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Hepatocellular Carcinoma Tumor Volume Doubling Time: A Systemic Review and Meta-analysis

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Abstract

Background: Tumor growth patterns have important implications for surveillance intervals, prognostication, and treatment decisions but have not been well described for hepatocellular carcinoma (HCC). The aim of our study was to characterize HCC doubling time and identify correlates for indolent and rapid growth patterns.

Methods: We performed a systematic literature review of Medline and EMBASE databases from inception to December 2019 and national meeting abstracts from 2010 to 2018. We identified studies reporting HCC tumor growth or tumor volume doubling time (TVDT), without intervening treatment, and abstracted data to calculate TVDT and correlates of growth patterns (rapid defined as TVDT <3 months and indolent as TVDT >9 months). Pooled TVDT was calculated using a random effects model.

Results: We identified 20 studies, including 1374 HCC lesions in 1334 patients. The pooled TVDT was 4.6 months (95%CI 3.9 – 5.3 months I^2=94%), with 35% classified as rapid, 27.4% intermediate, and 37.6% indolent growth. In subgroup analysis, studies from Asia reported shorter TVDT than studies elsewhere (4.1 vs. 5.8 months). The most consistent correlates of rapid tumor growth included hepatitis B etiology, smaller tumor size (continuous), AFP doubling time, and

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Author Contributions:

Drs. Singal and Nathani had full access to all of the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design (Singal and Parikh); Acquisition of the data (Nathani); Analysis and interpretation of the data (Nathani); Drafting of the manuscript (Nathani); Critical revision of the manuscript for important intellectual content (all authors); Obtained funding (Singal); Administrative, technical, and material support (Singal); Study supervision (Singal)

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poor tumor differentiation. Studies were limited by small sample sizes, measurement bias, and selection bias.

Conclusion: Tumor volume doubling time of HCC is approximately 4–5 months; however, there is heterogeneity in tumor growth patterns, including more aggressive patterns in Asian hepatitis B-predominant populations. Identifying correlates of tumor growth patterns is important to better individualize HCC prognostication and treatment decisions.

Keywords

liver cancer; HCC; tumor growth rate; tumor biology; overdiagnosis

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 4th leading cause of cancer-related mortality worldwide, contributing to approximately 800,000 deaths annually.[1] It is one of the few cancers whose incidence and mortality is increasing in the United States and Europe over recent years, related to an increased burden of chronic liver disease including hepatitis C (HCV) and non-alcoholic steatohepatitis (NASH).[2] Further, despite improvements in treatment, HCC survival remains dismal with 5-year survival below 20%.[3]

In light of these data, HCC has traditionally been considered an aggressive tumor with presumed rapid growth. However, recent multi-center data from the US and Europe have questioned this dogma, demonstrating heterogeneity in tumor growth patterns with over one-third of tumors demonstrating indolent growth patterns.[4] These data are important to confirm given the multi-faceted importance of tumor growth patterns. For example, the current recommendation to perform HCC surveillance every 6 months is largely based on early literature suggesting (tumor volume doubling time) TVDT of approximately 70–120 days[5]. However, semi-annual surveillance is prone to missed lesions in patients with rapidly growing tumors and overdiagnosis in those with indolent tumors[6]. Similarly, tumor growth patterns likely affect treatment response and are important to understand for accurate prognostication. Data regarding tumor growth patterns in other cancer types, such as prostate[7], have highlighted the potential for overdiagnosis and overtreatment. In light of the competing risk of liver-related mortality in most patients with HCC, select patients with indolent tumors may opt for close surveillance, rather than be exposed to potential harms of treatment. Accurate assessment of tumor growth patterns could facilitate individualized treatment decisions, such as transplant eligibility for larger tumors, the need for bridging therapy while awaiting liver transplantation, and potential use of adjuvant therapy after ablation or resection.

Therefore, the aims of our systematic review were to 1) characterize HCC tumor volume doubling time and tumor growth patterns and 2) identify correlates for rapid, intermediate, and indolent growth patterns.

METHODS

Data Sources and Searches

We conducted a computer-assisted search of Medline and EMBASE databases from inception to December 1, 2019 with the following keyword combinations: 1) doubl$ or natural history or lead time AND 2) hepatocellular ca$ or hcc or hepatoma or liver ca$. The search was restricted to human studies and articles published in English. Manual searches of reference lists from applicable studies were performed to identify any studies that may have been missed by the electronic search. Additional searches of national meetings including Digestive Disease Week, American Association for the Study of Liver Diseases, American College of Gastroenterology from 2010–2018 were performed. Finally, consultation with expert hepatologists was performed to identify any references that may have been missed. The study was conducted in accordance with PRISMA guidelines[8].

