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Hepatocellular Carcinoma Demonstrates Heterogeneous Growth Patterns in a Multicenter Cohort of Patients With Cirrhosis

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BACKGROUND AND AIMS: There are limited data on hepatocellular carcinoma (HCC) growth patterns, particularly in Western cohorts, despite implications for surveillance, prognosis, and treatment. Our study's aim was to quantify tumor doubling time (TDT) and identify correlates associated with indolent and rapid growth.

APPROACH AND RESULTS: We performed a retrospective multicenter cohort study of patients with cirrhosis diagnosed with HCC from 2008 to 2017 at six US and European health systems with two or more contrast-enhanced imaging studies performed ≥ 30 days apart prior to HCC treatment. Radiologists independently measured tumors in three dimensions to calculate TDT and specific growth rate (SGR). We used multivariable ordinal logistic regression to identify factors associated with indolent (TDT > 365 days) and rapid (TDT < 90 days) tumor growth. In the primary cohort (n = 242 patients from four centers), median TDT was 229 days (interquartile range [IQR], 89-627) and median SGR was 0.3% per day (IQR, 0.1%-0.8%). Over one-third (38%) of HCCs had indolent growth, 36.8% intermediate growth, and 25.2% rapid growth. In multivariable analysis, indolent growth was associated with larger tumor diameter (odds ratio [OR], 1.15, 95% confidence interval [CI], 1.03–1.30) and alpha-fetoprotein < 20 ng/mL (OR, 1.90; 95% CI, 1.12-3.21). Indolent growth was more common in nonviral than viral cirrhosis (50.9% versus 32.1%), particularly in patients with T1 HCC (OR, 3.41; 95% CI, 1.08-10.80). Median TDT (169 days; IQR 74-408 days) and SGR (0.4% per day) were similar in an independent cohort (n = 176 patients from two centers).

CONCLUSIONS: In a large Western cohort of patients with HCC, we found heterogeneous tumor growth patterns, with one-fourth exhibiting rapid growth and over one-third having indolent growth. Better understanding different tumor growth patterns may facilitate a precision approach to prognostication and treatment. (Hepatology 2020;72:1654-1665).

Tumor growth patterns have several implications for clinical care including informing optimal surveillance intervals and understanding prognosis. Cancer screening programs are typically most effective when tumors grow gradually and predictably, allowing for detection at an early stage and subsequent treatment to improve survival. Detection of indolent tumors can result in overdiagnosis, i.e.,

Abbreviations: AFP, alpha-fetoprotein; BMI, body mass index; CI, confidence interval; CT, computerized tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IQR, interquartile range; LI-RADS, Liver Imaging Reporting and Data System; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; QEHB, Queen Elizabeth Hospital Birmingham; SGR, specific growth rate; TDT, tumor doubling time; UCSF, University of California San Francisco.

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detection of disease that would not otherwise impact a person's life span,[1] and overtreatment, resulting in physical, psychological, and financial harms without demonstrated benefit,[2] whereas aggressive tumors are more likely to be missed by screening, present at a late stage, and have poor response to cancer-directed therapies.[3-5] Studies have demonstrated wide variation in growth patterns between cancers, with prostate cancer[6] epitomizing indolent tumor biology and pancreatic cancer[7,8] aggressive tumor biology.

Tumor growth patterns have not been well characterized for hepatocellular carcinoma (HCC), the fastest-rising cause of cancer-related death in the United States.[9] HCC is traditionally regarded as an aggressive malignancy with overall 5-year survival of < 20%[10,11]; however, its natural history and response to treatment can be heterogeneous, and tumor growth patterns have not been well characterized. Most data describing HCC growth patterns were derived from hepatitis B virus (HBV)–infected patient populations from Asia, which may not accurately reflect tumor biology in Western patient populations, where chronic hepatitis C virus (HCV) and nonviral liver disease are the predominant causes of HCC.[12-14] Further, existing literature is limited by small sample sizes, use of inadequate imaging techniques with less precise tumor measurements, outdated definitions for HCC, and reliance on unidimensional or bidimensional tumor measurements.[12-15] As most patients with HCC are diagnosed based on imaging characteristics,[16] it is also important to identify clinical and radiological factors that can help predict tumor growth.

In this study, we aimed to characterize HCC growth patterns in a large, contemporary, and diverse cohort of patients with various etiologies of cirrhosis from six health systems in the United States and Europe.

Methods

PRIMARY COHORT STUDY POPULATION

Eligible patients were identified using prospectively maintained databases of consecutive patients diagnosed with HCC between 2008 and 2017 at four medical centers in the United States (University of Texas Southwestern Medical Center, Parkland Health and Hospital System, McGuire VA Medical Center, and University of Michigan). Each site has a multidisciplinary tumor board, where imaging studies are reviewed and management of HCC is discussed. We

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included patients with two or more contrast-enhanced multiphase computed tomography (CT) or magnetic resonance imaging (MRI) examinations performed ≥ 30 days apart, prior to any HCC treatment. Subsequent cross-sectional imaging was performed for several reasons including delays in treatment,[17] poor liver function precluding treatment, patient refusal of treatment, small tumors undergoing "watchful waiting" while on a liver transplant waiting list, and routine follow-up. Patients were required to have met current imaging criteria for HCC (Liver Imaging Reporting and Data System [LI-RADS] 5 as defined per American Association for the Study of Liver Diseases guidelines and LI-RADS, version 2018)[18,19] on both imaging studies upon independent radiology review for the purposes of this study, as detailed below. We excluded patients without cirrhosis; patients with only ultrasound imaging, including contrast-enhanced ultrasound, given imperfect characterization of tumor diameter; and patients with infiltrative-type tumors or macrovascular invasion on index imaging study, given the inability to accurately determine initial tumor diameter. This study was approved by the institutional review board at each site, including the University of Texas Southwestern Medical Center, which served as the data coordinating center.

