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Original Article

Tumor growth rates and recurrence-free survival in chronic viral hepatitis patients with hepatocellular carcinoma

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Abstract

Aim: Survival in patients with hepatocellular carcinoma (HCC) is impacted by stage of liver disease, tumor characteristics, and HCC surveillance in high-risk individuals. Factors associated with HCC tumor growth rate (TGR) and its influence on recurrence-free survival after treatment was investigated.

Methods: TGR was calculated in 164 HCC patients with chronic viral hepatitis who had two consecutive magnetic resonance imaging or computed tomography scans $\geq$ 30 days apart prior to treatment and who were followed prospectively to determine the rates of recurrence-free survival.

Results: The median TGR in 164 patients was 17.8% per month (mean 33.3% per month). Regression tree analysis indicated that the top three predictors of TGR were alpha-fetoprotein (AFP) levels ($\geq$ 16.7 ng/mL), platelet counts ($\geq$ 140,000 mm^3), and serum albumin level (< 3.55 g/dL). The regression tree identified patient groups with TGRs ranging from 0.65% to 39.4% per month. At a median follow-up of 22 months, the overall recurrence-free survival was 53.8%. The Cox model with backwards AIC search identified TGR (HR = 1.34, P = 0.029), age > 56 years (HR = 1.08, P = 0.072), hepatitis C virus (HR = 1.44, P = 0.091), macrovascular invasion (HR = 1.94, P = 0.092), and the most definitive treatments (orthotopic liver transplantation, HR 0.14, P < 0.001; surgical resection, HR = 0.54, P = 0.072; radiofrequency ablation, HR = 0.58, P = 0.060) as independent predictors of recurrence-free survival. For all treatment modalities, slow

TGR was significant for prolonged survival (P = 0.029). The poorest survival rates were observed in patients with fast TGRs treated by transarterial chemoembolization.

Conclusion: The TGR correlated with AFP, platelet count, and albumin level. Patients with fast TGRs had shorter recurrence-free survival after HCC treatments. TGR is a potential imaging biomarker to predict clinical outcomes in HCC.

Keywords: Liver cancer, growth rates, hepatitis B, hepatitis C, hepatocellular carcinoma treatments

INTRODUCTION

Worldwide, hepatocellular carcinoma (HCC) is the fifth most frequently encountered malignancy and is the third leading cause of cancer-related deaths[1]. In the United States, the incidence of HCC has significantly increased and is projected to be among the top three causes of cancer-related deaths by 2030[2]. In addition, the financial burden of HCC in the United States has continued to increase over the last decade[3]. Numerous studies showed that the most common etiologies are chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), with HBV accounting for at least 42% and HCV accounting for at least 27% of HCC cases globally[4]. The remaining cases are associated with excessive alcohol intake and non-alcoholic steatohepatitis.

Over the last two decades, improvements in HCC survival have been made by advances in HCC treatments in surgery and interventional radiology. Furthermore, the implementation of surveillance protocols in high-risk populations has resulted in early HCC detection and improved post-treatment survival[5]. Additional factors that predict HCC survival include the degree of liver dysfunction as well as the initial tumor size and number of tumors.

Another potential factor is the tumor volume doubling time (TVDT) which is assessed by two serial radiologic imaging studies prior to HCC treatments. Initially, TVDT was used to determine suitable screening intervals for early HCC detection. Previous imaging studies reported TVDTs ranging from a median of 117 days to a mean of 127 days, and suggested intervals of 4 to 5 months for HCC screening[6,7]. Other reports showed that shorter TVDTs were correlated with earlier deaths after hepatectomies as well as higher recurrence rates after surgical resection and radiofrequency ablation[8-10].

These papers on TVDT highlight its potential value as a prognostic tool for predicting HCC survival rates. Nevertheless, some of these studies were limited by early imaging technology, variations in screening intervals, and small sample sizes. Further, a recent report indicated that the TVDT is a less suitable variable for tumor growth rate because (1) mean TVDT estimates are not accurate if the time interval measurements are short; (2) the TVDT is not defined if the consecutively estimated volumes are similar; and (3) the asymmetrical frequency distribution of the TVDT makes it less suitable for statistical analysis[11]. In contrast, the mean tumor growth rate (TGR) gives a more correct value for average growth rate and has a symmetrical frequency distribution. Thus, an improved understanding of tumor growth, as measured by TGR, may help in guiding prognostic evaluations and aid in determining treatment options for patients with HCC. In the report herein, we assessed factors associated with TGR in 164 patients with chronic viral hepatitis and HCC. In addition, we evaluated the potential value of TGR as a factor in predicting recurrence-free survival after HCC treatment in these patients.