Study Selection

We reviewed all titles and abstracts to identify potentially relevant articles. Two investigators (PN and AS) reviewed all potentially relevant full texts for inclusion, with disagreements resolved through discussion and consensus. We included cohort studies (retrospective or prospective) that reported HCC TVDT, growth patterns, and/or correlates of tumor growth patterns without any intervening treatment as the primary outcomes of interest. Studies reporting correlates of tumor growth patterns but not point estimates for TVDT or tumor growth patterns were still included for the correlates outcome analysis. We excluded studies with non-human data or lack of original data. Although we did not restrict studies based on methodology of assessing tumor size, we performed a pre-planned subgroup analysis of studies exclusively using cross-sectional imaging (multi-phase CT or contrast-enhanced MRI). If publications used overlapping cohorts of patients, we used data from the study with more granular data regarding tumor growth patterns.

Data Extraction and Quality Assessment

We used standardized data extraction forms to collect the following items: geographic region and years of the study, size and characteristics of the patient cohort, inclusion/exclusion criteria, method for assessing tumor size, and relevant data characterizing TVDT or tumor growth patterns. Most included studies reported summary measures for TVDT (with standard deviation) or tumor growth patterns, although granular data on tumor sizes at different times, permitting calculation of TVDT, were collected if available. Calculation of TVDT, when needed, was performed using Schwarz's formula: $TVDT = [(T - T_0)\ ln2] / [\ln (V/V_0)]$, where V and V_0 are tumor volumes at time point T and T_0, respectively.[9] We also collected any reported correlates of TVDT or tumor growth patterns, typically identified through linear or logistic regression analyses.

We assessed the risk of bias for each study using a modified Newcastle-Ottawa scale[10], which assesses selection of the patient cohort, comparability of study groups, and adequacy of assessing the outcome of interest. Specifically, quality assessment was based on potential selection bias, sample size, representativeness of patient cohort, validity of imaging

modality, number of tumor diameters assessed, bias in the assessment of outcome, and appropriateness of statistical analysis.

Data Synthesis and Analysis

Our primary outcome of interest was TVDT, defined in days, and tumor growth patterns. For any studies in which tumor growth patterns were not pre-specified, we *a priori* defined rapid as TVDT <3 months, intermediate as TVDT 3–9 months, and indolent as TVDT >9 months. These definitions were in part based on guideline recommendations for semi-annual surveillance for HCC early detection[1112]. A pooled TVDT estimate was calculated by pooling study-specific estimates, using a random effects model. Heterogeneity was assessed graphically by examination of forest plots and then statistically using the inconsistency index (I^2), with an I^2 of >75% indicating significant heterogeneity.[13] Pre-planned subgroup analyses were performed by region (USA and Europe versus Asia), imaging modality (ultrasound versus CT/MRI), and study year (prior to the year 2000 vs after 2000). We evaluated subgroup analyses by region given potential differences in tumor biology by liver disease etiology, imaging modality given likely differences in accuracy of assessing tumor size, and study year given evolution of HCC characterization and advances in imaging technology over time. A post-hoc subgroup analysis was performed by study sample size given results of funnel plot analysis, which was performed to graphically assess for publication bias. In addition to between-study analyses, we also recorded within-study correlates of tumor growth patterns. All data analyses were conducted using Stata version 14.2 (College Station, TX).

RESULTS

Study Selection and Characteristics

The electronic search returned 7675 total results, which was narrowed to 169 studies after review of study titles and abstracts. After full text review, we identified 20 studies with sufficient data for estimation of TVDT and tumor growth patterns. An additional 5 studies had incomplete data for TVDT but had data regarding correlates of tumor growth patterns. Reasons for exclusion at time of full-text review are detailed in Figure 1. On the basis of funnel plot analysis (Supplemental Figure 1), we could not exclude the possibility of publication bias. Smaller studies reported longer TVDT than those with larger sample sizes, and there was a paucity of small studies reporting short TVDT.

Characteristics of the included studies are detailed in Table 1. Overall, there were 1572 patients (n=1621 HCC), including 1334 patients (n=1374 HCC) in the 20 studies reporting point estimates for TVDT or tumor growth patterns. Among included studies, the majority were small including less than 50 patients, with a median sample size of 28 patients, and the two largest studies (each including >200 patients) being published in 2017 or later.[14, 4] Most studies had a retrospective design (n=16) and were conducted in Asia (n=15). Most studies published prior to 2000 used ultrasound as the modality to assess tumor sizes, whereas those published after 2000 exclusively used cross-sectional imaging.