VERIFICATION COHORT STUDY POPULATION

We used data characterizing an independent cohort from the Queen Elizabeth Hospital Birmingham (QEHB) and the University of California San Francisco (UCSF) to verify tumor growth rates observed in the primary study cohort. Patients were recruited to the QEHB study from 2012 to 2015 and at UCSF from 2005 to 2013. As above, all patients had LI-RADS 5 lesions with two or more contrast-enhanced CTs or MRIs performed ≥ 30 days apart, prior to any HCC treatment. All of the patients from UCSF had T1 lesions (i.e., unifocal lesions 1-2 cm in size), whereas patients from QEHB mirrored that of the primary cohort; however, all tumors were within the Milan criteria. Both centers excluded patients with infiltrative tumors, vascular invasion, metastatic disease, and alpha-fetoprotein (AFP) > 1,000 ng/mL at the time of HCC diagnosis. Tumor measurements were obtained on review of radiology reports from the electronic medical record.

DATA COLLECTION

For both cohorts, detailed demographic, clinical, laboratory, and radiologic data were collected from the electronic medical record at each site. Race/ethnicity was determined by self-report from patients at the time of clinic visits and characterized as non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other.[20] Variables of interest included liver disease etiology, body mass index (BMI), AFP, Child-Pugh score, Model for End-Stage Liver Disease (MELD) score, and neutrophil-to-lymphocyte ratio at the time of initial imaging. Liver disease etiology was determined using clinical notes and laboratory data and classified as chronic HCV, HBV, alcohol-related, nonalcoholic fatty liver disease (NAFLD), or other.[21] Patients were classified as having alcohol-related liver disease if they had a history of alcohol abuse and lack of other known etiologies of liver disease, as best determined using available clinical notes. Patients were classified as having NAFLD if they had evidence of hepatic steatosis and/or metabolic risk factors in the absence of significant alcohol use or other causes of liver disease. Patients with underlying chronic HCV or HBV were classified as having viral liver disease, and patients with NAFLD, alcohol-related, or other liver disease were classified as having nonviral liver disease.

TUMOR MEASUREMENTS AND TUMOR GROWTH RATE CALCULATION

Tumor growth was assessed using tumor doubling time (TDT) and tumor specific growth rate (SGR)—two widely used clinical tools that have been used in several other cancers.[22,23] HCC growth rates were assessed by review of dynamic contrast-enhanced multiphase CT and MRI examinations by experienced, abdominal fellowship-trained diagnostic radiologists at each center (G.K., S.M.T., M.A., M.M.-L.) with 8, 6, 13, and 9 years of experience, respectively, specifically for the purposes of this study. Radiologists were blinded to patients' clinical information and documented tumor location and tumor diameter in three orthogonal dimensions. Unidirectional and bidirectional measurements assume that tumors are spherical and can overestimate tumor volume,[23,24] whereas measuring tumors in three dimensions calculates ellipsoid volume and decreases error in volume calculations. Per LI-RADS 2018 criteria, radiologists used the phase or sequence

that best demonstrated the margins of the lesions, with the arterial phase being the least preferred for measuring lesions, secondary to tumor neovascularization surrounding the tumor resulting in falsely enlarged sizes when compared to the other phases.[18] When present, the outer capsule of the lesion on delayed phase was included in the measurement. For patients with multifocal HCC, we used the single largest tumor for growth rate calculations. Additionally, in patients with multiple imaging studies, the two studies with the longest intervening time were used. Tumor volume (V) was calculated using the equation for an ellipsoid,

$$V = \frac{4}{3}\pi\left[\left(\frac{a}{2}\right)\left(\frac{b}{2}\right)\left(\frac{c}{2}\right)\right]$$

where a, b, and c denote the three maximum tumor diameters, respectively. TDT was calculated using the Schwartz equation[25]:

$$\mathrm{TDT} = \frac{(\mathrm{T}-\mathrm{T}_0)\ln 2}{\ln\left(\frac{V}{V_0}\right)}$$

In addition to TDT, we calculated SGR, which is a measure of the percentage increase in tumor volume over time and calculated using the following equation[23]:

$$\mathrm{SGR} = \frac{\ln\left(\frac{V}{V_0}\right)}{(\mathrm{T}-\mathrm{T}_0)}$$

TDT and SGR are closely related and inversely proportional[23], as shown:

$$\mathrm{TDT} = \frac{\ln 2}{\mathrm{SGR}}$$

SGR, unlike TDT, is normally distributed and thus advantageous for statistical analyses; however, TDT has been more commonly reported in cancer studies and is more easily conceptualized. Therefore, we report both TDT and SGR, to allow for comparison with prior studies and ease of clinical interpretation.