METHODS

Patient population

Between 1984 and 2014, 357 patients with HCC were evaluated at the Liver Center in Pasadena, California. A database was created to collate and anonymize patient records, including laboratory tests, tumor size,

HCC treatments, and current status. Amongst the 357 patients, 24 individuals were excluded from this study due to diffuse appearing tumor in which the size could not be determined (22 patients) or due to an HCC diagnosis made within six months of final patient entry into the database (2 patients). Of the remaining 333 patients, 169 who began HCC treatment prior to a second tumor size measurement were also excluded. The remaining 164 patients had two consecutive imaging studies prior to HCC treatment and are the subjects in the present study. HCC lesions were detected via surveillance in 113 patients with alpha-fetoprotein (AFP) testing and US scans. The remaining 51 patients were either diagnosed by their referring physicians or during their first visit to our Liver Center. The number and size of lesions, as reported by CT scan or MRI, were recorded. The diagnostic criteria for cirrhosis were by imaging findings of a nodular surface, platlet count < 140,000 mm^3, presence of esophageal varices or ascites, or by liver biopsy.

The TGR was determined for all 164 patients. The diagnosis of HCC by MRI or CT scan were according to AASLD criteria from their 2005 and 2011 recommendations[12,13]. Prior to that time period, imaging criterion for HCC diagnosis relied on findings of a hypervascular lesion, elevated levels of AFP, tumor growth on subsequent imagin, and biopsy of the lesion if the above criteria were not clear. The dates and corresponding tumors sizes from the first and second imaging studies (CT or MRI) were recorded. The time interval between the first and second images were ≥ 30 days (median time 92 days), and all were prior to any treatments for HCC[5].

Baseline laboratory tests

Baseline laboratory tests were obtained from all patients. These included platelet counts, serum albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and AFP. For HBV patients, virus genotype, HBV DNA levels, precore mutation, basal core promoter mutation, and HBeAg were recorded. For HCV patients, virus genotype and HCV RNA levels were recorded. Sera from patients whose HCC was diagnosed prior to 1991 were retrospectively tested for anti-HCV antibodies and HCV RNA.

HCC treatments

Of the 164 patients followed in this study, 113 received definitive treatments, 7 received chemotherapy, and 44 were offered supportive care. HCC patients were referred to academic centers for surgical and/or locoregional therapies. Treatment options included orthotopic liver transplantation (OLT), surgical resection, RFA, transcatheter arterial chemoembolization (TACE), or percutaneous ethanol injection (PEI). If a patient had multiple treatments, they were assigned to the most definitive treatment category. OLT, surgical resection, and RFA were considered to be the most definitive treatments. Patients who did not receive one of the above treatments were given chemotherapy or supportive care.

Post-treatment outcomes

Patients who returned for regular follow-up care were continuously screened with imaging studies and laboratory tests. In order to calculate dates of recurrence-free survival, dates of diagnosis, initial treatment, recurrence, and latest follow-up or death were recorded.

Statistical analyses

Tumor growth rate calculation

The TGR was calculated using Schwartz's equation: $TGR = \log(V/V_0)/(T - T_0)$ where $T - T_0$ indicates the time interval between the two measurements and V_0 and V represent the tumor volumes ($V = 4/3pR^2$) at the two measurement points[14]. The Schwartz equation assumes early, exponential stage growth with the TGR reported in % per month. In the analyses below, $\log_{10}$ TGR is used since log TGR has a distribution closer to the normal distribution.

Predictors of tumor growth rate
Bivariate analysis - The bivariate analysis for assessing each categorical predictor *vs.* log TGR was computed using *t*-tests/analysis of variance. The correlation between $\log_{10}$ TGR and continuous variables was computed via the Spearman correlation (r_s).

Multivariate analysis - The multivariable regression tree (binary partition) analysis was used to determine the simultaneous association between $\log_{10}$ TGR and 19 potential predictors, including age, gender, ethnicity, HCC surveillance, serum albumin, serum AFP, platelet count, cirrhosis, diabetes, initial tumor size, HBV or HCV infection, and antiviral treatment. For hepatitis B patients, HBV genotype, HBV DNA, precore mutation, basal core promoter mutation, and HBeAg values were included. For hepatitis C patients, HCV RNA and genotype were included. In this tree model, every value of each predictor variable was considered. Patients with slow *vs.* fast TGRs were separated via a progression of binary splits (partitions). The best split was determined by the impurity criterion, a reduction of the residual sum of squares due to the binary split (GINI criterion). Missing values were allowed. Each split resulted in one parent node and two child nodes. Child nodes, in turn, were split until further splits did not significantly improve the predicted TGR. The final result was an intuitive and interpretable decision tree[15]. A *P* < 0.07 was considered statistically significant.