Tumor Volume Doubling time of HCC

Across 20 studies with available data, study-level mean TVDT ranged from 2.2 months to 11.3 months. The pooled mean TVDT was 4.6 (95%CI: 3.9 – 5.4) months, although there was significant heterogeneity both on visual inspection of forest plots and analytically (I^2=94%) (Figure 2). Sensitivity analysis, in which one study is removed at a time, failed to demonstrate a change in TVDT exceeding 10 days. In subgroup analyses, we did not observe notable differences in pooled TVDT by imaging modality (4.7 months [95% CI 3.7–5.7 months, I^2= 86%] for studies using ultrasound vs. 4.6 months [95% CI 3.5–5.5 months, I^2= 94%] for studies using CT or MRI), although there appeared to be differences by study year (5.2 months [95% CI 4.0–6.5 months, I^2= 90%] for studies published prior to 2000 vs. 4.1 months [95% CI 3.2–5.1 months, I^2= 95%] for those published after 2000) and by location (4.1 months [95% CI 3.4–4.8 months, I^2= 91%] for studies conducted in Asia vs. 5.4 months [95% CI 4.0–6.9 months, I^2= 94%] for those in the US and Europe. (Supplemental Figure 2). Post-hoc subgroup analysis revealed potential differences by study sample size (4.8 months [95% CI 3.9–5.7 months, I^2 = 88%] for studies with <50 patients vs. 4.3 months [95% CI 3.0–5.6 months, I^2 = 94%] for studies with >50 patients).

Tumor growth patterns were reported in 25 studies. As presented in Table 3, 35% of HCC had rapid growth patterns, 27.4% intermediate growth, and 37.6% had an indolent growth pattern. There appeared to be differences in growth patterns by study location, with a higher proportion of patients with aggressive tumors among studies conducted in Asia (43.8% vs. 25.5%, respectively, p<0.001).

Correlates of Tumor Growth Patterns within Studies

Supplemental Table 1 describes factors correlated with HCC growth patterns as reported within individual studies. None of the studies found an association between growth patterns and patient demographics, including age and sex, and most failed to find an association with degree of liver dysfunction, e.g. Child Pugh score. Although there were limited data examining any association between liver disease etiology and TVDT, three studies reported shorter TVDT among patients with chronic HBV infection as compared to other etiologies.[15–17] Similarly, Rich et al observed that HCC in the setting of HCV or HBV-related cirrhosis had shorter TVDT than those with non-viral etiologies.[4] In contrast, Kim et al[14] and An el al[15] failed to find an association between liver disease etiology and TVDT. Several studies[14151820] have reported a linear association between smaller tumor diameter and shorter TVDT (i.e. more rapid growth), with tumor diameter evaluated continuously. Recently, Rich et al[4] noted a similar association between TVDT and tumor diameter, analyzed using categories of 1–2 cm. 2–5 cm, and >5 cm.

Several studies found an association between higher alpha fetoprotein (AFP) levels and rapid HCC growth,[4152122]; however, this was inconsistent with other studies failing to find an association.[14192123–26]. In contrast, the association between AFP doubling times and HCC growth patterns appeared to be consistently observed across studies[171927–28]. In these studies, AFP doubling time was typically calculated using a modification of the Schwartz equation using to calculate TVDT and authors reported high degrees of correlation (r = 0.70 – 0.97). There were few data evaluating the association between other novel biomarkers and

tumor growth patterns. Although data on radiomics predicting tumor growth patterns were limited, there were not any baseline imaging features consistently associated with tumor growth patterns. Saitoh and colleagues found tumors with increased arterial blood supply and hypervascularity had more rapid tumor growth,[30] although this was not evaluated by others.[24] Jha and colleagues evaluated imaging findings in small HCC and found increased signal intensity on T2-weighted imaging was associated with rapid growth whereas increased intensity on T1-weighted imaging was associated with more indolent growth.[18]

Several studies found an association between degree of differentiation and tumor growth patterns,[21222729–31] although this was not significant in others.[4233233] Other studies reported a positive association between rapid tumor growth and higher proliferation indices[253133] and microvascular invasion.[2122] A recent prospective study with 132 patients (78 training set and 54 validation set) found a 5-gene transcriptomic signature with angiopoietin-2, delta-like ligand 4, neuropilin/tolloid-like2, endothelial cell-specific molecule-1, and nuclear receptor subfamily 4 group A, member 1 (NR4A1) was associated with rapid growth and worse survival.[21]

