed in only 65.4% (n = 17) of our patients with recurrence. It signifies that about one-third of the recurrence cases failed to show an upward AFP trend. Therefore, serial AFP monitoring is of limited value, and AFP results should thus be interpreted along with imaging findings (US and CT). Despite the limitations, the elevation of AFP values was associated with recurrence of HCC, as reflected by the significant difference between median AFP in recurrent and non-recurrent cases ($p < 0.001$). Preoperative AFP and AFP values at

Table IV. Differences in AFP values across hepatitis B and tumour size.

	Preoperative AFP (µg/L)*	p-value	AFP at recurrence/last follow-up (µg/L)*	p-value
Hepatitis B				
Positive	42.9; 1.3–51,100.0	0.05	6.5; 1.2–200,001.0	0.167
Negative	11.4; 1.4–857.2		3.95; 1.2–1,810.0	
Tumour size				
≤ 5 cm	29; 1.4–51,100.0	0.50	9.7; 1.2–200,01.0	0.034
< 5 cm	21; 1.3–982.9		4.6; 1.2–2,690.0	

*Data is presented as median; range. AFP: alpha-foetoprotein

Table V. Sensitivity, specificity, PPV and NPV for AFP cut-off at 5.45 µg/L and 15.00 µg/L.

AFP cut-off value	Percentage
5.45 µg/L	
Sensitivity	84.4
Specificity	77.1
PPV	77.1
NPV	84.4
15.0 µg/L	
Sensitivity	62.5
Specificity	94.3
PPV	90.9
NPV	73.3

PPV: positive predictive value; NPV: negative predictive values; AFP: alpha-foetoprotein

recurrence or follow-up were found to be independent of alcohol consumption, hepatitis C status and cirrhosis status. However, patients with hepatitis B and those with larger tumours were found to have higher AFP at recurrence or at follow-up.

This study included only a select group of patients who had resectable HCC and no metastases. It cannot be compared to the overall HCC group, which included non-resectable cases. Hence, additional studies are required in order to determine the value of AFP in non-resectable HCC. Moreover, as this was a retrospective study, AFP monitoring was not done in a strict and regular manner. Its retrospective nature had also limited the study of the timing and frequency of AFP. Therefore, prospective randomised control studies are warranted so as to determine the timing and frequency of AFP monitoring for recurrence surveillance.

We conclude that AFP alone is not an adequate surveillance for HCC recurrence, since even at the best cut-off value of 5.45 µg/L, the sensitivity and specificity were only 84.4% and 77.1%, respectively. We suggest that patients undergo further imaging if their AFP levels are higher than this value, especially in the setting of a rising trend. However, one-third of the recurrence cases in our study did not show an upward AFP trend. Despite its inadequacy as a screening test, high AFP levels are undisputedly associated with HCC recurrence and high preoperative AFP levels are associated with high AFP level on recurrence.

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