Predictors of recurrence-free survival
Predictors of HCC recurrence-free survival were analysed. The outcome (event) was HCC recurrence or death. The primary predictor was $\log_{10}$ TGR. The other 9 potential predictors were age, gender, ethnicity, HCV or HBV, diabetes, cirrhosis, macrovascular invasion, HCC surveillance, and the most definitive treatments (OLT, surgical resection, RFA, PEI, TACE, chemotherapy, or supportive) for a total of 10 potential predictors. There were 125 events, 39 HCC recurrences and 85 deaths with no recurrence.

Bivariate analysis - Hazard ratios (HR) for each potential predictor, ignoring the other 9 predictors, were computed along with its 95% confidence bounds and *P*-values. Restricted cubic splines were used to determine if the relation between a continuous predictor *vs.* the log hazard ratio was linear.

Multivariate analysis - The 10 potential predictors simultaneous to the event rate were assessed using a Cox proportional hazard model. A backwards minimal AIC search was used to determine which of the potential predictors were significant, with the restriction that $\log_{10}$ TGR was included in all models. For the final model, all possible two-way interactions were evaluated. Statistical significance was taken as *P* < 0.07. Model accuracy was assessed using Harrell's C concordance statistic with values of C ranging from 0.50 (worse) to 1.0 (best).

RESULTS

The baseline characteristics of 164 HCC patients who had two consecutive imaging studies with either MRI or CT scans prior to treatments are listed in Table 1. The average age was 64.48 ± 10.38 years, 64.6% were male, and the majority were Asian (64.0%), followed by white (18.3%), Hispanic (14.0%), and African American (3.70%). Hepatitis B infection was detected in 39.6% of patients, Hepatitis C infection in 59.8%, and the remaining patients were co-infected with both viruses. In the HBV infected HCC patients with measurable tests, 21.5% were HBeAg positive, 29.2% were genotype C, 30.8% had basal core promoter mutations, 23.1% had precore mutations, and the mean HBV DNA level was 2.41×10^6 IU/mL (IQR: 1.00-1.23 $\times 10^5$). In the HCV infected HCC patients with measurable tests, 45.9% had genotype 1 and the mean HCV RNA was 1.44×10^6 IU/mL (IQR: 594.5 - 1.27×10^6). The mean albumin level was 3.80 ± 0.66 g/dL, platelet count was 138,000 ± 75,600 mm^3, and AFP level was 45.2 ± 11.8 ng/mL. Of 164 HCC patients, 68.9% were detected by surveillance. 19.5% had diabetes, 78.7% had cirrhosis, and 5.50% had macrovascular invasion.

Table 1. Baseline characteristics of 164 patients with hepatocellular carcinoma

Characteristic	Number (%) or Mean $\pm$ SD
Age at diagnosis (years)	64.48 $\pm$ 10.38
Gender	
Female	58 (35.4)
Male	106 (64.6)
Ethnicity	
African American	6 (3.70)
Asian	105 (64.0)
Hispanic	23 (14.0)
White	30 (18.3)
Virology	
HBV	65 (39.6)
HCV	98 (59.8)
HBV + HCV	1 (0.60)
HBV genotype	
A	3 (4.62)
B	10 (15.4)
C	19 (29.2)
F	1 (1.54)
Missing	32 (49.2)
HBV precore mutation	
Yes	15 (23.1)
No	18 (27.7)
Missing	32 (49.2)
HBV basal core promoter mutation	
Yes	20 (30.8)
No	8 (12.3)
Missing	37 (56.9)
HBeAg	
Negative	42 (64.6)
Positive	14 (21.5)
Missing	9 (13.8)
HBV DNA (IU/mL)*	2,411,000 (IQR: 1.00-123,400)
HCV genotype	
1	45 (45.9)
2	17 (17.3)
3	6 (6.12)
6 or 7	7 (7.14)
Mixed	2 (2.04)
Missing	21 (21.4)
HCV RNA (IU/mL)*	1,442,000 (IQR: 594.5-1,270,000)
Antiviral treatment	
Yes	50 (30.5)
No	108 (65.9)
Missing	6 (3.60)
Albumin (g/dL)	3.80 $\pm$ 0.66
Total bilirubin (mg/dL)	1.30 $\pm$ 1.20
Alkaline phosphate (U/L)	128 $\pm$ 129
AST (U/L)	78.2 $\pm$ 59.2
ALT (U/L)	70.1 $\pm$ 54.3
Platelet count ($\times 10^3$ mm^3)	138 $\pm$ 75.6
AFP (ng/mL)	45.2 $\pm$ 11.8
Surveillance	
Yes	113 (68.9)
No	51 (31.1)
Diabetes	
Yes	32 (19.5)
No	125 (76.2)
Missing	7 (4.27)

Cirrhosis	
Yes	129 (78.7)
No	35 (21.3)
Macrovascular invasion	
Yes	9 (5.50)
No	149 (90.9)
Missing	6 (3.60)
Initial tumor size (cm)	3.62 ± 2.27