Study Quality

Results of the quality assessment are detailed in Table 2. In brief, several limitations in study design were prevalent. First, all studies were limited by an inherent selection bias given the inclusion of untreated patients who underwent repeat imaging, who are likely different than those who undergo treatment without interval imaging. Most notably, patients with aggressive tumor biology are less likely to remain sufficiently stable to allow repeated imaging than those with indolent tumors. Second, several older studies further restricted patient cohorts by only including those with biopsy-proven HCC or excluding patients with prolonged stability in tumor volume. Third, most studies had small sample sizes, with less than 100 patients each, resulting in imprecise point estimates. Fourth, many studies had potential measurement bias, given nearly half used ultrasound imaging to measure tumor volumes and others used different imaging modalities to compare tumor sizes at different time points. Further, most studies measured tumors in only one dimension, which falsely assumes that tumors are perfectly spherical, and were dependent upon the measurements of a single radiologist, despite recognized inter-observer variability in tumor measurements. Finally, all analyses assume TVDT is constant, however tumor biology and TVDT may be dynamic, with changes over time.

DISCUSSION

An accurate understanding of tumor growth patterns is critical for many aspects of cancer care, most notably prognostication and treatment decisions. We found a pooled TVDT for HCC of approximately 4.6 months, although there was significant variation across studies ranging from 2.2 to 11.3 months. Studies also reported variation in tumor growth patterns, with over one-third of HCC described as having rapid growth, one-fourth as intermediate growth, and over one-third as having indolent growth. There are limited data describing correlates of tumor growth patterns, although some studies report more rapid growth for smaller tumors, poorly differentiated tumors, and HCC in patients with viral liver disease.

Overall, available literature highlights the variation in HCC growth patterns and the need for further studies to better differentiate patients with rapid versus indolent tumors.

In addition to clear implications for prognostication and treatment decisions, expected tumor growth patterns also impact the potential benefit of HCC surveillance. A cancer screening program is most effective when tumors have intermediate and dependable growth. Rapidly growing tumors are unlikely to be detected by screening and often present symptomatically, whereas indolent tumors are more likely to be detected but prone to overdiagnosis. Overdiagnosis in such situations leads to overtreatment, economic harms, and detriment in quality of life without any benefit in prognosis or mortality.[34] Given the lack of level I data evaluating HCC surveillance in patients with cirrhosis, we rely on cohort studies using statistical methods to adjust for potential lead-time and length-time bias based on TVDT assumptions[535]. However, most studies used TVDT of 70–90 days, which likely led to inaccurate assumptions for lead-time and length time biases. Longer TVDT estimates, as suggested by our study, may increase potential lead and length time biases, thereby abating observed benefits of HCC surveillance in prior studies. Further, patient-level predictors of tumor biology could help inform personalized surveillance strategies among at-risk patients.

Although there were inconsistent correlates for TVDT across studies, a few observations were relatively consistent. First, we observed variation in TVDT based on geographic location, likely based on differences in liver disease etiology. Subgroup analyses found a higher proportion of rapidly growing tumors among studies conducted in Asia, and recent studies with diverse liver disease etiologies reported more indolent growth among patients with non-viral liver disease. If confirmed, these differences could be related to variation in molecular pathways of HCC pathogenesis and growth between liver disease etiologies[36]. These data are particularly important in the Western world, where HCC is increasingly related to non-viral etiologies such as NASH and alcohol-related cirrhosis[3738]. Second, several studies suggest HCC may exhibit logarithmic growth, with rapid early growth followed by more indolent growth as the tumor becomes larger.[414–1618] It is unclear if this growth pattern would be related to changes in mutational burden and tumor biology, changes in blood supply related to tumor burden (i.e. outgrowing its blood supply), or an artifact of measurement bias and small differences in tumor diameter making a larger difference when tumors are smaller in size. Finally, several studies have reported more rapid growth in patients with poorly differentiated tumors.[21222729–31] Tumor growth patterns and better understanding of the tumor biology of early-stage patients are relevant for several treatment decisions such as need for bridging therapy while awaiting liver transplantation or optimal surveillance interval (versus early ablation) for UNOS stage T1 lesions[39]. It may also help predict response to HCC treatments such as TACE or systemic therapy.[40] These data can particularly affect relative weights placed on HCC-related mortality versus liver-related complications when making treatment decisions in patients with significant portal hypertension or decompensated cirrhosis.

In light of heterogeneity in tumor growth patterns, a biomarker for tumor biology would be of great clinical utility. Several studies have shown that AFP can be prognostic, with high levels associated with poorer response to therapy, including higher risk of post-resection and post-transplant recurrence[4142]. However, in our analysis, studies were discordant in finding

an association between baseline AFP levels and tumor growth patterns. It is unclear if the lack of association in these studies is simply related to tumor heterogeneity with AFP only being elevated in approximately half of all tumors[43–45]. However, studies found a consistent association between AFP doubling time and TVDT, which could be a readily available marker for identifying aggressive tumors. Future studies should continue to evaluate longitudinal changes in biomarkers, other novel biomarkers (including biomarker panels), and radiomic features, such as degree of enhancement or timing of washout, as potential indicators of tumor biology. Although the rare use of biopsy for HCC histologic confirmation likely limits the routine use of tissue-based biomarkers, it is possible that continued refinement of liquid biopsy techniques may help identify a prognostic biomarker and surrogate of TVDT[46].