STATISTICAL ANALYSIS

We classified tumor growth patterns into three categories based on TDT: indolent (TDT > 365 days), intermediate (TDT 90-365 days), and rapid (TDT < 90 days) growth, corresponding to SGRs of < 0.19%, 0.19%-0.77%, and > 0.77% per day, respectively. These cutoffs were selected *a priori*, given clinical relevance for HCC surveillance, e.g., 3-month interval for repeat imaging of indeterminate nodules.[19]

We compared demographic, clinical, and tumor features between the three groups using the Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables. Multivariable ordered logistic regression was performed to identify correlates of indolent and rapid tumor growth. Potential correlates (age, race, sex, BMI, liver disease etiology, Child-Pugh score, MELD score, AFP level, initial tumor diameter, and initial tumor count) that were significantly associated with indolent or rapid tumor growth in univariate analyses ($P < 0.1$) were used as input variables in the multivariable models. In a secondary analysis, we performed multivariable linear regression to identify correlates of log-transformed TDT as a continuous variable. We performed subgroup analyses for patients with early-stage HCC, defined by the Milan criteria, and those with T1 HCC (unifocal lesion < 2 cm). In a *post hoc* exploratory analysis, we used univariate and multivariable Cox proportional hazard models to evaluate any potential association between tumor growth patterns and overall survival. All tests were two-sided and performed at the 5% significance level. Statistical analysis was performed using Stata 14.0 (College Station, TX).

Results

PATIENT CHARACTERISTICS

Of 3,180 total patients with HCC during the study period, 242 (7.6%) patients met study inclusion and exclusion criteria. Baseline patient characteristics of the primary cohort are summarized in Table 1. The mean age at HCC diagnosis was 60.3 years. The cohort was predominantly male (87.1%) and racially/ethnically diverse (49.2% non-Hispanic white, 28.9% non-Hispanic black, 15.7% Hispanic, 2.5% Asian). Most patients had HCV infection (68.3%), while 15.8% had alcoholic liver disease, 6.8% had NAFLD, and 3.6% had HBV infection. Nearly half (44.6%) of the patients had Child-Pugh A cirrhosis, with no significant differences in liver function between patients with indolent, intermediate, and aggressive tumor growth patterns ($P = 0.94$). Nearly three-fourths (73.6%) of

TABLE 1. Patient and Tumor Characteristics at HCC Diagnosis, Stratified by Tumor Growth Patterns*

Variable	Indolent (TDT > 365 d) (n = 92)	Intermediate (365 > TDT > 90 days) (n = 89)	Rapid (TDT < 90 days) (n = 61)	*P*
Age, years (SD)	61.1 (8.4)	59.3 (8.1)	60.4 (6.3)	0.36
Sex (% male)	82 (89.1)	73 (82.9)	55 (90.2)	0.33
Race/ethnicity				0.89
White	46 (50.0)	42 (47.2)	31 (50.8)	
Black	26 (28.3)	28 (31.5)	16 (26.2)	
Hispanic	16 (17.4)	13 (14.6)	9 (14.7)	
Asian	2 (2.2)	3 (3.4)	1 (1.6)	
Other/unknown	2 (2.2)	3 (3.4)	4 (6.5)	
BMI				0.06
Normal (< 25)	27 (29.3)	43 (48.3)	20 (33.3)	
Overweight	34 (37.0)	30 (33.7)	22 (36.7)	
Obese (> 30)	31 (33.7)	16 (18.0)	18 (30.0)	
Hospital site				0.27
Parkland	23 (25.0)	36 (40.4)	20 (32.8)	
University of Texas Southwestern	13 (14.1)	7 (7.9)	5 (8.2)	
University of Michigan	13 (14.1)	15 (16.8)	8 (13.1)	
McGuire VA	43 (46.7)	31 (34.8)	28 (45.9)	
Cirrhosis etiology				0.11
HCV	57 (61.9)	69 (77.6)	43 (70.5)	
Alcohol-related	18 (19.5)	13 (14.6)	5 (8.2)	
NAFLD	7 (7.6)	5 (5.6)	4 (6.6)	
HBV	3 (3.4)	1 (1.1)	4 (6.6)	
Other	5 (5.4)	0 (0.0)	3 (4.8)	
Unknown	2 (2.2)	1 (1.1)	2 (3.3)	
Hepatic encephalopathy	26 (28.4)	21 (23.9)	15 (24.6)	0.77
Ascites	39 (43.8)	34 (38.6)	30 (49.2)	0.44
Child-Pugh class				0.94
A	40 (45.4)	42 (47.7)	26 (42.6)	
B	35 (39.8)	36 (40.9)	27 (44.3)	
C	12 (14.8)	10 (11.4)	8 (13.1)	
MELD score	9.4 (7.5-13.2)	9.7 (8.2-12.1)	9.1 (7.5-13.4)	0.98
Platelet count	105 (75-168)	108 (69-153)	103 (73-155)	0.78
AFP (ng/mL)	10.5 (5.0-36.5)	16.7 (6.0-56.0)	28.4 (7.0-108.0)	0.07
AFP				0.08
<20 ng/mL	56 (60.9)	45 (50.6)	26 (42.6)	
20-199 ng/mL	16 (17.4)	26 (29.2)	20 (32.8)	
>200 ng/mL	11 (11.9)	8 (9.0)	10 (16.4)	
Missing	9 (9.8)	10 (11.2)	5 (8.2)	
NLR	2.02 (1.35-3.37)	1.98 (1.29-3.03)	2.10 (1.12-3.13)	0.95
First imaging modality				0.21
CT	41 (44.6)	46 (51.7)	36 (59.0)	
MRI	51 (55.4)	43 (48.3)	25 (41.0)	
Time between imaging, days	112.5 (68.5-253.3)	151 (69-252)	101 (57-192)	0.10
Initial HCC diameter	2.9 (2.0-4.8)	2.6 (1.9-3.7)	2.4 (1.7-3.1)	0.03
Number of lesions				0.44
1	65 (70.7)	56 (62.9)	45 (73.8)	
2	21 (22.8)	22 (24.7)	11 (18.0)	
3 or more	6 (6.5)	11 (12.3)	5 (8.2)	
Within Milan (%)	65 (70.7)	65 (73.3)	48 (78.7)	0.54

*Data provided as median (IQR) or n (%) except where otherwise specified.
Abbreviation: NLR, neutrophil-lymphocyte ratio.

patients were within Milan criteria, with 166 (68.6%) having one lesion, 54 (22.3%) having two lesions, and 22 (9.1%) having three or more lesions. Compared to patients who did not meet inclusion criteria, those included in the primary cohort had smaller tumors, a higher proportion of unifocal HCC, and a higher proportion within Milan criteria (Supporting Table S1).