*Interquartile range (IQR) opted over mean ± SD for accuracy. HBV: hepatitis B virus; HCV: hepatitis C virus; HBeAg: hepatitis B e-antigen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; AFP: alpha-fetoprotein

The tumor growth rate

The mean initial tumor size was 3.62 ± 2.27 cm. The TGR in 164 HCC patients ranged from 0% per month to 440.2% per month with a median growth rate of 17.8% per month and a mean growth rate of 33.3% per month. Bivariate predictors of log TGR are shown in Table 2. HCC patients with serum albumin levels ≤ 3.50 g/dL had a median TGR of 27.0% per month while those with albumin levels of > 3.50 g/dL had a median growth rate of 14.2% per month (P = 0.016). HCC patients with AFP levels ≤ 10.0 ng/mL had slower average growth rates compared to patients with AFP levels of 11.0-191 ng/mL and > 191 ng/mL (11.1%, 18.7%, and 30.3% respectively, P = 0.029). Also, HCC patients with diabetes had slower growth rates compared to those without diabetes (10.5% and 21.6% respectively, P = 0.051).

Of the 19 variables evaluated, the regression tree model identified AFP < or > 16.7 ng/mL as the best single discriminator between slow and fast growing tumors expressed in log TGR. The next best predictor of TGR in the high AFP node was platelet counts < or > 140,000 mm^3. For the node with patients having an AFP ≥ 16.7 ng/mL and a platelet count < 140,000 mm^3, an albumin level < or > 3.55 g/dL provided additional prognostic value. Further analysis identified age at < or > 56 years and ethnicity as other significant variables. As shown in Figure 1, an AFP value of < or > 16.7 ng/mL best discriminated slow and fast-growing tumors (10.9% per month and 23.8% per month respectively, P = 0.050). Within the AFP ≥ 16.7 ng/mL node, platelet counts of < or > than 140,000 mm^3 next discriminated TGRs of 21.0% per month and 39.4% per month respectively (P = 0.085). In the platelet count < 140,000 mm^3 node, albumin level ≥ 3.55 g/dL identified the slower growing tumors with a TGR of 9.15% per month, while those with albumin level < 3.55 g/dL had a TGR of 31.4% per month (P = 0.0004). Within the albumin level < 3.55 g/dL node, ethnicity other than Hispanic had a faster TGR (36.4% per month *vs.* 11.4% per month, P = 0.005). Finally, within the albumin ≥ 3.55 g/dL node, age < or > than 56 years had TGRs of 0.65% per month and 15.7% per month respectively.

The survival outcomes

The overall recurrence-free survival for 164 HCC patients is shown in Figure 2. At a median time of 22 months, 53.8% of the HCC patients were alive and recurrence-free. A bivariate analysis which included 10 potential predictors showed that the TGR (HR = 1.27, P = 0.061), age (HR = 1.02, P = 0.006), HCV (HR = 1.42, P = 0.061), surveillance (HR = 0.70, P = 0.065), and the most definitive treatments (OLT, HR = 0.13, P < 0.0001; surgical resection, HR = 0.40, P = 0.004; RFA, HR = 0.50, P = 0.010) were significant predictors of tumor free survival [Table 3].

Multivariate analysis using the Cox model with backward AIC search identified TGR (HR = 1.34, 95%CI: 1.03-1.74, P = 0.029), age > 56 years (HR = 1.08, 95%CI: 0.99-1.18, P = 0.072), HCV (HR = 1.44, 95%CI: 0.94-2.20, P = 0.091), macrovascular invasion (HR = 1.94, 95%CI: 0.90-4.18, P = 0.092), and the most definitive treatments (OLT, HR = 0.14, P < 0.0001; surgical resection, HR = 0.54, P = 0.072; RFA, HR = 0.58, P = 0.060) as simultaneous independent risk factors for recurrence-free survival. To evaluate the effect of the same level of slow or fast growth rate on recurrence-free survival, the 164 patients were divided into equal-sized groups below and above the median TGR (17.8% per month). The median TGR in the slower group was 4.58%

