The impact of portal vein tumor thrombosis on survival in patients with hepatocellular carcinoma treated with different therapies: A cohort study

Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Sebastian Schotten, Felix Hahn, Irene Schmidtmann, Jan Bernd Hinrichs, Christoph Düber, Peter Robert Galle, Hauke Lang, Arndt Weinmann

1 Department of Diagnostic and Interventional Radiology, University Medical Center Mainz, Mainz, Germany, 2 Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Heidelberg, Germany, 3 Department of Internal Medicine I, University Medical Center Mainz, Mainz, Germany, 4 Institute for Diagnostic and Interventional Radiology and Neuroradiology, HSK Wiesbaden, Germany, 5 Department of Medical Biostatistics, Epidemiology and Informatics, Johannes Gutenberg University Mainz, Mainz, Germany, 6 Department of Radiology, Medical School Hannover, Hannover, Germany, 7 Department of General, Visceral and Transplant Surgery, University Medical Center Mainz, Mainz, Germany, 8 Clinical Registry Unit (CRU), University Medical Center Mainz, Mainz, Germany

Abstract

Background
Portal vein tumor thrombosis (PVTT) is a frequent complication of hepatocellular carcinoma (HCC), which leads to classification as advanced stage disease (regardless of the degree of PVTT) according to the Barcelona Clinic Liver Cancer Classification. For such patients, systemic therapy is the standard of care. However, in clinical reality, many patients with PVTT undergo different treatments, such as resection, transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), or best supportive care (BSC). Here we examined whether patients benefited from such alternative therapies, according to the extent of PVTT.

Methods
This analysis included therapy-naïve patients with HCC and PVTT treated between January 2005 and December 2016. PVTT was classified according to the Liver Cancer study group of Japan as follows: Vp1 = segmental PV invasion; Vp2 = right anterior or posterior PV; Vp3 = right or left PV; Vp4 = main trunk. Overall survival (OS) was analyzed for each treatment subgroup considering the extent of PVTT. We performed Cox regression analysis with adjustment for possible confounders. To further attenuate selection bias, we applied propensity score weighting using the inverse probability of treatment weights.

Results
A total of 278 treatment-naïve patients with HCC and PVTT were included for analysis. The median observed OS in months for each treatment modality (resection, TACE/SIRT,
sorafenib, BSC, respectively) was 32.4, 8.1, N/A, and 1.7 for Vp1; 10.7, 6.9, 5.5, and 1.2 for Vp2; 6.6, 7.5, 2.9, and 0.6 for Vp3; and 8.0, 3.6, 5.3, and 0.7 for Vp4. Thus, the median OS in the resection group in case of segmental PVTT (Vp1) was significantly longer compared to any other treatment group (all \( p \) values <0.01).

**Conclusions**

Treatment strategy for HCC with PVTT should not be limited to systemic therapy in general. The extent of PVTT should be considered when deciding on treatment alternatives. In patients with segmental PVTT (Vp1), resection should be evaluated.

**Introduction**

Hepatocellular carcinoma (HCC) is a major global health problem [1], which is commonly complicated by portal venous tumor thrombosis (PVTT) [2,3]. The clinical relevance of PVTT is remarkable because of both its high incidence in patients with HCC (10–40%) [2,3] and its massive impairment of prognosis [4]. PVTT is a criterion for classifying HCC as advanced stage according to the widely accepted Barcelona Clinic Liver Cancer Classification (BCLC) [5], which is endorsed by the European Association for the Study of the Liver (EASL) [6] and the American Association of the Study of Liver Diseases (AASLD) [7].

The BCLC recommends palliative systemic therapy for patients with advanced stage disease, regardless of the extent of PVTT [8]. Despite the approval of new agents, the standard of care for patients with advanced stage HCC is still sorafenib, which is proven to be safe and effective in this patient subgroup [9,10]. However, in clinical reality, a high proportion of patients with PVTT are not treated strictly according to the BCLC algorithm but rather undergo individualized therapies, including resection, transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), or best supportive care (BSC) [11,12]. Moreover, several studies from Asia indicate that well-selected patients might benefit from such alternative therapies [13–15]. However, there is no consensus regarding how to identify these patients, and the level of evidence supporting such alternative treatments is low, especially among Western patients.

In the present study, we aimed to identify patients who might benefit from surgical or locoregional therapies, considering the extent of PVTT.