Despite the recognized importance of characterizing tumor growth patterns, we noted the current literature evaluating TVDT has several limitations. First, most studies were conducted in Asia, with a predominant HBV-infected patient population, with fewer data from the Western countries with more diverse disease etiologies. It is possible that tumor growth patterns may vary by liver disease etiology so it is unknown if the available data would apply to contemporary cohorts with NASH, alcohol-related cirrhosis, or patients with hepatitis C after sustained viral response. Second, funnel plot analysis suggested the possibility of publication bias, with a paucity of small studies reporting short TVDT. Third and most importantly, most included studies had notable limitations including small sample sizes, potential measurement bias, and an assumption that TVDT is constant over time. Notably, studies conducted prior to 2005 preceded noninvasive diagnostic criteria of HCC and relied on ultrasound for HCC tumor measurement, resulting in increased selection and measurement biases. To evaluate these potential biases, we performed subgroup analyses by geographic location (Asia vs. Europe and US), imaging modality (ultrasound vs. CT/MRI), study year (pre- and post-2000), and study sample size (<50 vs. >50). We found consistent results in most subgroup analyses, although shorter TVDT in studies from Asia compared to Europe and the US. Further subgroup analyses by liver disease etiology were unfortunately not possible without patient-level data. Fourth, there was significant between-study heterogeneity observed in our meta-analysis with an I^2 >90%, increasing the degree of uncertainty around the point estimate for pooled TVDT. We evaluated this heterogeneity through sensitivity and subgroup analyses, although heterogeneity persisted, perhaps reflecting the inherent heterogeneity in tumor growth patterns described in our results. Lastly, there is a selection bias inherent to all studies of HCC natural history; however, this may be unavoidable due to ethical concerns regarding design of a prospective study to observe tumor biology in the absence of treatment for all patients with HCC. We believe understanding these limitations of prior studies can inform design of high quality studies evaluating this important topic in the future.

Conclusion

In this systematic review and meta-analysis, we found wide variation in tumor growth patterns, with over one-third of HCC exhibiting rapid growth and over one-third having indolent growth. Correlates of rapid tumor growth include hepatitis B etiology, smaller tumor diameter, AFP doubling time, and poor tumor differentiation. However, current

studies have notable limitations, highlighting the need for high quality studies in this area as well a need for novel prognostic biomarkers that correlate with tumor biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AFP	alpha fetoprotein
CT	computed tomography
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
MRI	magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
TVDT	tumor volume doubling time

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What is already known about this subject?

- Hepatocellular carcinoma is traditionally considered an aggressive tumor
- Understanding HCC growth patterns has implications for prognostication as well as treatment decisions.

What are the new findings?

- HCC has notable variation in tumor growth patterns, with over one-third of HCC being categorized as having indolent growth and over one-third as rapid growth
- Correlates of rapid tumor growth include viral liver disease etiology, small tumor size, and poor tumor differentiation.

How might it impact on clinical practice in the foreseeable future

- Our data highlight a need for studies to identify prognostic biomarkers that can differentiate tumor growth patterns.
- Identification of a subgroup of indolent HCC highlight the potential for overtreatment in some patients.