Table 2. Bivariate predictors of tumor growth rate

	n	Median TGR (%/mo)	Q1-Q3 (%/mo)	*P*-value
Gender				
Female	58	15.6	4.60-35.9	0.6560
Male	106	19.3	4.90-40.4	
Ethnicity				
African American	6	9.10	0.70-19.3	0.2526
Asian	105	18.0	5.40-38.4	
Hispanic	23	11.8	2.40-34.4	
White	30	26.3	6.00-47.9	
Virology				
HBV	65	23.2	5.40-42.4	0.3284
HCV	98	16.6	4.10-33.4	
HBV + HCV	1	2.20	--	
HBV genotype				
A	3	33.0	4.60-59.6	0.5253
B	10	17.9	3.30-38.5	
C	19	21.8	9.60-51.7	
F	1	--	--	
HBV precore mutation				
Yes	15	28.7	8.10-54.0	0.4053
No	18	22.5	11.3-76.8	
HBV basal core promoter mutation				
Yes	20	22.5	10.3-50.4	0.7229
No	8	17.8	6.30-41.1	
HBeAg				
Negative	42	20.5	4.90-37.8	0.3877
Positive	14	30.8	7.70-68.5	
HBV DNA				
Negative	3	42.4	5.30-64.9	0.7686
Positive	54	21.1	5.20-35.6	
HCV genotype				
1	45	12.9	2.30-28.1	0.1408
2	17	22.0	9.20-42.3	
3	6	29.3	23.5-44.3	
6/7/mixed	9	3.00	2.20-32.5	
HCV RNA				
Negative	15	14.4	4.70-26.2	0.3802
Positive	61	15.2	3.10-28.5	
Antiviral treatment				
Yes	50	18.6	2.30-37.8	0.8826
No	108	17.8	7.10-36.8	
Albumin (g/dL)				
≤ 3.50	55	27.0	8.00-46.3	0.0161
> 3.50	109	14.2	2.60-32.5	
AFP (ng/mL)				
≤ 10.0	54	11.1	2.50-28.3	0.0294
10.0-191	66	18.7	7.40-34.8	
> 191	40	30.3	4.20-75.2	
Platelet count ($\times 10^3$ mm^3)				
≤ 75.0	34	23.7	7.70-39.5	0.2834
75.0-150	62	15.4	2.50-31.7	
> 150	64	20.4	7.10-41.8	
Surveillance				
Yes	113	18.0	4.30-38.4	0.5565
No	51	15.2	5.00-37.6	
Diabetes				
Yes	32	10.5	2.00-28.1	0.0506
No	125	21.6	5.60-42.3	
Cirrhosis				

Yes	129	17.7	4.10-38.4	0.5418
No	35	17.9	8.10-36.9	

TGR: tumor growth rate; HBV: hepatitis B virus; HCV: hepatitis C virus; HBeAg: hepatitis B e-antigen; AFP: alpha-fetoprotein
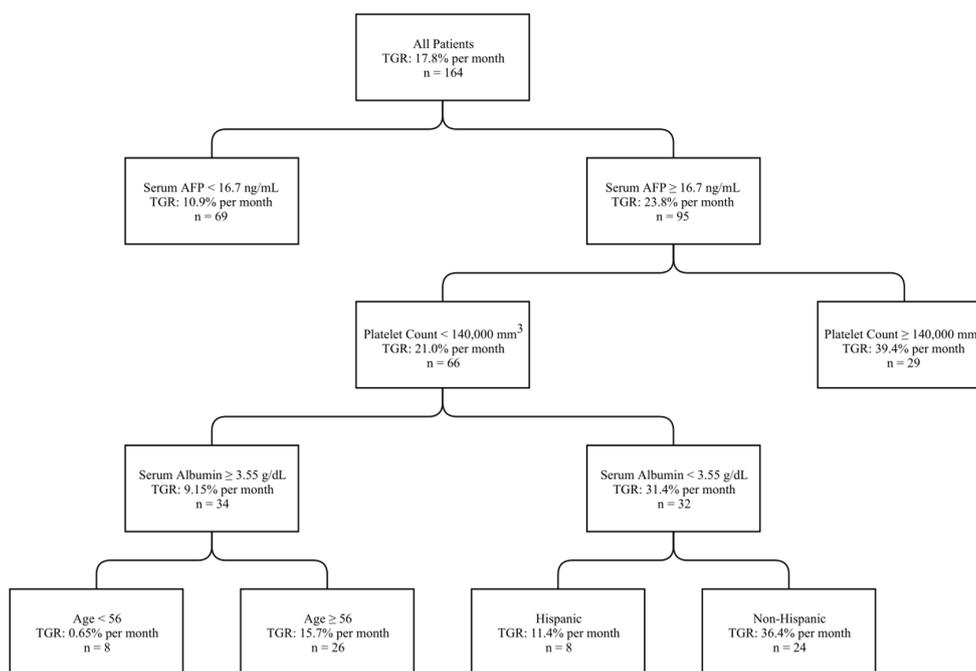
Figure 1. Regression tree analysis: predictors of hepatocellular carcinoma tumor growth rates. Each node is based on available data for each predictive variable presented. TGR is reported as a median. TGR: tumor growth rate; AFP: alpha-fetoprotein

per month and the median TGR in the faster group was 38.9% per month. As illustrated in Figure 3, the recurrence-free survival in patients who received OLT, surgical resection, or RFA was significantly longer in patients with slow TGRs for each treatment modality (P = 0.029). Patients who received OLT who had slow TGRs had the longest recurrence-free survival. Those HCC patients who received surgical resection or RFA had similar survival rates in both the slow and fast TGR groups. The poorest recurrence-free survivals were observed in the TACE treated or supportive care patients with fast TGRs.