The verification cohort consisted of 176 patients, with patient characteristics described in Table 2. Similar to the primary cohort, patients were predominantly male (74.4%) and a majority had HCV (53.4%), followed by HBV (18.1%), alcohol-related liver disease (15.3%), and NAFLD (8.5%). All patients were within Milan criteria, with most (90.9%) having a single lesion. Median tumor diameter was 1.4 cm (interquartile range [IQR], 1.2-1.6 cm) in the UCSF cohort and 2.6 cm (IQR, 1.8-3.1 cm) in the QEHB cohort.

TABLE 2. Verification Cohort Patient and Tumor Characteristics at Time of HCC Diagnosis

Variable	Birmingham, UK (n = 57)	UCSF (n = 119)
Age, years (SD)	58.2 (7.5)	60.0 (8.0)
Sex, male (%)	44 (77.2)	87 (73.1)
Cirrhosis etiology		
HCV	24 (42.1)	70 (58.8)
Alcohol-related	17 (29.8)	10 (8.4)
NAFLD	5 (8.8)	10 (8.4)
HBV	4 (7.0)	28 (23.5)
Other	7 (12.3)	1 (0.8)
AFP (ng/mL)	7 (4-30)*	12 (5-42)†
AFP		
<20 ng/mL	35 (61.4)	63 (52.9)
20-199 ng/mL	13 (22.8)	36 (30.3)
≥200 ng/mL	3 (5.3)	9 (7.5)
Missing	6 (10.5)	11 (9.2)
First imaging modality		
CT	10 (17.5)	82 (68.9)
MRI	47 (82.5)	19 (16.0)
Missing	0 (0.0)	18 (15.1)
Initial diameter (cm)	2.6 (1.8-3.1)	1.4 (1.2-1.6)
Number of lesions		
1	46 (80.7)	114 (95.8)
2	9 (15.8)	5 (4.2)
3	2 (3.5)	0 (0.0)
Within Milan (%)	57 (100)	119 (100)
Maximum interval between imaging investigations, days	121 (88.5-187.5)	210 (132-350)

Percentages may not equal 100% due to rounding.
*n = 51.
†n = 108.

TUMOR GROWTH PATTERNS IN THE PRIMARY COHORT

The distribution of TDT across the 242 patients in the primary cohort is demonstrated in Fig. 1. The overall median TDT was 228.6 days (IQR, 89.4-627.3), corresponding to a median SGR of 0.30% per day (IQR, 0.11%-0.78%). We found notable heterogeneity in tumor growth patterns, with 92 (38.0%) having indolent growth, 89 (36.8%) intermediate growth, and 61 (25.2%) rapid growth (Fig. 2). The median TDT of each group was 1,386 days (IQR, 526-2310), 182 days (IQR, 136-266), and 53 days (IQR, 44-76), respectively. The median interval between imaging studies was 116 days (IQR, 66-227), with the longest intervening time between imaging being 1,979 days. Given that median TDT may be overestimated by extrapolating short-interval growth patterns over longer periods of time, we characterized TDT stratified by imaging interval. Overall, TDT did not differ by imaging interval, with similar TDT between patients who had repeat imaging within 1-6 months and those with repeat imaging > 6 months apart (P = 0.94). Among the subgroup of patients with indolent tumors, median SGR was 0.04% in patients with repeat imaging within 1-6 months and 0.11% in those with repeat imaging > 6 months apart, corresponding to median TDTs of 1,733 days (IQR, 594-1982) and 623 days (IQR, 456-1033), respectively.

In univariate analyses, TDT was associated with liver disease etiology, tumor size, and baseline AFP levels. TDT was significantly longer in patients with nonviral liver disease than those with viral liver disease (median 11.7 versus 6.9 months, P = 0.03; Fig. 3A), corresponding to a lower SGR in the nonviral group (0.16% versus 0.35% per day, respectively). Figure 3B illustrates an inverse relationship between tumor size and TDT, with median TDTs of 6.1, 7.2, and 13.6 months (corresponding to SGRs of 0.38%, 0.32%, and 0.17%) for patients with initial tumor diameter 1-2 cm, 2-5 cm, and > 5 cm, respectively (P = 0.04); TDT and SGR are shown for these subgroups in Supporting Table S2. Indolent tumors were significantly larger than intermediate and rapidly growing tumors (median 2.9 versus 2.6 versus 2.4 cm, P = 0.03). Patients with indolent tumors also had lower AFP levels than those with rapidly growing lesions (median 10.5 versus 28.4 ng/mL, P = 0.07), including a higher proportion with AFP < 20 ng/mL. In the 31 (12.8%) patients with available histology,