**Material and methods**

**Study design, data acquisition, and patient recruitment**

We performed a registry-based cohort study, and followed the STROBE guidelines when writing our manuscript (S1 Checklist) [16]. The need for institutional review board approval was waived by the Ethics Committee of the Medical Association of Rhineland Palatinate, Mainz, Germany. Informed consent was not applicable due to the retrospective nature of this cohort study. Patient records and information were anonymized prior to analysis.

We collected data regarding etiology of liver disease, baseline patient characteristics, tumor characteristics, and treatment from a prospectively populated clinical database that was installed in 1998 at our university medical center [17]. Laboratory results from the time of the initial HCC diagnosis were extracted from our laboratory information system. If no test results were available for the exact date of diagnosis, we selected results from the date nearest to the
date of diagnosis if the interval was less than 90 days, otherwise the results were recorded as missing. For patients who were initially diagnosed outside of the university hospital, physician reports were requested, and the documented laboratory data were incorporated into our database.

Survival data were extracted from clinical records and by contacting registration offices. The recruitment period was January 1, 2005 to December 31, 2016. To ensure one year of follow-up, the final evaluation date was set as December 31, 2017. Inclusion criteria were HCC diagnosis according to EASL [6]/AASLD [7], and PVTT diagnosis. Furthermore, patients undergoing combination therapy were not included into the analysis. Patients who received therapy for HCC prior to PVTT diagnosis were excluded. The presented methodology was partly described in a previous project investigating the entire cohort of patients with HCC in order to determine the impact of PVTT on overall survival (OS) [4].

**Imaging analysis**

All imaging studies of the identified patients were semi-automatically requested. Subsequently, all analyzable patient images were transferred to a reserved and secured partition of our picture archiving and communication system (SECTRA, Linköping, Sweden). We identified all individual cross-sectional imaging examinations suitable for final analysis. Due to considerable heterogeneity of the labeling and the great variety of treatments performed, this selection process had to be performed manually. Then the imaging studies and the respective contrast-phases were arranged in the PACS viewer using predetermined layout rules.

Imaging analysis was performed through consensus by two board-certified radiologists with >10 years of experience in oncologic imaging of the liver (RK and SS). PVTT was retrospectively diagnosed by analyzing all available contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans. Bland thrombus and PVTT were differentiated using established criteria for CT and MRI [18]. In case of disagreement, both observers performed a joint second review to achieve a consensual decision. The extent of PVTT was documented in the HCC registry using the classification suggested by the Liver Cancer Study Group of Japan (LCSGJ) ranging from Vp0–Vp4, where Vp0 = no PVTT; Vp1 = segmental PV invasion; Vp2 = right anterior or posterior PV; Vp3 = right or left PV; and Vp4 = main trunk and/or contra-lateral portal vein branch to the primarily involved lobe [3,19], Fig 1.

![Fig 1. Figure describing the anatomical classification of portal vein tumor thrombosis as suggested by the Liver Cancer Study Group of Japan (LCSGJ).](https://doi.org/10.1371/journal.pone.0249426.g001)
Treatment

Our interdisciplinary tumor board, including members from the departments of Hepatology, Diagnostic and Interventional Radiology, Hepatobiliary/Transplant Surgery, and Pathology, discussed the indication for treatment of each patient. Patients were selected for surgical resection if they were classified as Child-Pugh A or B, based on their predicted future liver remnant volumes, and according to their tumor stage, and Eastern Cooperative Oncology Group (ECOG) performance status.

Patients treated with TACE received either conventional Lipiodol-based TACE (cTACE), or TACE using drug-eluting beads (DEB-TACE). Treatment was performed in a standardized manner, as previously described [20,21]. After treatment, all patients received a control CT on the same day (cTACE) or the next day (DEB-TACE) to assess tumor staining and to exclude postinterventional complications. TACE was repeated every six weeks until viable tumor was no longer detected by CT or MRI or until any contraindications occurred [22]. SIRT-treated patients received two separate treatments with Yttrium-90-loaded resin spheres, one for the right and one for the left liver lobe, with four weeks between the two sessions. Systemic therapy was started with an initial dose of 400 mg b.i.d. sorafenib. This dose was reduced or the treatment was stopped in case of intolerable toxicity or clinical disease progression. CT and/or MRI were performed every three months to evaluate tumor response.

Statistical analysis

Patient characteristics were described as mean or median and range for quantitative variables, and as absolute and relative frequency for categorical variables. OS was calculated as time from start of treatment to death. Censoring occurred at the end of the study or loss to follow-up. A descriptive analysis of survival was performed using Kaplan-Meier curves. Comparisons were based on the log-rank test.