DISCUSSION

Previous reports have utilized MRI or CT to find potential biomarkers to predict clinical outcomes in patients with HCC. Using MRI, one report showed that patients with fat-containing HCC had less tumor progression, less distant metastases, and a longer time to tumor progression when compared to patients with non-fat containing HCC[16]. Another report showed that patients with complete tumor encapsulation on MRI had lower AFP levels, an absence of vascular invasion, more patients in Child-Pugh class A, and significantly longer survivals[17]. Further, the authors also noted that the rates of downstaging and eventual liver transplantation were significantly higher. However, recognition of these imaging features depends on the expertise of the interpreting radiologist and may be challenging to implement as a practical clinical tool. Nevertheless, efforts to standardize imaging reporting (i.e., Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN) and Liver Imaging Reporting and Data System (LI-RADS) criterion) may allow incorporation of additional important imaging biomarkers for tumor prognosis[18,19]. As tumor size is already a basic measure reported with all detected tumors, the calculation of TGR is feasible when serial imaging is available and, thus, may be considered as another potential imaging biomarker.
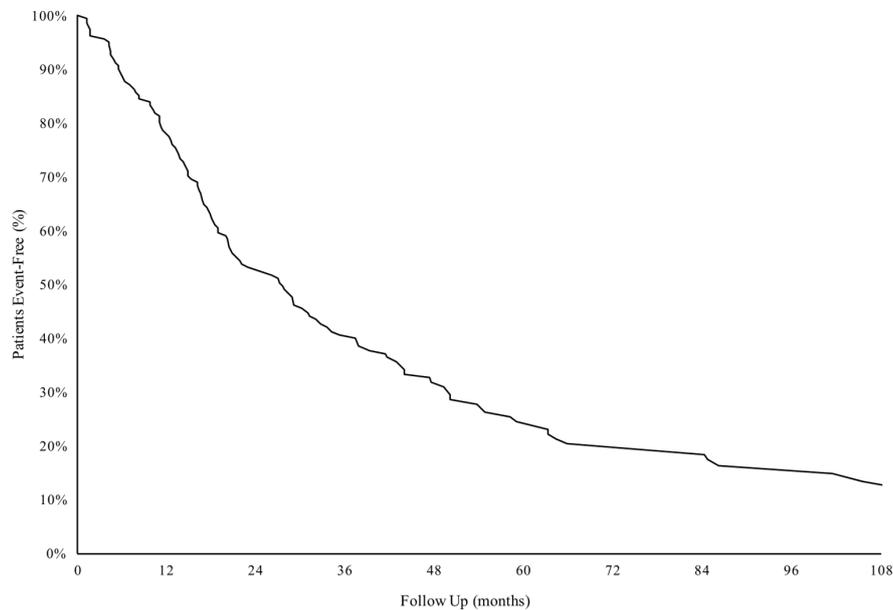
Figure 2. Recurrence-free survival of 164 patients with hepatocellular carcinoma

In the report herein, we first attempted to determine factors associated with tumor growth rate in patients with HBV- and HCV-related HCC. By regression tree analysis of 19 variables, AFP levels < or > 16.7 ng/mL best discriminated between slow and fast growing tumors respectively [Figure 1]. In a previous report, the initial AFP levels did not correlate with tumor growth rate but, in those patients with repeated AFP values which showed an exponential increase in AFP, the AFP doubling time was closely related to the tumor doubling time[6]. Other studies comparing AFP values > 100 ng/mL, > 200 ng/mL, and > 400 ng/mL showed that each of the AFP levels correlated with faster tumor doubling times[10,11,20]. These findings indicate that elevated AFP levels are significant indicators of tumor doubling time.

In patients with AFP ≥ 16.7 ng/mL, the next best discriminator was platelet counts < or > 140,000 mm^3. Within the platelet count ≥ 140,000 mm^3 node, the mean platelet count was 201,345 mm^3 (median 192,000 mm^3). There were only two patients with thrombocytosis (385,000 mm^3 and 420,000 mm^3). In previous reports, thrombocytosis was noted in 2.70% to 8.20% of HCC patients and was associated with overproduction of thrombopoietin by liver cancer cells[21,22]. In these studies, thrombocytosis was associated with larger tumor volumes and higher levels of serum AFP in Asian HCC patients, and with larger tumor sizes, younger patients, and less cirrhosis in European HCC patients. One possible explanation for large tumor sizes in patients with higher platelet counts or in cirrhotic patients with "higher than expected" platelet counts is that platelets are a source of a number of HCC growth stimulants including vascular endothelial growth factor, platelet-derived growth factor, serotonin, and fibroblast growth factor[22]. In the study herein, patients with platelet counts ≥ 140,000 mm^3 had a faster mean TGR compared to those with platelet counts < 140,000 mm^3 (39.4% per month *vs.* 21.0% per month, respectively).