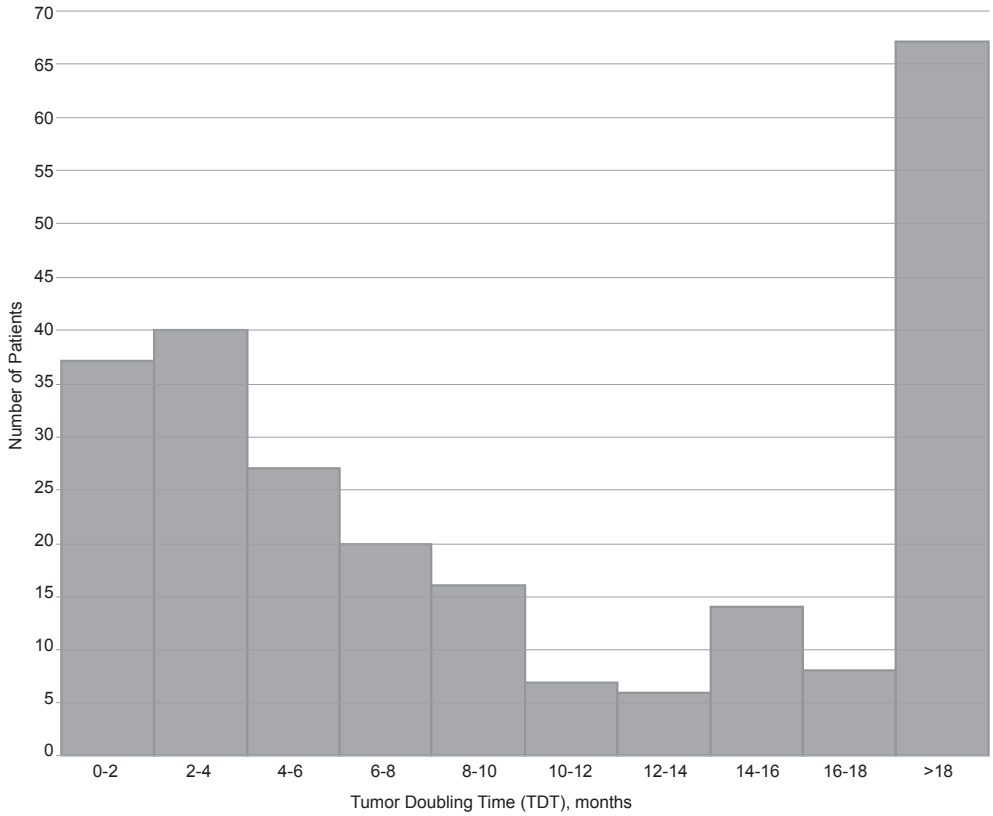

FIG. 1. Distribution of tumor doubling time among the 242 patients in the primary cohort.

we found no significant association between tumor growth patterns and degree of HCC differentiation (P = 0.46). Additionally, in the subgroup of patients with repeated AFP measurements (n = 181), we did not find an association between tumor growth patterns and change in AFP over time (P = 0.69).

In multivariable analyses (Table 3), indolent tumor growth was significantly associated with larger initial tumor diameter (continuous) (OR, 1.15; 95% CI, 1.03-1.30) and inversely associated with AFP > 20 ng/mL (OR, 0.60; 95% CI, 0.37-0.98). Although indolent tumor behavior was associated with nonviral etiology in univariate analysis, this did not remain statistically significant in multivariable analysis. Findings were unchanged when examining the subgroup of patients within Milan criteria and among those with unifocal lesions (data not shown). Correlates of rapid growth are inversely related to those of indolent growth, as shown in Supporting Table S3. Correlates of SGR as a continuous variable are shown in Supporting Table S4.

In an exploratory analysis, we evaluated the association between tumor growth patterns and outcomes including treatment receipt and overall survival. Of those in the primary cohort, 184 (76.0%) underwent treatment after repeat imaging. Characteristics of patients who received treatment compared to those who remained untreated are summarized in Supporting Table S5. As expected, a higher proportion of patients with indolent tumors were able to receive curative therapy compared to those with intermediate or rapidly growing tumors (50.0% versus 39.4% and 34.1%, respectively). Indolent tumor behavior was associated with improved survival in univariate analysis (hazard ratio [HR], 0.68; 95% CI, 0.45-1.04); however, this did not reach statistical significance. After adjusting for Child-Pugh score and tumor burden (i.e., within versus outside Milan criteria), indolent growth was associated with significantly lower mortality compared to rapid tumor growth (HR, 0.61; 95% CI, 0.40-0.95). However, after further adjusting for the difference in treatment receipt (in addition to Child-Pugh and tumor burden), the association between indolent tumor growth and survival was no longer significant (HR, 0.96; 95% CI, 0.56-1.63).

