ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Serum α-Fetoprotein Levels at Time of Recurrence Predict Post-Recurrence Outcomes Following Resection of Hepatocellular Carcinoma

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ABSTRACT

Introduction. Although preoperative α-fetoprotein (AFP) has been recognized as an important tumor marker among patients with hepatocellular carcinoma (HCC), the predictive value of AFP levels at the time of recurrence (rAFP) on post-recurrence outcomes has not been well examined.

Methods. Patients undergoing curative-intent resection of HCC between 2000 and 2017 were identified using a multi-institutional database. The impact of rAFP on post-recurrence survival, as well as the impact of rAFP relative to the timing and treatment of HCC recurrence were examined.

Results. Among 852 patients who underwent resection of HCC, 307 (36.0%) individuals developed a recurrence. The median rAFP level was 8 ng/mL (interquartile range

3–100). Among the 307 patients who developed recurrence, 3-year post-recurrence survival was 48.5%. Patients with rAFP > 10 ng/mL had worse 3-year post-recurrence survival compared with individuals with rAFP < 10 ng/mL (28.7% vs. 65.5%, $p < 0.001$). rAFP correlated with survival among patients who had early (3-year survival; rAFP > 10 vs. < 10 ng/mL: 30.1% vs. 60.2%, $p < 0.001$) or late (18.0% vs. 78.7%, $p = 0.03$) recurrence. Furthermore, rAFP levels predicted 3-year post-recurrence survival among patients independent of the therapeutic modality used to treat the recurrent HCC (rAFP > 10 vs. < 10 ng/mL; ablation: 41.1% vs. 76.0%; intra-arterial therapy: 12.9% vs. 46.1%; resection: 37.5% vs. 100%; salvage transplantation: 60% vs. 100%; all $p < 0.05$). After adjusting for competing risk factors, patients with rAFP > 10 ng/mL had a twofold higher hazard of death in the post-recurrence setting (hazard ratio 1.96, 95% confidence interval 1.26–3.04).

Conclusion. AFP levels at the time of recurrence following resection of HCC predicted post-recurrence survival independent of the secondary treatment modality used. Evaluating AFP levels at the time of recurrence can help inform post-recurrence risk stratification of patients with recurrent HCC.

Hepatocellular carcinoma (HCC) is the sixth most common cancer, with an increasing age-standardized incidence in both the US[1] and worldwide.[2,3] Surgery, in the form of resection or liver transplantation (LT), provides the best chance for a potential long-term 'cure' among patients with early-stage HCC.[4,5] Due to the shortage of deceased donor livers, liver resection largely remains the mainstay of treatment for the majority of patients with resectable HCC.[6] However, the efficacy of liver resection is limited by high recurrence in the postoperative period. In fact, recurrence may be as high as 60% at 5-years post-hepatectomy.[7,8] It is, therefore, important to determine the optimal treatment strategy for patients who recur after resection of primary HCC to optimize patient outcomes.

The management of patients with recurrent HCC is undoubtedly complex and should be decided in a multi-disciplinary setting that involves physicians from multiple specialties, including surgeons, radiologists, medical and radiation oncologists, pathologists, and specialized nurses.[9,10] A number of factors should be taken into account to decide on appropriate treatment strategies for recurrent HCC, including extent of recurrent disease, liver function, adequacy of liver remnant, availability of resources, as well as patient performance status and patient preferences.[9,10] Curative-intent treatment for recurrent HCC includes repeat hepatectomy, local ablation therapies (microwave ablation, radiofrequency ablation [RFA]), and salvage LT.[11] However, many recurrences are treated with transarterial chemoembolization (TACE) or systemic chemotherapy, especially for large recurrent tumors, multiple lesions, and recurrence in the setting of poor underlying liver function.[12,13]

Despite multiple reports on the predictors of outcomes among patients who undergo resection of primary HCC, data on predictors of post-recurrence outcomes have been less available.[9,10] In particular, despite the role of preoperative AFP in screening high-risk populations, as well as predicting outcomes following primary treatment,[14,15] the prognostic role of AFP levels at the time of recurrence has not been well-defined. In addition, most previous studies on recurrent HCC have been based on single-center experiences and have been limited by their small sample size.[10,16,17] In turn, whether AFP at the time of recurrence may predict post-recurrence outcomes irrespective of secondary treatment has not been defined. As such, the objective of the current study was to define patterns, treatment, and prognosis of patients who experienced a recurrence following resection for HCC using an international, multi-institutional cohort. In addition, we sought to characterize the prognostic role of AFP at the time of recurrence relative to the timing, type, and treatment of recurrent HCC.