As this study was not a randomized trial, it is highly likely that treatment decisions were influenced by PVTT sub-stage or other potentially prognosis-related factors. Thus, confounding is likely to be present. To adjust for possible confounders, we fitted a Cox regression model, with adjustment for PVTT extent, age, sex, Child-Pugh, ECOG, tumor size, and alpha-fetoprotein (AFP). We also applied propensity score weighting using the inverse probability of treatment weights in Cox regression models, to estimate both the average treatment effects (ATE) and the average treatment effects of the treated (ATT). Propensity scores were determined in a logistic regression model with therapy as a multinomial outcome and PVTT extent, age, sex, ECOG, tumor size, and AFP as covariates [23]. Patients with ECOG 2–3 or Child-Pugh C were excluded from all regression analyses because none of them underwent resection.

As this is a retrospective exploratory analysis, all $p$-values should be interpreted in a descriptive fashion. The term significant is used here to describe a $p$-value $< 0.05$.

Statistical analyses were performed using R 3.6.0 and SAS 9.4 [24,25].

Results

Patient characteristics at baseline

A total of 462 patients matched the inclusion criteria, of whom 184 patients were excluded for the reasons indicated in Fig 2. Thus, 278 patients with HCC and PVTT were included in our analysis.

The follow-up time ranged from 0.1 to 104.2 months (mean 8.4 months). Table 1 presents baseline demographic data (including etiology, Child-Pugh stage, ECOG, AFP, tumor histology and tumor load), as well as PVTT classification and treatment.
Survival of all patients

The median OS in months was 9.63 (5.73–23.23) with resection, 5.07 (4.17–7.00) with TACE/SIRT, 3.93 (2.40–5.43) with sorafenib, and 1.00 (0.57–1.37) with BSC. The Kaplan-Meier curves (Fig 3) demonstrated a significantly longer OS of patients undergoing resection compared to treatment with sorafenib or BSC ($p < 0.001$). Furthermore, patients receiving TACE/SIRT had an only marginally better OS than patients treated with sorafenib ($p = 0.059$), but had a substantially better OS than patients treated with BSC ($p < 0.001$). Among all treatments, patients undergoing BSC had the worst OS ($p < 0.001$).

Survival with different treatments according to PVTT extent

We further performed a subgroup analysis, comparing the different treatment modalities within each PVTT subgroup. Patients with segmental PVTT (Vp1) who underwent resection showed a considerably longer OS (32.4 months) compared to all other treatments (all $p$ values < 0.01). We observed no significant difference between the TACE/SIRT and sorafenib groups, except within the PVTT substage Vp3 ($p = 0.026$). In general, patients treated with
| Characteristic                                      | Value          |
|----------------------------------------------------|----------------|
| **Total number**                                   | 278            |
| **Age in years, mean (range)**                     | 65.6 (27–87)   |
| **Gender, n (%)**                                  |                |
| Male                                               | 231 (83.1)     |
| Female                                             | 47 (16.9)      |
| **Etiology, n (%)**                                |                |
| Alcoholic liver disease                            | 114 (41.0)     |
| Hepatitis C                                        | 48 (17.3)      |
| Hepatitis B                                        | 35 (12.6)      |
| NASH                                               | 16 (5.7)       |
| Hemochromatosis                                    | 5 (1.8)        |
| PBC/PSC                                            | 2 (0.7)        |
| Unknown etiology                                   | 58 (20.9)      |
| **Child-Pugh stage, n (%)**                        |                |
| No liver cirrhosis                                 | 46 (16.5)      |
| A                                                   | 78 (28.1)      |
| B                                                   | 107 (38.5)     |
| C                                                   | 47 (16.9)      |
| **ECOG, n (%)**                                    |                |
| 0                                                   | 108 (38.8)     |
| 1                                                   | 142 (51.1)     |
| 2                                                   | 23 (8.3)       |
| 3                                                   | 5 (1.8)        |
| **AFP in ng/mL, median (range)**                   | 492 (1.4–629592)|
| ≤200 ng/mL, n (%)                                  | 117 (42.1)     |
| >200 ng/mL, n (%)                                  | 161 (57.9)     |
| **Histological tumor type, n (%)**                 |                |
| Conventional HCC                                   | 230 (98.7)     |
| Fibrolamellar HCC                                  | 3 (1.3)        |
| **Growth pattern, n (%)**                          |                |
| Diffuse growth pattern                             | 104 (37.4)     |
| Nodular growth pattern                             | 174 (62.6)     |
| **Diameter of the largest lesion, n (%)**          |                |
| ≤5 cm                                              | 51 (18.3)      |
| >5 cm                                              | 123 (44.2)     |
| **Tumor number n (%)**                             |                |
| 1                                                   | 73 (41.9)      |
| 2                                                   | 29 (16.7)      |
| 3                                                   | 19 (10.9)      |
| 4                                                   | 15 (8.6)       |
| 5                                                   | 6 (3.4)        |
| 6                                                   | 4 (2.3)        |
| 7                                                   | 4 (2.3)        |
| 8                                                   | 3 (1.7)        |
| 9                                                   | 4 (2.3)        |
| ≥10                                                 | 17 (9.8)       |
| **Histological grading, n (%)**                    |                |
| G1                                                  | 42 (18.0)      |