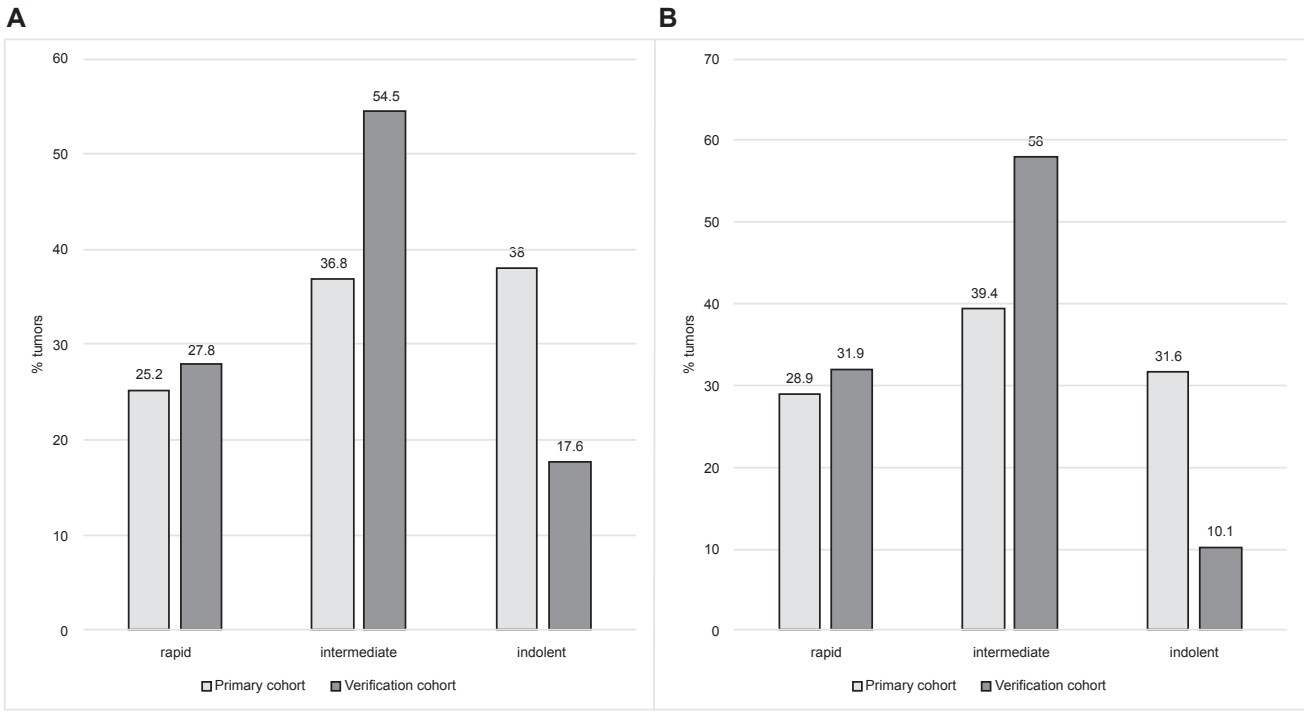

FIG. 2. Proportion of rapid, intermediate, and indolent tumors in the overall (panel A) and T1 (panel B) cohorts.

TUMOR GROWTH PATTERNS IN SUBGROUP OF THE PRIMARY COHORT WITH T1 LESIONS

In the subgroup of patients with T1 lesions (n = 60), the median TDT was 182 (IQR, 73-495) days and SGR was 0.38% (0.14%-0.95%) per day. Of these, 16 (17.4%), 23 (25.8%), and 21 (34.4%) were classified as having indolent, intermediate, and rapid growth, respectively. Within this subgroup, TDT was significantly longer in patients with nonviral liver disease compared to those with viral liver disease (median 15.4 versus 5.3 months, P = 0.02), corresponding to an SGR of 0.15% versus 0.44% per day. In multivariable analysis (Table 4), indolent growth was significantly associated with nonviral liver disease etiology (OR, 3.41; 95% CI, 1.08-10.80), while AFP and initial tumor diameter were no longer statistically significant.

TUMOR GROWTH PATTERNS IN THE VERIFICATION COHORT

Overall, tumor growth patterns were similar in the verification cohort, with a median SGR of 0.57% per day among UCSF patients and 0.35% per day for QEHB patients, corresponding to median TDTs of 122 days (65-217) and 198 days (102-990), respectively. In the QEHB cohort, 19 (33.3%) were classified as having indolent growth, 27 (47.4%) intermediate growth, and 11 (19.3%) rapid growth, whereas in the UCSF cohort (comprised only of T1 lesions) 12 (10.1%) had indolent growth, 69 (58.0%) intermediate growth, and 38 (31.9%) rapid growth. In multivariable analysis, nonviral liver disease was significantly associated with indolent growth in the UCSF cohort (OR, 3.28; 95% CI, 1.48-7.53) but not the QEHB cohort (OR, 1.26; 95% CI, 0.40-4.01); tumor diameter and AFP level were not associated with tumor growth patterns in the UCSF or QEHB cohort.

Discussion

Our multicenter study represents an evaluation of tumor growth patterns in a large contemporary Western cohort with patients of diverse liver disease etiologies. Overall, we observed a median TDT of 229 days and SGR of 0.30% per day; however, patients demonstrated heterogeneous growth patterns.

TABLE 3. Correlates of Indolent HCC Growth Patterns*,†

	Univariable Analysis		Multivariable Analysis	
Variable	OR	95% CI	OR	95% CI
Age	1.01	0.98-1.04		
Male sex	1.03	0.52-2.01		
BMI				
Normal	Ref	Ref		
Overweight	1.18	0.69-2.01		
Obese	1.41	0.78-2.57		
NLR	0.97	0.87-1.09		
Race/ethnicity				
White	Ref	Ref		
Black	1.03	0.60-1.77		
Hispanic	1.15	0.58-2.28		
Asian	1.06	0.25-4.53		
Child-Pugh class				
A	Ref	Ref		
B	0.90	0.54-1.49		
C	1.10	0.52-2.31		
AFP > 20	0.60	0.38-0.97	0.60	0.37-0.98
Initial tumor diameter (continuous)	1.14	1.02-1.28	1.15	1.03-1.30
Etiology				
Viral	Ref	Ref	Ref	Ref
Nonviral	1.68	0.98-2.88	1.49	0.86-2.60

*Results from ordinal logistic regression model comparing indolent versus intermediate versus rapid tumor growth patterns, respectively.
†Results for primary cohort.
Abbreviation: NLR, neutrophil-lymphocyte ratio.