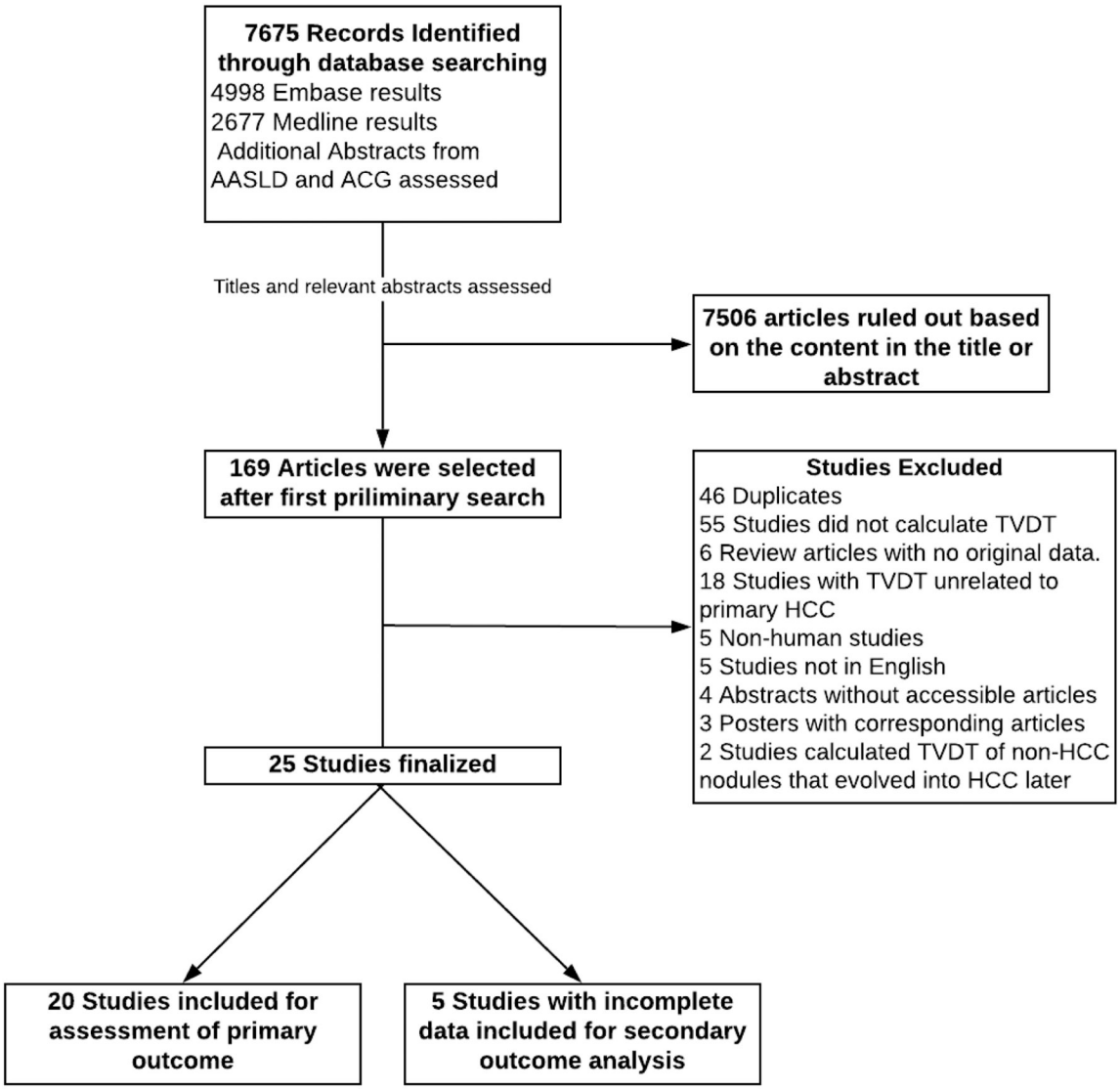

Figure 1.
Search and selection process

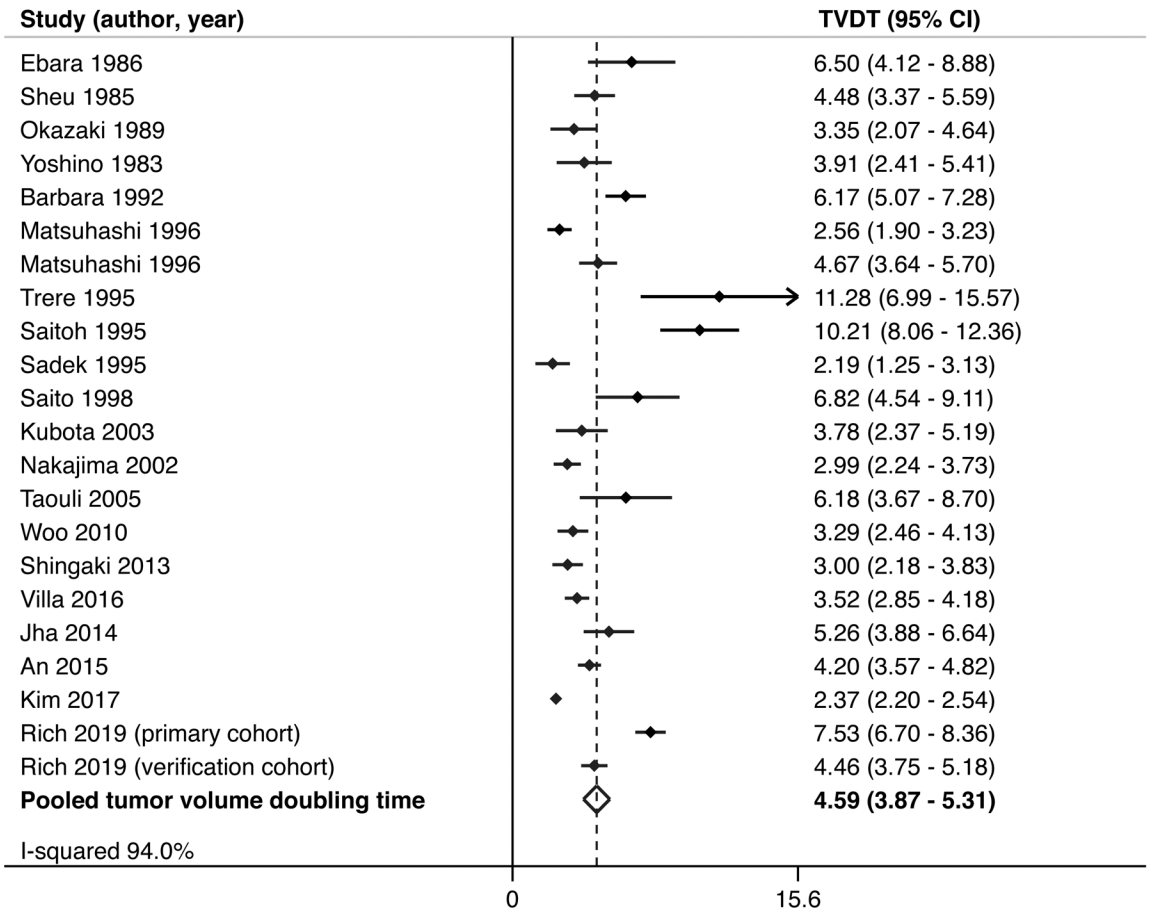

Figure 2.
Pooled tumor volume doubling time for hepatocellular carcinoma

Table 1.

Study Characteristics

Source	Study Site	Study design	Imaging modality	# patients	Primary HCC etiology	Tumor volume doubling time (months)
Ebara 1986[29]	Japan	Prospective	US	22	59 % EtOH 14% HBV	Mean 6.5 ± 5.73.9123 Median: 5.6
Sheu 1985[19]	China	Prospective	US	28	86% HBV	Mean: 4.5 ± 3.1 Median: 3.7
Okazaki 1989[25]	Japan	Prospective	US, CT	15	13% HBV	Mean 3.4 ± 2.5 Median: 2.3
Yoshino 1983[17]	Japan	Prospective	US, CT	13		Mean: 3.9 ± 3.2
Barbara 1992[26]	Italy	Retrospective	US	39	28% HBV 28% EtOH	Mean: 6.7± 4.3 Median: 5.6
Matsuhashi 1996[32]	Japan	Prospective	US	21	100% HCV 100% EtOH	Mean: 2.6 ± 1.5 Median: 1.9
Matsuhashi 1996[32]	Japan	Prospective	US	14	100% HCV	Mean: 4.7 ± 2.0
Trere 1995[47]	Italy	Prospective	US	24		Mean: 11.1 ± 2.2 Median: 8.0
Saitoh 1995[30]	Japan	Retrospective	CT	15	93% HCV	Mean: 10.2 ± 5.0 Median: 9.8
Sadek 1995[48]	USA	Prospective	MRI	5	40 % HBV 20% HCV	Mean:2.2 ± 1.2 Median: 2.0