METHODS

Study Population and Inclusion Criteria

Patients who underwent curative-intent liver resection for HCC between 2000 and 2017 were identified from an international multi-institutional database incorporating data from 11 major hepatobiliary centers: The Ohio State University Wexner Medical Center, Columbus, OH, USA; Yokohama City University School of Medicine, Yokohama, Japan; University of Verona, Verona, Italy; Ospedale San Raffaele, Milano, Italy; Curry Cabral Hospital, Lisbon, Portugal; APHP, Beaujon Hospital, Clichy, France; Westmead Hospital, Sydney, NSW, Australia; Stanford University, Stanford, CA, USA; Fundeni Clinical Institute, Bucharest, Romania; University of Ottawa, Ottawa, ON, Canada; The University of Sydney, School of Medicine, Sydney, NSW, Australia. Patients who did not undergo curative-intent resection, had Barcelona Clinic Liver Cancer (BCLC) stage C tumors, had missing follow-up data, or had missing data on the AFP levels at the time of recurrence were excluded from the analytic cohort. The Institutional Review Board of all participating institutions approved the current study.

Variables, Definitions, and Outcomes

Demographic and clinicopathologic data included age, sex, American Society of Anesthesiologist performance status (ASA-PS), history of hepatitis B (HBV) and C (HCV) virus infection, preoperative α-fetoprotein (AFP), operative approach (i.e. open surgery or minimally invasive surgery [MIS]), extent of liver resection (i.e. minor or major), primary tumor size and number, BCLC stage,[15] differentiation grade, presence of lymphovascular invasion, liver capsule involvement, and resection margin status (i.e. R0, R1).

Following liver resection, patients were followed for recurrence, with serum AFP and imaging studies, including ultrasonography, computed tomography, and/or magnetic resonance imaging once every 3–4 months for the first 3 years, once every 6 months from years 4–5, and then annually, as previously described.[18] Recurrence was defined as suspicious or positive findings on surveillance imaging or histologically confirmed disease. Recurrence data included serum AFP levels at the time of recurrence detection, recurrence site (i.e. intrahepatic, extrahepatic, both), recurrence type (i.e. within and beyond the Milan criteria),[18] timing of recurrence (i.e. early recurrence [≤ 24 months], late recurrence [> 24 months]), and treatment of recurrence. Patients with recurrent tumors were treated with repeat resection (with or without concomitant ablation), ablation (i.e. microwave ablation, RFA) with or

without chemotherapy, intra-arterial therapies (IATs; i.e. embolization, TACE, peptide receptor radionuclide therapy [PRRT]) with or without chemotherapy, salvage transplantation, palliative chemotherapy, or best supportive therapy at the discretion of the treating physicians in different participating centers.

Overall survival (OS) was defined as the time interval between the date of liver resection and the date of death or last follow-up. Disease-free survival (DFS) was defined as the time between resection of primary HCC and detection of recurrence or last follow-up, while post-recurrence survival was defined as the time interval between the date of recurrence detection and the date of death or last follow-up

Statistical Analysis

Descriptive statistics were presented as median (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables were compared using the Chi-square or Fisher's exact tests, as appropriate. Bivariate analyses of OS and post-recurrence survival were performed using the Kaplan–Meier method and the log-rank test. A bivariate Cox regression analysis was used to assess the association of baseline patient and primary tumor characteristics with DFS. Factors significant on bivariate analysis ($p < 0.05$) were entered into the multivariable Cox regression model and backward step selection was used to eliminate nonsignificant variables using a p value < 0.10. Furthermore, a multivariable Cox regression analysis was performed to examine the association of patient characteristics, as well as pathologic primary tumor and recurrence data with post-recurrence survival after adjusting for factors that were significant on bivariate analysis. To ensure adequate statistical power, and given that the median AFP level at the time of recurrence was 8 ng/mL, an AFP cut-off of 10 ng/mL (close to median) was selected to categorize patients into two arms based on the AFP levels at the time of recurrence. The level of statistical significance for all tests was set at $\alpha = 0.05$. All statistical analyses were performed using the SPSS version 26 (IBM Corporation, Armonk, NY, USA) and JMP version 14 (SAS Institute Inc., Cary, NC, USA) statistical packages.

RESULTS

Baseline Characteristics of Patients

A total of 852 patients underwent curative-intent resection for HCC and were included in the final cohort. Median age was 67 years (IQR 59–74) and most patients were male ($n = 647$, 76.1%) and had an ASA score of ≤ 2 ($n = 490$, 63.6%). Median tumor size was 4.8 cm (IQR 3.0–8.5) and approximately one-third of patients underwent major liver resection ($n = 283$, 34.1%). Overall, 6.8% ($n = 58$) of patients had BCLC stage 0 HCC, 77.3% ($n = 659$) had BCLC stage A tumors, and 15.8% ($n = 135$) had BCLC stage B tumors. On pathology, 37.0% ($n = 283$) of patients had lymphovascular invasion and 30.0% ($n = 191$) had liver capsule involvement. The vast majority of patients underwent an R0 resection ($n = 742$, 89.6%) (Table 1).