Notably, nearly 40% exhibited indolent growth, with TDTs exceeding 1 year, whereas we observed rapid growth in one-fourth of patients, with a TDT of < 3 months.

HCC tumor growth patterns in our study are similar to or slightly slower than what has been reported in other cancers such as breast,[22] lung,[12] and pancreas,[26] in which SGR has ranged from 0.5% to 3% per day.[23] In contrast, studies on prostate cancer have demonstrated substantially more indolent behavior, with doubling times ranging from 2 to 6 years in some cases.[27] Although some studies have reported shorter median TDTs for HCC, ranging from 85 to 127 days,[28] these studies were primarily conducted in Asia among HBV-predominant cohorts. A study by An et al. similarly suggested that TDT may differ between viral etiologies, with longer TDT among HCV-infected than HBV-infected patients (137.2 versus 76.8 days).[29] Our results extend these findings that TDT may differ by cirrhosis etiology, with longer TDT in patients with nonviral cirrhosis, particularly those with T1 lesions, in both the primary and verification cohorts. Further studies are needed to confirm the potential association between liver disease etiology and TDT, including potential mechanisms for why tumor growth patterns may differ. These data are particularly relevant given the shift in HCC epidemiology from a virus-mediated phenomenon to an increasing number of nonalcoholic steatohepatitis–related cases.[30,31]

Additionally, we found that larger tumor diameter was associated with longer TDT, i.e., slower growth. Although this may appear unexpected, this finding is consistent with data from prior studies[29,32] and the theory that HCC exhibits a sigmoidal growth pattern, with smaller tumors demonstrating a more rapid, exponential growth pattern than larger tumors, which may begin to grow more slowly as they outgrow their blood supply.[33-35] Notably, we observed no relationship between liver function and HCC growth rates. We otherwise found that AFP levels were associated with tumor growth patterns, consistent with prior studies demonstrating the prognostic importance of AFP levels.[36,37] However, overall these associations likely only explain a small proportion of the observed variation in tumor biology, and future studies are needed to identify other correlates to better predict and tailor management strategies to individual patient tumor biology.

The data from our study have several important clinical implications. First, the value of cancer screening programs is driven by tumor biology, with less benefit in very rapid or very slowly growing tumors, albeit for different reasons. Surveillance is unlikely to detect rapidly growing tumors at an early stage when curative treatments are still available. Conversely, surveillance is likely to detect indolent tumors but is prone to overdiagnosis and overtreatment. Thus, the benefit of early detection must be balanced against the harms of cancer screening and the risk of overtreating "benign" disease.[38,39] Second, tumor growth rates inform optimal surveillance intervals, with the current 6-month interval based on older data for TDT.[40] Although we found that a high proportion of HCCs may have indolent growth patterns, the TDT was substantially shorter in T1 lesions, supporting current surveillance recommendations. Third, an indolent tumor, particularly in the setting of decompensated cirrhosis, may represent overdiagnosis as the tumor itself is unlikely to impact overall