(Continued)
BSC presented the lowest OS across all PVTT stages. Fig 4 shows all combinations of PVTT stages and types of treatment.

**Adjustment for risk factors**

To adjust for possible confounders and to investigate how our results depended on possible influencing factors, we performed Cox regression and propensity score analyses.

**Cox regression analysis with adjustment for risk factors.** Cox regression analysis was performed with adjustment for established risk factors, including PVTT extent, age, sex, Child-Pugh, ECOG, tumor size, and AFP. With adjustment, resection still yielded the best OS compared to all other therapies: resection vs. TACE/SIRT, HR 0.52, 95% CI [0.32, 0.83]; resection vs. sorafenib, HR 0.45, 95% CI [0.26, 0.77]; and resection vs. BSC, HR 0.12, 95% CI [0.06, 0.23]. TACE/SIRT showed little survival benefit over sorafenib: HR 0.87, 95% CI [0.60, 1.26]. BSC was associated with the worst survival: resection vs. BSC, HR 0.12, 95% CI [0.06, 0.23]; TACE/SIRT vs. BSC, HR 0.22, 95% CI [0.13, 0.39]; and sorafenib vs. BSC, HR 0.26, 95% CI [0.15, 0.45]. In this analysis we also observed a reduced risk in females (HR 0.62, 95%CI [0.41, 0.92]) and an increased risk for patients with ECOG 1 (compared to ECOG 0) with HR 1.41, 95%CI [1.05, 1.90] and for patients with Vp4 compared to Vp1 (HR 1.75, 95%CI [1.08, 2.81]). The other adjustment variables (age, Child Pugh, tumor size and AFP) did not exhibit strong association with survival.
Cox regression analysis with adjustment for risk factors and additional propensity score analysis (ATE analysis). We next performed a Cox regression analysis with adjustment for all risk factors (as above) as well as additional propensity score weighting (doubly robust analysis). This analysis essentially confirmed the results of the first analysis. Again, OS was better with resection compared to all other therapies: resection vs. TACE/SIRT, HR 0.58, 95% CI [0.36, 0.92]; resection vs. sorafenib, HR 0.55, 95% CI [0.34, 0.89]; and resection vs. BSC, HR 0.09, 95% CI [0.04, 0.19]. Little difference was observed between TACE/SIRT vs. sorafenib: HR 0.95, 95% CI [0.64, 1.41]. BSC was associated with the worst survival: resection vs. BSC, HR 0.09, 95% CI [0.04, 0.19]; TACE/SIRT vs. BSC, HR 0.16, 95% CI [0.08, 0.30]; and sorafenib vs. BSC, HR 0.16, 95% CI [0.08, 0.32].

ATT analysis. Finally, we performed an ATT analysis to investigate what would have happened if patients treated with TACE/SIRT had undergone resection instead. ATT analysis was performed looking at a Cox regression model with PVTT, as well as at therapies and at their interactions. The results showed that patients with segmental PVTT (Vp1) might have benefited from resection (HR 0.43, 95% CI [0.19, 0.95]). For all other PVTT subgroups (Vp2–Vp4), we found no significant evidence that they would have benefited from surgery. Among patients with Vp1, those who were actually resected showed an HR of 0.26 (95% CI [0.12, 0.58]) when comparing resection to TACE/SIRT.