At a median follow-up of 37.3 months (95% confidence interval [CI] 34.6–40.0), 36% ($n = 307$) of patients experienced a recurrence, while 64% ($n = 545$) did not. Compared with individuals who did not have a recurrence, patients with recurrent disease had larger size tumors (5.5 cm [IQR 3.5–9.0] vs. 4.5 cm [IQR 3.0–4.5]), higher preoperative AFP levels (> 400 ng/mL: $n = 74$ [25.7%] vs. $n = 63$ [14.0%]), and more frequently had poor/undifferentiated tumors ($n = 82$ [27.6%] vs. $n = 86$ [16.8%]), lymphovascular invasion ($n = 130$ [44.5%] vs. $n = 153$ [32.4%]) and BCLC stage B tumors ($n = 76$ [24.8%] vs. $n = 59$ [10.8%]; all $p < 0.05$) (Table 1).

Risk Factors for Recurrence

The median and 5-year DFS following curative-intent resection of HCC was 54.4 months (IQR 27.8–80.9) and 47.7%, respectively. Several patient-, resection-, and tumor-related characteristics were associated with 5-year DFS on bivariate analysis, including platelet count ($< 100,000$/mL [23.5%] vs. $> 100,000$/mL [48.5%]), resection margin status (R0 [48.9%] vs. R1 [38.1%]), tumor size (≤ 5 cm [50.9%] vs. > 5 cm [43.2%]), tumor number (single [51.3%] vs. multiple [30.7%]), BCLC stage (BCLC 0 [57.1%] vs. BCLC A [50.8%] vs. BCLC B [29.4%]), preoperative AFP levels (≤ 400 ng/mL [47.8%] vs. > 400 ng/mL [28.5%]), tumor grade (well/moderate [50.3%] vs. poor/undifferentiated [36.5%]), lymphovascular invasion (absent [49.1%] vs. present [34.7%]), and liver capsule involvement (absent [46.3%] vs. present [37.6%]) (Table 2). On multivariable analysis, platelet count, tumor size, tumor number, preoperative AFP levels, and the presence of lymphovascular invasion remained independent predictors of DFS after curative-intent resection (Table 2). Patients who experienced a recurrence had a 5-year OS of 48.7% versus 78.9% among individuals who did not experience a recurrence ($p < 0.001$) (Fig. 1).

TABLE 1 Clinicopathologic characteristics of the entire cohort (N = 852)

Variables	Total [N = 852]	Recurrence [n = 307, 36.0%]	No recurrence [n = 545, 64.0%]	p value
Age, years [median (IQR)]	67 (59–74)	67 (60–73)	67 (59–74)	0.80
Sex				0.13
Male	647 (76.1)	242 (79.1)	405 (74.4)	
Female	203 (23.9)	64 (20.9)	139 (25.6)	
ASA-PS				0.07
≤ 2	490 (63.6)	190 (67.9)	300 (61.2)	
> 2	280 (36.4)	90 (32.1)	190 (38.8)	
HBV infection				0.22
No	628 (74.4)	218 (71.9)	410 (75.8)	
Yes	216 (25.6)	85 (28.1)	131 (24.2)	
HCV infection				0.19
No	592 (69.9)	204 (67.1)	388 (71.5)	
Yes	255 (30.1)	100 (32.9)	155 (28.5)	
AFP, ng/mL				**< 0.001**
≤ 400	600 (81.4)	214 (74.3)	386 (86.0)	
> 400	137 (18.6)	74 (25.7)	63 (14.0)	
PLT				**0.003**
< 100,000/mL	80 (10.0)	42 (14.2)	38 (7.6)	
> 100,000/mL	719 (90.0)	254 (85.8)	465 (92.4)	
MIS				0.02
No	625 (73.7)	239 (78.6)	386 (71.0)	
Yes	223 (26.3)	65 (21.4)	158 (29.0)	
Type of resection				0.58
Minor	546 (65.9)	192 (64.6)	354 (66.5)	
Major	283 (34.1)	105 (35.4)	178 (33.5)	
Tumor size, cm [median (IQR)]	4.8 (3.0–8.5)	5.5 (3.5–9.0)	4.5 (3.0–4.5)	**0.001**
Tumor number [median (IQR)]	1 (1–1)	1 (1–2)	1 (1–1)	**< 0.001**
Grade				**< 0.001**
Well/moderate	641 (79.2)	215 (72.4)	426 (83.2)	
Poor/undifferentiated	168 (20.8)	82 (27.6)	86 (16.8)	
Lymphovascular invasion				**0.001**
No	481 (63.0)	162 (55.5)	319 (67.6)	
Yes	283 (37.0)	130 (44.5)	153 (32.4)	
Liver capsule involvement				0.14
No	445 (70.0)	168 (66.7)	277 (72.1)	
Yes	191 (30.0)	84 (33.3)	107 (27.9)	
Margin status				0.16
R0	742 (89.6)	262 (87.6)	480 (90.7)	
R1	86 (10.4)	37 (12.4)	49 (9.3)	
BCLC stage				**< 0.001**
0	58 (6.8)	14 (4.6)	44 (8.1)	
A	659 (77.3)	217 (70.7)	442 (81.1)	
B	135 (15.8)	76 (24.8)	59 (10.8)	