Saito 1998[33]	Japan	Retrospective	US	21	91% HCV	Mean: 6.8 ± 5.3 Median 4.7
Kubota 2003[49]	Japan	Retrospective	CT	22	69% HCV	Mean: 3.8 ± 3.4 Median: 2.7
Nakajima 2002[31]	Japan	Retrospective	US, CT, MRI	34	94% HCV	Mean: 3.0 ± 2.2 Median: 2.5
Taouli 2005[20]	USA	Retrospective	CT, MRI	11	27% HBV 27% Hep C	Mean: 6.2 ± 5.3 Median: 4.4
Cucchetti 2005[22]	Italy	Retrospective	US, CT, MRI	62	65% HCV	
Kudo 2008[50]	Japan	Prospective	US	52		
Woo 2010[51]	Korea	Retrospective	CT	5	100% HBV	Mean: 3.3 ± 1.0 Median: 3.6
Furlan 2012[24]	USA, Italy, Rome	Retrospective	CT, MRI	48	79% HCV	
Mochizuki 2012[28]	Japan	Prospective	CT	19		Mean: 3.6
Shingaki 2013[27]	Japan	Retrospective	CT	53	77% HCV	Mean: 3.0 ± 3.1
Rowe 2014[23]	UK	Retrospective		57	>50% HCV	Mean: 5.0
Villa 2016[21]	Italy	Prospective	CT	78	56% HCV	Mean: 3.5 ± 3.0 Median: 2.7
Jha 2014[18]	USA	Retrospective	MRI	52	63% HCV	Mean: 5.3 ± 5.4
An 2015[15]	Korea	Retrospective	CT, MRI	175	66% HBV	Mean: 4.2 ± 4.2 Median: 2.8
Kim 2017[14]	Korea	Retrospective	CT, MRI	269	73% HBV	Median: 2.4
Rich 2019 primary cohort[4]	USA	Retrospective	CT, MRI	242	68% HCV	Median: 7.5