We also performed another ATT analysis to investigate what would have happened if patients treated with sorafenib had instead undergone resection. There were too few patients with segmental PVTT (Vp1) who received sorafenib to assess their potential benefit from resection. Among all other PVTT subgroups (Vp2–Vp4), we found no significant evidence that they would have benefited from surgery.

Discussion

In this study, we aimed to identify patients with HCC and PVTT who might benefit from individualized therapeutic approaches other than systemic therapy, particularly considering the
We demonstrated that survival among patients with advanced HCC considerably varied according to different therapies and to the extent of PVTT. Notably, patients with segmental PVTT (Vp1) who underwent resection had a significantly longer OS compared to any other treatment group. This prompts the hypothesis that for well-selected patients with minor segmental PVTT, hepatic resection might provide better outcomes than TACE/SIRT or sorafenib, even within this Western patient cohort.

In various Asian guidelines, PVTT is not a strict contraindication for potentially curative treatment options like resection; instead, more aggressive management recommendations have been established for such cases [26–29]. This stands in contrast to the Western world, where, following the BCLC recommendations, the AASLD and EASL guidelines consider systemic palliative therapy as the only recommended standard of care [5–8]. However, in clinical practice, patients receive a wide variety of therapies not only in Asia, but also in the Western world, including resection, TACE, and SIRT [11,12]. Since sorafenib therapy provides only a

---

**Fig 4. Median overall survival according to treatment modalities and PVTT stage (Vp1–Vp4).** Middle text field: Median OS; lower left corner: Number of patients; NA: Not available because n = 2. PVTT, Portal vein tumor thrombosis; TACE, Transarterial chemoembolization; SIRT, Selective internal radiation therapy; BSC, Best supportive care.

https://doi.org/10.1371/journal.pone.0249426.g004

---

| Extent of PVTT | Resection | TACE/SIRT | Sorafenib | BSC |
|---------------|-----------|-----------|-----------|-----|
| Vp4           | 8.0       | 3.6       | 5.3       | 0.7 |
| n = 6         | n = 40    | n = 25    | n = 19    |     |
| Vp3           | 6.6       | 7.5       | 2.9       | 0.6 |
| n = 12        | n = 33    | n = 22    | n = 22    |     |
| Vp2           | 10.7      | 6.9       | 5.5       | 1.2 |
| n = 12        | n = 27    | n = 8     | n = 7     |     |
| Vp1           | 32.4      | 8.1       | NA        | 1.7 |
| n = 9         | n = 28    | n = 2     | n = 6     |     |

---

extent of PVTT. We demonstrated that survival among patients with advanced HCC considerably varied according to different therapies and to the extent of PVTT. Notably, patients with segmental PVTT (Vp1) who underwent resection had a significantly longer OS compared to any other treatment group. This prompts the hypothesis that for well-selected patients with minor segmental PVTT, hepatic resection might provide better outcomes than TACE/SIRT or sorafenib, even within this Western patient cohort.
modest OS benefit, it is quite common that patients are offered other treatment options in the hope for a better outcome. This likely happens at least partly due to underestimation of the negative prognostic impact of a minor PVTT. Furthermore, PVTT is frequently missed in imaging during daily clinical practice [30].

Our present study is the first analysis of a Western patient cohort to demonstrate that selected Caucasian patients may also benefit from resection in case of Vp1-PVTT. However, this was not the case for more advanced stages of PVTT (Vp2–Vp4). In Asian liver centers, hepatic resection with or without tumor thrombectomy is currently a widespread practice for selected patients with HCC and PVTT, even when PVTT is more extensive than Vp1 [13,31,32]. Kokudo et al. found that in patients with PVTT stages Vp1–Vp3, resection conferred a survival benefit compared to patients who were not resected (treated with TACE, chemotherapy or hepatic arterial infusion chemotherapy, ablation therapy, best supportive care, and other treatments); however, patients with Vp4 did not benefit from resection in terms of OS [13]. In the meta-analysis by Liang et al., among patients with Vp1–3, the hazard ratios for the 1-, 3-, and 5-year OS rates were also in favor of the resection subgroup compared to the non-resection subgroup undergoing various therapies (TACE, sorafenib, TACE combined with sorafenib, TACE combined with radiotherapy) [32]. Again, for patients with Vp4, they found no significant difference between the resection and non-resection subgroups [32]. Overall, several Asian studies indicate that surgery can yield survival benefits and enhanced quality of life for selected patients (Vp1–Vp3), but should be cautiously considered for patients with PVTT invading the main trunk of the portal vein (Vp4), as this may increase the risk of postoperative complications and liver failure [13,31,32]. Our present findings are basically in line with these prior results, with the exception that in our Western patient cohort, resection led to a survival benefit only in patients with Vp1.