Data are expressed as n (%) unless otherwise specified

IQR interquartile range, *ASA-PS* American Society of Anesthesiologists performance score, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* α-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *PLT* platelets, *MIS* minimally invasive surgery

TABLE 2 Association of baseline clinical and primary tumor characteristics with 5-year DFS

Variables	Bivariate		Multivariable[a]	
	5-year DFS (%)	p value	HR (95% CI)	p value
Age, years		0.25		
≤ 65	50.9			
> 65	44.0			
Sex		0.07		
Male	45.5			
Female	55.6			
ASA-PS		0.61		
≤ 2	46.0			
> 2	46.6			
HBV infection		0.43		
No	49.7			
Yes	43.2			
HCV infection		0.21		
No	50.4			
Yes	42.2			
PLT		**< 0.001**		
< 100,000/mL	23.5		1.96 (1.35–2.83)	**< 0.001**
> 100,000/mL	48.5		Ref	
MIS		0.10		
No	47.1			
Yes	46.6			
Type of resection		0.33		
Minor	47.1			
Major	49.2			
Resection margins		**0.02**		
R0	48.9		Ref	
R1	38.1		1.39 (0.97–2.00)	0.07
Tumor grade		**< 0.001**		
Well/moderate	50.3			
Poor/undifferentiated	36.5			
Tumor size, cm		**0.001**		
≤ 5	50.9		Ref	
> 5	43.2		1.40 (1.09–1.81)	**0.01**
Tumor number		**< 0.001**		
Single	51.3		Ref	
Multiple	30.7		1.67 (1.27–2.21)	**< 0.001**
BCLC stage		**< 0.001**		
0	57.1			
A	50.8			
B	29.4			
AFP, ng/mL		**< 0.001**		
≤ 400	47.8		Ref	
> 400	28.5		1.56 (1.17–2.08)	**0.002**
Lymphovascular invasion		**< 0.001**		
No	49.1		Ref	
Yes	34.7		1.54 (1.18–2.00)	**0.001**
Liver capsule involvement		**0.007**		
No	46.3			
Yes	37.6			

DFS disease-free survival, *HR* hazard ratio, *CI* confidence interval, *ASA-PS* American Society of Anesthesiologists performance score, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *PLT* platelets, *MIS* minimally invasive surgery, *AFP* α-fetoprotein, *BCLC* Barcelona Clinic Liver Cancer

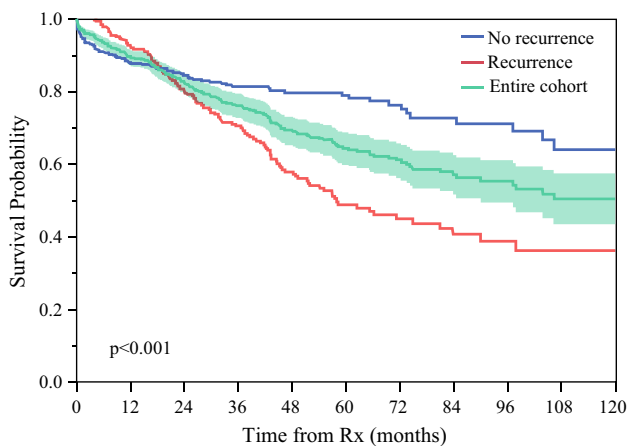[a]The final step of the backward stepwise model is presented

FIG. 1 Kaplan–Meier curves demonstrating differences in overall survival among patients who did and did not have recurrence

Recurrent Tumors: Characteristics, Treatment, and Correlation with Primary Tumors

The majority of recurrent tumors were limited to the liver ($n = 231$, 75.5%), 15.0% ($n = 46$) were extrahepatic only, and 9.5% ($n = 29$) recurred in both intra- and extrahepatic locations. Approximately three-quarters of patients recurred within 24 months after initial resection ($n = 237$, 77.2%) and half of the patients ($n = 147$, 51.8%) had a recurrence beyond the Milan criteria. Median AFP levels at the time of recurrence were 8.0 ng/mL (IQR 3.0–100.0) (Table 3). Of note, AFP levels prior to initial HCC resection correlated strongly with AFP levels at the time of recurrence (correlation coefficient 0.334, $p < 0.001$), as did the size of primary and recurrent tumors (correlation coefficient 0.230, $p < 0.001$).

The majority of patients received curative-intent treatments for recurrent disease, including repeat hepatectomy ± ablation ($n = 33$, 10.7%), ablation ± chemotherapy ($n = 83$, 27.0%), IAT ± chemotherapy ($n = 69$, 22.5%), and salvage LT ($n = 14$, 4.6%), while 35.2% of patients ($n = 108$) received chemotherapy only or best supportive care (Table 3).

Post-Recurrence Outcomes and Prognostic Role of α-Fetoprotein at the Time of Recurrence

Among 307 patients who developed recurrence, median and 3-year post-recurrence survival was 34 months (95% CI 25.7–43.1) and 48.5%, respectively. Post-recurrence outcomes differed according to the treatment modality utilized to treat recurrent disease (3-year post-recurrence survival; salvage LT: 82.5%; resection ± ablation: 73.6%; ablation ± chemotherapy: 64.3%; IAT ± chemotherapy:

28.1%; systemic chemotherapy ± best supportive treatment: 31.0%; $p < 0.001$) (Fig. 2a).