There have been few reports on the relationship between serum albumin levels and tumor doubling time. In earlier studies, Child-Pugh scores did not influence tumor doubling times[6,20]. A recent study showed that Korean HCC patients with tumor doubling times < 2 months had significantly lower mean albumin levels than those with tumor doubling times > 2 months (3.20 g/dL *vs.* 3.50 g/dL, $P = 0.003$)[23]. In our report, the TGR of patients in the platelet count < 140,000 mm^3 node were further discriminated into fast and slow TGR by albumin levels < or > than 3.55 g/dL (31.4% per month *vs.* 9.15% per month). This finding suggests that cirrhosis patients with poor liver synthetic function have less ability to confine the growth of HCC.

Table 3. Bivariate and multivariate analysis of recurrence-free survival

	Bivariate analysis				Multivariate analysis			
	n	HR	95%CI	*P*-value		HR	95%CI	*P*-value
TGR (%/mo)	164	1.27	0.99-1.63	0.0612	TGR (%/mo)	1.34	1.03-1.74	0.0289
Age (years)	164	1.02	1.01-1.04	0.0059	Age (years)	1.08	0.99-1.18	0.0717
Hepatitis virus					Hepatitis virus			
HBV	65	ref			HBV	ref		
HCV	98	1.42	0.98-2.06	0.0606	HCV	1.44	0.94-2.20	0.0905
HBV + HCV	1	--	--		HBV + HCV			
Sex								
Female	58	ref						
Male	106	0.87	0.60-1.25	0.449				
Ethnicity								
African American	6	ref						
Asian	105	1.57	0.50-4.97	0.4441				
Hispanic	23	2.31	0.67-7.90	0.1826				
White	30	1.78	0.53-5.92	0.3502				
Diabetes								
No	125	ref						
Yes	32	0.90	0.57-1.42	0.6410				
Macrovascular invasion					Macrovascular invasion			
No	149	ref			No	ref		
Yes	9	1.64	0.80-3.38	0.1789	Yes	1.94	0.90-4.18	0.0916
Cirrhosis								
No	35	ref						
Yes	129	1.08	0.69-1.67	0.7429				
Surveillance								
No	51	ref						
Yes	113	0.70	0.48-1.02	0.0647				
Treatment					Treatment			
Supportive	44	ref			Supportive	ref		
Chemotherapy	7	1.78	0.79-4.00	0.1654	Chemotherapy	3.00	1.28-7.01	0.0112
OLT	26	0.13	0.06-0.27	0	OLT	0.14	0.07-0.30	0
Resection	21	0.40	0.21-0.74	0.0039	Resection	0.54	0.28-1.06	0.0716
RFA	29	0.50	0.29-0.84	0.0099	RFA	0.58	0.33-1.02	0.0596
PEI	7	0.59	0.25-1.40	0.2324	PEI	0.67	0.25-1.79	0.4249
TACE	30	0.92	0.57-1.50	0.7464	TACE	1.15	0.68-1.93	0.6056

TGR: tumor growth rate; HBV: hepatitis B virus; HCV: hepatitis C virus; OLT: orthotopic liver transplantation; RFA: radiofrequency ablation; PEI: percutaneous ethanol injection; TACE: transarterial chemoembolization

In our study, TGR significantly influenced recurrence-free survival in patients who received OLT, surgical resection, or RFA. In each of these treatments, recurrence-free survival was significantly longer in patients with slow TGRs. Prolonged recurrence-free survival was observed in patients with slow TGRs who received OLT. The recurrence-free survival was similar in patients with slow or fast TGRs who received surgical resection or RFA. Also, survival was similar in patients who had TACE or supportive care, regardless of TGRs. The poorest recurrence-free survival was observed in patients who received either of the latter two treatments and who had fast TGRs. These findings indicate that TGRs may be a useful biomarker when evaluating HCC patients for treatments and in predicting outcomes to therapies.