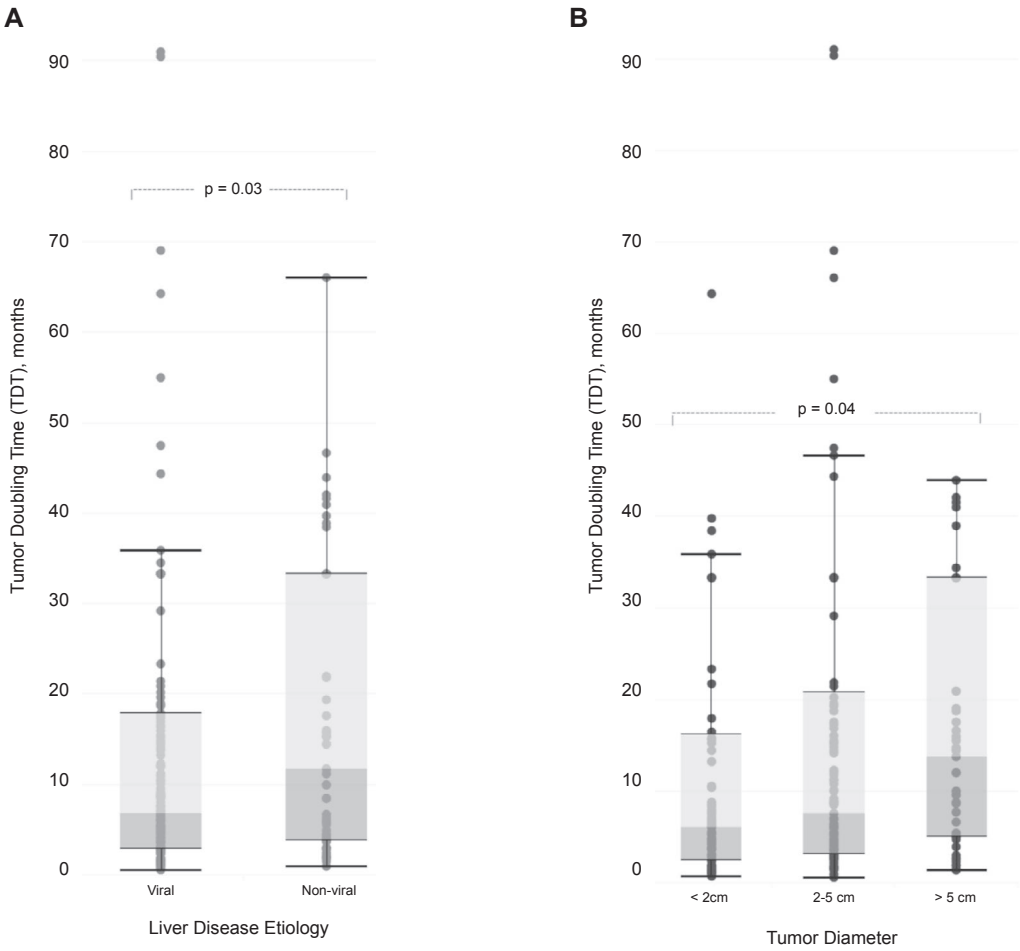

FIG. 3. Tumor doubling time in the primary cohort by (panel A) liver disease etiology and (panel B) initial tumor diameter.

survival. Rather, HCC treatment of an indolent tumor, particularly in patients with portal hypertension and/or hepatic decompensation, poses a risk of further hepatic decompensation and may actually adversely affect prognosis.[1] Finally, distinguishing indolent-growing and rapid-growing tumors can also guide more tailored HCC treatment decisions. For example, a better assessment of tumor biology could more accurately identify patients at highest risk for wait list dropout, help tailor bridging locoregional therapy while on the wait list, and even facilitate changes in transplant priority policies.[41] However, at this point, it is premature to base HCC treatment decisions solely on predicted tumor growth patterns; and prospective data from larger cohorts, particularly among patients with nonviral liver disease, are needed to confirm our findings.

Limitations of this study include its retrospective nature and inherent selection bias. Although we evaluated consecutive patients with HCC from prospectively maintained tumor registries for study inclusion, only patients who did not receive treatment or received delayed treatment were included, which comprised < 10% of the overall sample. Some patients with very rapidly growing tumors and/or severe liver dysfunction may not have survived long enough to have had two consecutive imaging studies and were thus excluded from the study, resulting in possible immortal time bias. We found that patients included in the primary cohort had significantly smaller tumors and less multifocal disease than excluded patients, suggesting that these results may not be generalizable to patients with larger tumors and highlighting the need for further data in this patient group. Notably, this limitation may be unavoidable for characterizing HCC natural history as it would be difficult to design an ethical study to prospectively observe tumor biology in

TABLE 4. Correlates of Indolent Tumor Growth Patterns in Patients With T1 HCC*,†

	Univariable Analysis		Multivariable Analysis	
Variable	OR	95% CI	OR	95% CI
Age	0.94	0.88-1.01	0.95	0.88-1.02
Male sex	0.44	0.13-1.58		
NLR	1.02	0.81-1.28		
Race/ethnicity				
White	Ref	Ref		
Black	0.67	0.21-2.17		
Hispanic	3.53	0.71-17.60		
Asian	0.38	0.03-5.15		
Child-Pugh class				
A	Ref	Ref		
B	1.35	0.50-3.67		
C	1.47	0.32-6.80		
AFP	0.99	0.99-1.00		
Initial tumor diameter (continuous)	1.66	0.30-9.11		
Etiology				
Viral	Ref	Ref	Ref	Ref
Nonviral	3.87	1.25-11.97	3.41	1.08-10.80

*Results from ordinal logistic regression model comparing indolent versus intermediate versus rapid tumor growth patterns, respectively.
†Results for primary cohort.
Abbreviation: NLR, neutrophil-lymphocyte ratio.

all-comers with HCC. Second, there is a possibility of misclassification bias, with some indolent lesions not truly representing HCC; however, all included lesions were LI-RADS 5, which has a positive predictive value > 95% for HCC in the setting of cirrhosis. Third, it is possible that the tumor growth rate trajectory may change over time, and periods of interrupted growth or change in tumor growth patterns within a single tumor are not necessarily accounted for in our analyses. Fourth, our findings are not generalizable to patients with infiltrative tumors or macrovascular invasion as the nature of these tumors precluded accurate measurements; and thus, they were excluded from the study. Finally, we evaluated the association between tumor growth patterns and outcomes including overall survival; however, this exploratory analysis was limited by residual confounding, selection bias of included patients, and limited statistical power. We believe these weaknesses are outweighed by our study's strengths, including its multicenter nature and large size, use of a contemporary cohort reflecting improved imaging technology compared to older cohorts, and prospective measurement of tumors in three dimensions by experienced fellowship-trained abdominal radiologists to allow for more accurate TDT calculations.

In conclusion, in this multicenter Western cohort study characterizing HCC growth rates, we found heterogeneous growth patterns, with rapid growth in one-fourth of patients and indolent growth in over one-third of patients. Indolent tumor behavior appeared to be more common in patients with nonviral liver disease, whereas a higher proportion of T1 lesions exhibited rapid growth. Further studies of tumor growth rates and predictive models are needed to better understand tumor growth patterns for patients with HCC and achieve a precision approach to HCC surveillance and treatment.

Author Contributions: A.G.S. and N.E.R. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for acquisition of the data and critical revision of the manuscript for important intellectual content. A.G.S. and N.E.R. were responsible for analysis and interpretation of the data as well as study concept and design. N.E.R. was responsible for drafting of the manuscript. A.G.S. obtained funding and was responsible for administrative, technical, and material support as well as study supervision.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.31159/suppinfo.