Patients with AFP > 10 ng/mL at the time of recurrence had worse 3-year post-recurrence survival compared with individuals with AFP < 10 ng/mL (28.7% vs. 65.5%, $p < 0.001$) (Fig. 2b). On subset analyses stratified by year of treatment, AFP at the time of recurrence remained an important predictor of post-recurrence outcomes among patients treated for HCC recurrence before 2010 (AFP at recurrence < 10 ng/mL vs. > 10 ng/mL; 3-year post-recurrence survival: 64.4% vs. 32.1%, $p = 0.001$), as well as after 2010 (3-year post-recurrence survival: 65.3% vs. 22.4%, $p < 0.001$).

AFP also correlated with survival among patients who had early (3-year survival; AFP > 10 vs. < 10 ng/mL: 30.1% vs. 60.2%, $p < 0.001$) or late (18.0% vs. 78.7%, $p = 0.03$) recurrence. In addition, AFP levels predicted survival among individuals with recurrence within (3-year survival; AFP > 10 vs. < 10 ng/mL: 40.6% vs. 75.4%, $p < 0.001$) and beyond (AFP > 10 vs. < 10 ng/mL: 17.8% vs. 51.9%, $p = 0.02$) the Milan criteria. Furthermore, AFP levels predicted 3-year post-recurrence survival among patients independent of the therapeutic modality used to treat recurrent HCC (AFP > 10 vs. ≤ 10 ng/mL; ablation ± chemotherapy: 41.1% vs. 76.0%; IAT ± chemotherapy: 12.9% vs. 46.1%; resection ± ablation: 37.5% vs. 100%; salvage LT: 60% vs. 100%; all $p < 0.05$). After adjusting for competing risk factors, patients with AFP >10 ng/mL at the time of recurrence had almost a twofold higher hazard of death in the post-recurrence setting (hazard ratio [HR] 1.96, 95% CI 1.26–3.04, $p = 0.003$) (Table 3).

DISCUSSION

Despite liver resection being a potentially curative treatment option for patients with HCC, recurrence can be as high as 60% at 5 years postoperatively. The management of recurrent HCC can be challenging and needs to be individualized based on certain patient-, tumor-, and liver-related characteristics. To date, only a few studies have focused on the management of recurrent HCC, as well as the predictors of post-recurrence outcomes.[9,10] In particular, the prognostic role of serum AFP at the time of recurrence has not been previously examined. The current study was important because it specifically focused on an assessment of recurrence patterns, as well as treatment and outcomes of patients who recurred following HCC resection. Of note, approximately one-third (36%) of patients recurred following curative-intent resection of HCC. Most recurrences were limited to the liver (75.5%) and occurred within 2 years after initial resection (77.2%). The majority

TABLE 3 Cox regression analysis of patient, primary, and recurrent tumor characteristics relative to post-recurrence survival

	Total	Bivariate			Multivariable		
	N (%)	HR	95% CI	p value	HR	95% CI	p value
Patient baseline characteristics							
Age, years							
≤ 65	129 (42.6)	Ref					
> 65	174 (57.4)	1.13	0.79–1.62	0.50	–		
Sex							
Male	242 (79.1)	Ref					
Female	64 (20.9)	0.81	0.52–1.26	0.35	–		
ASA-PS							
≤ 2	190 (67.9)	Ref					
> 2	90 (32.1)	1.25	0.84–1.86	0.28	–		
PLT							
< 100,000/mL	42 (14.2)	0.90	0.52–1.55	0.71	–		
> 100,000/mL	254 (85.8)	Ref					
Primary tumor pathology							
History of major resection							
No	192 (64.6)	Ref					
Yes	105 (35.4)	1.43	0.99–2.06	0.06	–		
Resection margins							
R0	262 (87.6)	Ref			Ref		
R1	37 (12.4)	1.79	1.03–3.11	**0.04**	1.58	0.83–2.99	0.16
Tumor grade							
Well/moderate	215 (72.4)	Ref			Ref		
Poor/undifferentiated	82 (26.7)	2.04	1.40–2.97	**< 0.001**	1.48	0.96–2.29	0.08
Liver capsule involvement							
No	84 (33.3)	Ref					
Yes	168 (66.7)	1.42	0.96–2.11	0.08	–		
Lymphovascular invasion							
No	162 (55.5)	Ref			Ref		
Yes	130 (44.5)	1.80	1.24–2.61	**0.002**	1.01	0.66–1.54	0.98
Recurrence characteristics							
Recurrence site[a]							
Intrahepatic	231 (75.5)	Ref			–		
Extrahepatic	46 (15.0)	1.07	0.63–1.82	0.80			
Both	29 (9.5)	1.57	0.88–2.82	0.13			
Recurrence type[b]							
Within Milan	137 (48.2)	Ref			Ref		
Beyond Milan	147 (51.8)	2.70	1.84–3.96	**< 0.001**	1.65	1.12–2.76	**0.01**
Timing of recurrence, months							
≤ 24	237 (77.2)	Ref			Ref		
> 24	70 (22.8)	0.61	0.37–0.99	**0.04**	0.91	0.49–1.68	0.76
Treatment of recurrences							
Chemotherapy or supportive tx	108 (35.2)	Ref			Ref		
Repeat hepatectomy ± ablation	33 (10.7)	0.29	0.15–0.57	**< 0.001**	0.83	0.48–1.43	0.51
Ablation ± chemotherapy	83 (27.0)	0.25	0.15–0.41	**< 0.001**	0.35	0.18–0.68	**0.002**
IAT ± chemotherapy	69 (22.5)	0.64	0.41–0.99	**0.047**	0.47	0.11–2.07	0.32
Salvage transplantation	14 (4.6)	0.15	0.05–0.47	**0.001**	0.39	0.16–0.96	**0.04**
AFP > 10 ng/mL at recurrence	137 (44.6)	2.47	1.72–3.55	**< 0.001**	1.96	1.26–3.04	**0.003**