While this study strongly supports TGR as a simple imaging-based prognostic biomarker, we should comment that both OPTN and LI-RADS use 6 month threshold growth of 50% as an ancillary criteria for HCC diagnosis, largely based on expert opinion from the OPTN imaging committee[20,21]. We believe that this diagnostic definition may be too restrictive in patients with fast TGRs and may possibly affect prognosis since potential HCCs with a fast TGR may be left untreated for an extended period if the OPTN and LI-RADS criterion is used. Therefore, measurement of TGR may also be of use in establishing criteria
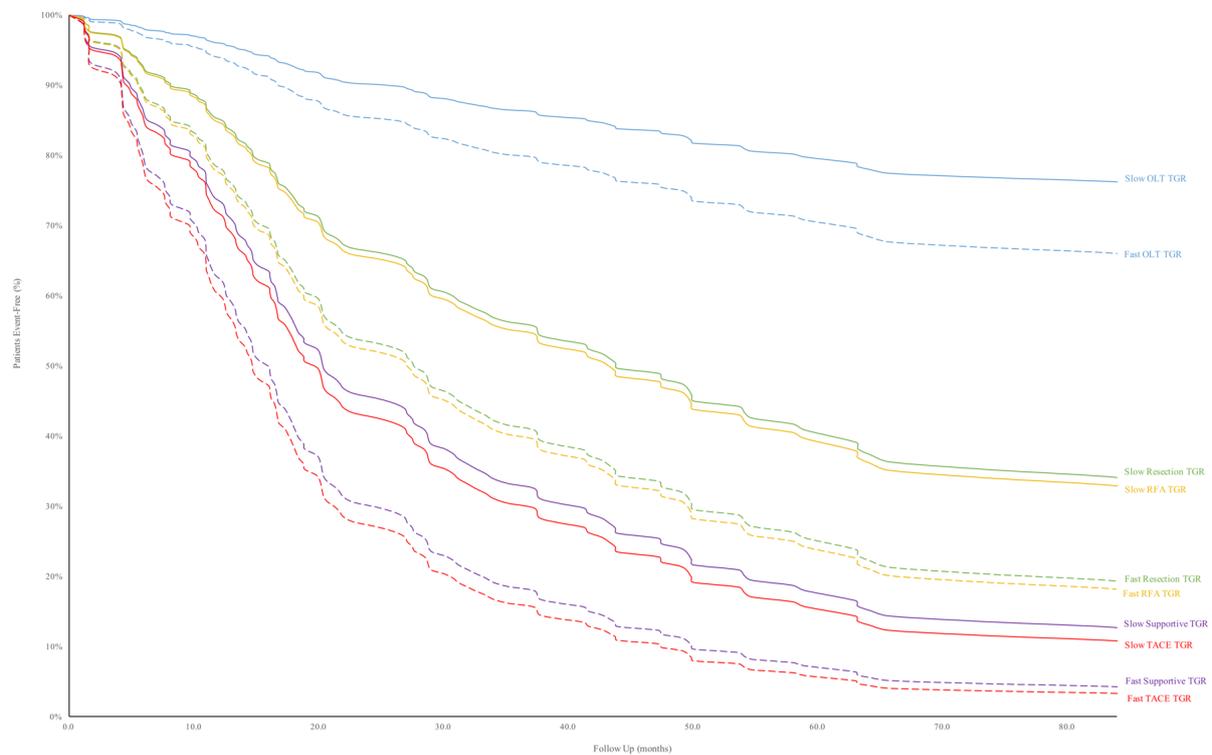
Figure 3. Recurrence-free survival in hepatocellular carcinoma patients with slow vs. fast tumor growth rate by treatment category. TGR: tumor growth rate; OLT: orthotopic liver transplantation; RFA: radiofrequency ablation; TACE: transarterial chemoembolization

for diagnosis of early HCC. Future studies using TGR along with other imaging criteria will assist in this endeavor.

There are limitations to our study. This was a retrospective analysis of HCC patients from a single community specialty clinic. However all HCC treatments were performed at a university center where multi-disciplinary subspecialities were active in the care of these patietns. This scenario is much more representative of the real world setting since issues of long-term follow-up, financial constraints, and day to day care all came into play. Also, patients who did not have a second imaging study prior to HCC treatments were excluded from our analysis which may have biased patient selection. We did not compare the clinical outcome between patients who did or did not have a second imaging study, which may have clarified this issue. Also, we excluded patients with diffuse tumors since the diameter of the tumor could not be determined. However, these patients are usually not eligible for surgical or interventional radiologic treatment and have much shorter life expectancies. Further, only HCC patients with HBV or HCV were evaluated in this report. As such, additional studies should include other disease entities such as alcohol-related and nonalcoholic fatty liver disease-related HCC cases.

In summary, our findings suggest that TGR is influenced by AFP, platelet counts, and albumin levels. TGR significantly influenced recurrence-free survival and response to surgical and locoregional treatments and may be another potential imaging biomarker to predict clinical outcomes in patients with HCC.

DECLARATIONS

Acknowledgments

Authors' contributions
Study concept and design: Tong MJ
Acquisition of data: Kaki DA, Huynh CT
Analysis and interpretation of data: Tong MJ, Raman SS, Lu DS
Drafting the manuscript: Tong MJ, Kaki DA, Raman SS, Lu DS
Critical revision of the manuscript: Tong MJ, Raman SS, Lu DS

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All authors declared that there are no conflicts of interest.

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