Source	Study Site	Study design	Imaging modality	# patients	Primary HCC etiology	Tumor volume doubling time (months)
Rich 2019 validation cohort[4]	USA, UK	Retrospective	CT, MRI	176	53% HCV	Median: 4.5

CT – computed tomography; EtOH – alcohol-related liver disease; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; MRI – magnetic resonance imaging; NASH – nonalcoholic steatohepatitis

Table 2.

Quality Assessment of Eligible Studies via Newcastle-Ottawa scale

Study	Selection bias	Sample Size	Patient inclusion criteria	Imaging test	Tumor volume measurement	Interpretation by >1 radiologist	Statistical analysis
Ebara 1986[29]							✓
Sheu 1985[19]							✓
Okazaki 1989[25]			✓				✓
Yoshino 1983[17]			✓				✓
Barbara 1992[26]		✓			✓		✓
Matsuhashi 1996[32]		✓					✓
Trere 1995[47]			✓				✓
Saitoh 1995[30]							✓
Sadek 1995[48]				✓			
Saito 1998[33]			✓	✓			✓
Kubota 2003[49]			✓	✓		✓	
Nakajima 2002[31]		✓	✓	✓			✓
Taouli 2005[20]			✓			✓	✓
Woo 2010[51]				✓		✓	✓
Shingaki 2013[27]		✓		✓		✓	✓
Villa 2016[21]		✓		✓	✓	✓	✓
Jha 2014[18]		✓	✓	✓		✓	✓
An 2015[15]		✓		✓		✓	✓
Kim 2017[14]		✓	✓	✓			✓
Rich 2019[4]		✓	✓	✓	✓	✓	✓

*Checkmarks denote high-quality metrics and empty cells denote low-quality metrics

Table 3

Hepatocellular carcinoma tumor growth patterns

Study	Rapid growth n (%)	Intermediate growth n (%)	Indolent growth n (%)
Ebara 1986[29]	9 (40.9)	5 (22.7)	8 (36.4)
Sheu 1985[19]	10 (32.3)	17 (54.8)	4 (12.9)
Okazaki 1989[25]	10 (66.7)	4 (26.7)	1 (6.7)
Yoshino 1983[17]	7 (43.8)	7 (43.8)	2 (12.5)
Barbara 1992[26]	8 (20.5)	20 (51.3)	11 (28.2)
Matsuhashi 1996[32]	14 (66.7)	7 (33.3)	0
Matsuhashi 1996[32]	2 (14.3)	12 (85.7)	0
Trere 1995[47]	2 (10.0)	7 (35.0)	11 (55.0)
Saitoh 1995[30]	1 (4.8)	4 (19.0)	16 (76.2)
Sadek 1995[48]	4 (66.7)	2 (33.3)	0
Saito 1998[33]	1 (4.8)	14 (66.7)	6 (2.9)
Kubota 2003[49]	12 (54.5)	9 (40.9)	1 (4.5)
Nakajima 2002[31]	21 (61.8)	12 (35.3)	1 (2.9)
Taouli 2005[20]	4 (25.0)	8 (50.0)	4 (25.0)
Cucchetti 2005[22]	34 (54.8)	25 (42.4)	3 (4.8)
Woo 2010[51]	1 (20.0)	4 (80.0)	0
Villa 2014[21] *	19 (24.4)	N/A	59 (75.6)
Rowe 2014[23] *	39 (59.1)	N/A	27 (40.9)
Kim 2017[14] *	110 (40.9)	N/A	159 (59.1)
Rich 2019 primary cohort[4]	61 (25.2)	75 (31.0)	106 (43.8)
Rich 2019 validation cohort[4] *	49 (27.8)	96 (54.6)	31 (17.6)
Total	**418 (35.0)**	**328 (27.4)**	**450 (37.6)**

* Study-specific definition for tumor growth patterns were used. Indolent vs. rapid defined using cut-off of 53 days for Villa 2014 and cut-off of 2 months for Kim 2017. For Rowe 2014, rapid vs. indolent defined using specific growth rate at cut-off of 1%. For Rich 2019 validation cohort, rapid, intermediate and indolent were defined as <90 days, 90–365 days, and >365 days respectively.