HR hazard ratio, *CI* confidence interval, *ASA-PS* American Society of Anesthesiologists performance score, *AFP* α-fetoprotein, *IAT* intra-arterial therapy, *tx* treatment

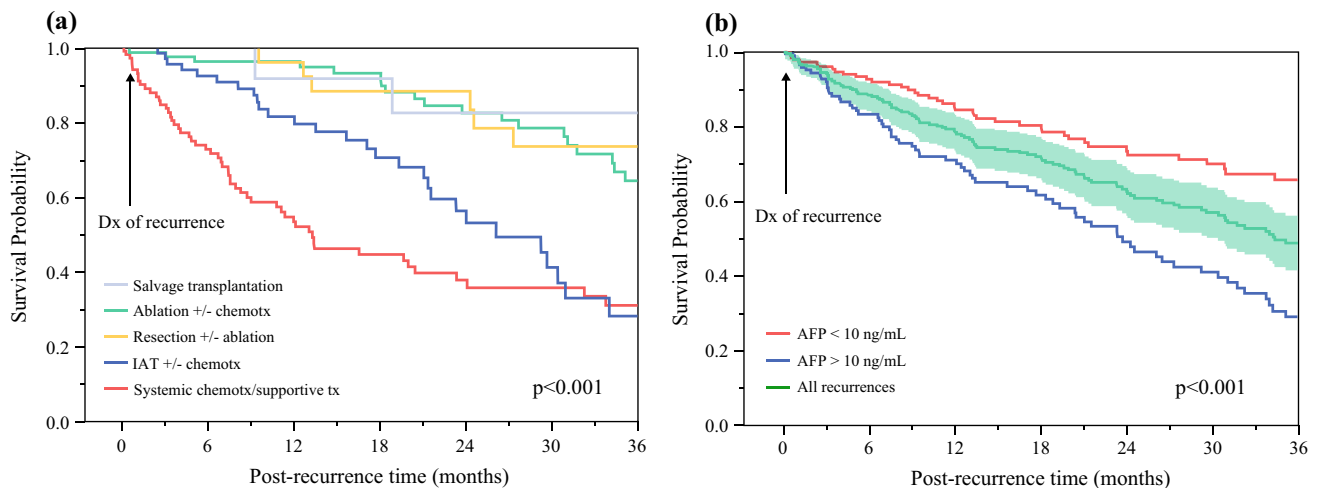[a]Among 306 patients (99.7%)

[b]Among 284 patients (92.5%)

FIG. 2 Kaplan–Meier curves demonstrating differences in post-recurrence survival according to (**a**) treatment of recurrence and (**b**) AFP levels at the time of recurrence. *AFP* α-fetoprotein, *chemotx* chemotherapy, *tx* treatment, *Dx* diagnosis, *IAT* intra-arterial therapy

of patients received aggressive curative-intent treatment for recurrent disease, which was associated with long-term survival. Importantly, AFP levels at the time of recurrence predicted post-recurrence outcomes irrespective of the timing (i.e. early vs. late), extent of recurrence (i.e. within vs. beyond the Milan criteria), and treatment modality used. After adjusting for relevant covariates, high AFP (>10 ng/mL) levels at the time of recurrence were independently associated with almost twofold higher hazards of death in the post-recurrence setting.

Previous investigators have analyzed patterns of recurrence following curative-intent resection of HCC. Of note, the vast majority of recurrences present as isolated, liver-only tumors, whereas only a minority develop at extra-hepatic locations.[9,10,19] In the current study, 75.5% of patients recurred with disease limited to the liver only, while 15.0% of patients had extrahepatic recurrence. In addition, 77.2% of HCC recurrences were diagnosed within 2 years after initial curative-intent resection, which was consistent with previous data.[9,19] Interestingly, AFP levels prior to primary tumor resection correlated significantly with AFP levels at the time of recurrence, as did the size of primary and recurrent tumors. Tabrizian et al. also reported a strong correlation between tumor size of primary and recurrent tumors and AFP levels prior to resection and after recurrence detection.[9] Several factors have been associated with prognosis in the setting of recurrent disease, including extrahepatic versus liver-only recurrence patterns.[10,17,20,21] Similarly, early recurrence following curative-intent resection has been considered an indicator of aggressive tumor biology.[10,17,20,21] Multiple recurrences, as well as recurrent disease beyond the Milan Criteria,[16] have been associated with poor outcomes.[10,17,20,21] The current study demonstrated that early recurrence was indeed associated with post-recurrence outcomes on bivariate analysis, while

recurrence beyond the Milan criteria was a strong independent predictor of poor post-recurrence outcomes (HR 1.65, 95% CI 1.12–2.76) after adjusting for other relevant clinicopathologic characteristics.

Currently there is no universal algorithm to manage recurrence after HCC resection. Patient performance status and baseline liver function, as well as burden (focality, size), location (intrahepatic, extrahepatic, both), and patterns of recurrence (within/beyond the Milan criteria, timing of recurrence) are factors that guide management.[8,10,19,22] In the present study, almost two-thirds (64.8%) of patients received curative-intent treatments for their recurrence, while the remaining individuals (35.2%) were offered palliative chemotherapy or best supportive care. Of interest, only 10% of patients with recurrence underwent repeat resection in the cohort, which was somewhat lower compared with previous case-series reports.[10,16,17,20,21,23–25] These disparate findings highlight the lack of consistency in managing patients with recurrent HCC at an individual or institutional level, as well as the high degree of heterogeneity in disease biology and clinical presentation at the time of recurrence. In addition, only 4.6% of patients underwent salvage transplantation, a treatment modality that has been used in only a few patients to date, but with promising results.[26] Perhaps not surprisingly, post-recurrence outcomes differed significantly based on the treatment modality used. Of note, patients who underwent curative-intent treatment such as surgery or ablation for recurrent disease had the best post-recurrence outcomes (Fig. 2a). The chosen treatment modality likely reflected the extent of recurrent disease and patient performance status, which presumably were more favorable among individuals who underwent liver-directed treatments for recurrence. To this point, patients undergoing salvage LT achieved a 3-year post-recurrence survival
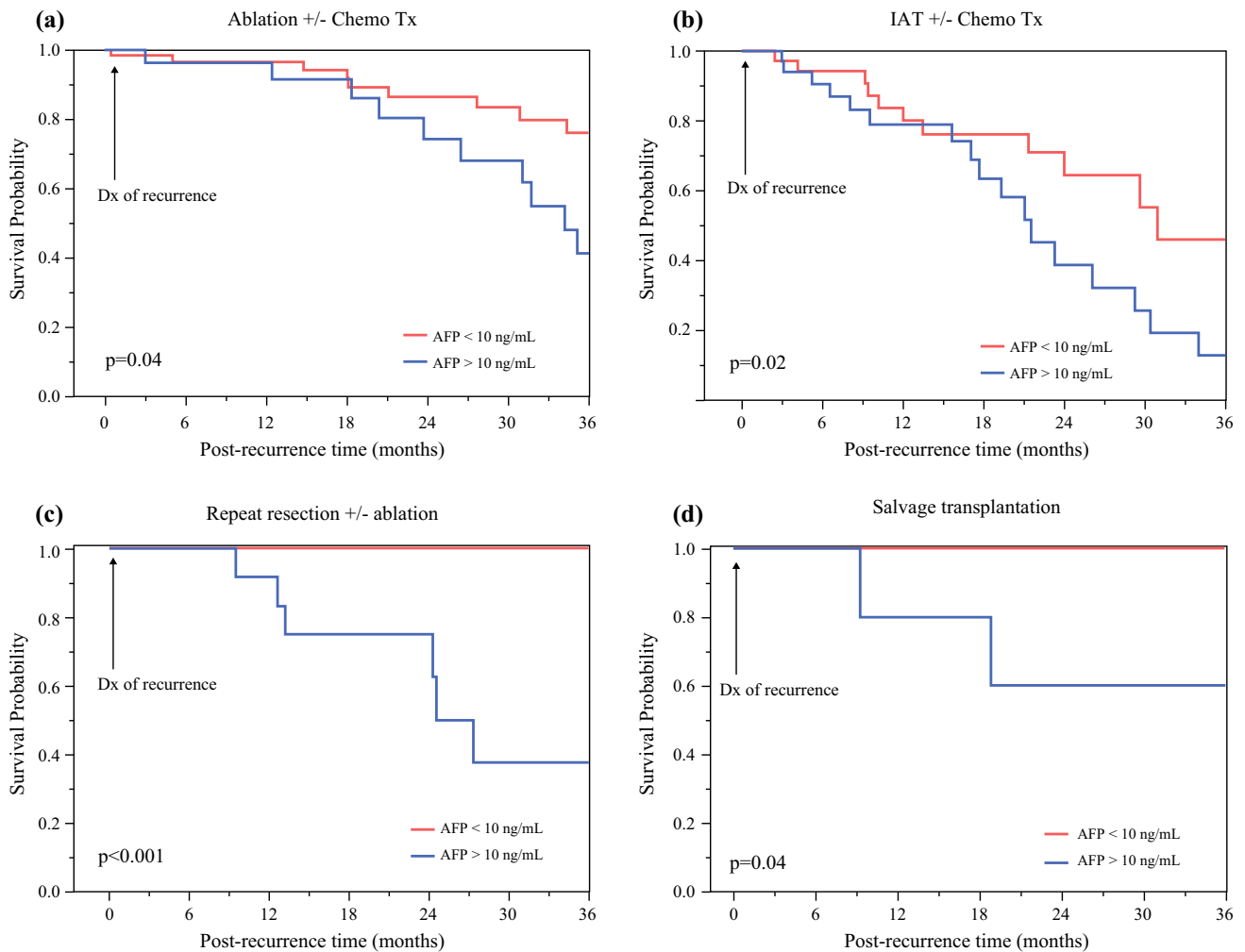
FIG. 3 Kaplan–Meier curves demonstrating differences in post-recurrence survival by AFP levels at the time of recurrence detection, stratified by treatment of recurrences (**a-d**). *AFP* α-fetoprotein, *Chemo Tx* chemotherapy, *Dx* diagnosis

of 82.5%, whereas repeat resection and ablation were associated with a 3-year post-recurrence survival of 73.6% and 64.3%, respectively. In turn, the data suggest that curative-intent treatments should be strongly considered for a subset of select patients with recurrent HCC when feasible, as this approach can be associated with improved post-recurrence survival.[9,27]

Despite the established role of preoperative AFP to screen high-risk patients, as well as inform prognosis of patients following primary HCC treatment,[28,29] the predictive role of serum AFP levels at the time of HCC recurrence has not been well examined. Elevated serum AFP at the time of HCC recurrence may be associated with worse outcomes[9] and, in some cases, with non-transplantable disease.[30] Importantly, the current study noted that patients with AFP >10 ng/mL at the time of recurrence had worse 3-year post-recurrence survival compared with individuals with AFP <10 ng/ml (28.7% vs. 65.5%, $p < 0.001$) (Fig. 2b). Of particular note, high AFP levels

were predictive of survival after HCC recurrence irrespective of the timing of recurrence (i.e. early or late recurrence) and recurrence patterns (i.e. within or beyond the Milan criteria). In fact, following curative-intent treatment of HCC, patients presenting with high AFP without radiographically evident recurrence during surveillance may frequently progress to imaging-evident recurrence.[31] Interestingly, the current study is the first to show that AFP levels at the time of recurrence were associated with post-recurrence outcomes among patients irrespective of the therapeutic modality used to treat recurrent HCC. In particular, patients who underwent ablation, IAT, resection, or salvage LT for recurrent HCC with an AFP < 10 ng/mL at the time of recurrence had improved post-recurrence outcomes compared with individuals who received the same treatment modalities with an AFP > 10 ng/mL (Fig. 3). Notably, among patients who received the most aggressive treatments for HCC resection (i.e. resection or salvage LT), no patients with

AFP < 10 ng/mL died within 3 years. After adjusting for competing risk factors, patients with AFP>10 ng/mL at the time of recurrence had almost a twofold higher hazards of death in the post-recurrence setting (HR 1.96, 95% CI 1.26–3.04, p = 0.004). Collectively, the data suggest that AFP at the time of recurrence was a strong predictor of post-recurrence outcomes and might help guide post-recurrence treatment strategies.

The current study had several limitations that should be taken into consideration when interpreting the results. Owing to the retrospective nature of the study, selection bias related to treatment options offered to patients for recurrence was possible. Decisions around treatment recurrence were at the discretion of the treating physicians at the different participating centers and thus may reflect local expertise and program capacity (i.e. transplantation). Although treatment of recurrences had an impact on post-recurrence outcomes, the retrospective nature of the study did not allow for definitive conclusions regarding the superiority of one treatment approach relative to another; however, this question was not an aim of the current work. However, the prognostic role of recurrent AFP was ascertained irrespective of the treatment modalities utilized for recurrent HCC. While the same surveillance protocol was in place for all participating institutions, deviation from these protocols may have impacted detection of recurrence. Any deviations were likely 'random' in nature and should not have biased the finding that AFP was strongly associated with outcomes after HCC recurrence.

CONCLUSION

Approximately one-third of patients developed a recurrence following curative-intent resection of HCC. The majority of patients received aggressive treatments for their recurrent disease that contributed to their long-term survival. AFP levels at the time of recurrence predicted post-recurrence survival independent of the secondary treatment modality used. Evaluating AFP levels at the time of recurrence can help inform post-recurrence risk stratification of patients with recurrent HCC.

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