In cases of unresectable HCC, TACE plays an established role in treatment [33–35]. However, TACE is theoretically contraindicated in the presence of PVTT because of the potential risk of liver necrosis due to post-TACE ischemia. In a meta-analysis, Zhang et al. demonstrated that hepatectomy was superior to TACE in patients with peripheral PVTT, but did not find a significant survival difference between hepatectomy and TACE among patients with main trunk PVTT [14]. Furthermore, another group performed a meta-analysis and found a survival benefit of resection compared to TACE among patients with Vp1–3, but not Vp4 [36].

Compared to BSC, TACE has yielded a better OS in patients with any extent of PVTT in several Asian trials [37–39]. However, another research group found that TACE achieved an OS benefit for patients with Vp1–3, but not Vp4 [40]. Overall, these previous findings are in accordance with our present results in which patients undergoing BSC exhibited the lowest OS across all PVTT substages.

Regarding the use of sorafenib as standard therapy, our present results are consistent with the findings of the phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study (OS of 10.7 months in the sorafenib group vs. 7.9 months in the placebo group, \(p < 0.001\)) and the Asia-Pacific trial (OS of 6.5 months in the sorafenib group vs. 4.2 months in the placebo group, \(p < 0.05\)) [9,10]. Notably, a subgroup analysis of the SHARP trial revealed that among patients with macrovascular invasion, sorafenib therapy yielded a longer median OS (8.1 months vs. 4.9 months) and time to progression (4.1 months vs. 2.7 months) compared to placebo [41]. However, neither trials did take into account PVTT extent [9,10].

The present study has several limitations. The most important limitation was the lack of randomization. Treatment decisions were determined in clinical reality, accounting for numerous factors such as patient characteristics or tumor characteristics. This poses the risk of a potential selection bias in our population, as patients in a better clinical condition (for
example patients with ECOG 0) are more likely to undergo more aggressive therapies, like TACE/SIRT or even resection. In the absence of data from randomized controlled clinical trials, we performed analyses with adjustment for possible confounders and used propensity score weighting (doubly robust analysis), thus mimicking a randomized clinical trial and compensating for differences in the covariates between patients receiving different treatments. However, even with this approach, we may not have completely avoided the biases arising from the retrospective study design. Another limitation was the relatively small number of patients in the PVTT subgroups of each treatment, which might have led to underpower. However, most studies in the literature do not differentiate between different PVTT substages, and thus do not account for possible differences in patients’ prognosis. Notably, CT and MRI scanners and protocols have been continuously improved, such that it is now easier to diagnose small PVTT. Both investigators had a high level of expertise in HCC imaging, and paid particular attention to PVTT detection. Additionally, they analyzed the images retrospectively, considering the course of disease. Therefore, considerably more PVTTs were detected in our present study than in clinical practice. It should be noted that our patient cohort may have shown a tendency towards more advanced tumors, as our hospital is a specialized tertiary care liver center. Finally, due to differences in underlying liver diseases, our results may not be applicable to patients with HCC and PVTT in other countries. For example, Asian studies report a much higher proportion of patients with chronic hepatitis B—a population that often develops HCC in a non-cirrhotic liver [2,42]. Moreover, Asian patients generally have fewer comorbidities. Thus, it may not be possible to transfer our results to Asian patients.

In this study, all patients undergoing systemic therapy received sorafenib. However, in the last two years, several new agents have become available for systemic therapy. Lenvatinib is proven to be a non-inferior first-line treatment option compared to sorafenib; however, that study excluded patients with main portal trunk PVTT [43]. Regorafenib [44] and Cabozantinib [45] have been demonstrated to be effective as second-line option in selected patients with sorafenib-resistant HCC. The immunotherapeutic drug Pembrolizumab [46] (NCT02702414) is already approved by the Food and Drug Administration (FDA) as second-line treatment. Nivolumab has been approved by the FDA, but did not reach the primary endpoint in CheckMate-459 (NCT02576509). The combination of Atezolizumab and Bevacizumab has shown promising results in the IMBRAVE 150 trial [47]. However, sorafenib is still the mainstay of systemic therapies. Further studies investigating these new agents are warranted.

Conclusions

This study was the first to compare different treatments in different PVTT substages among Western patients. Our results showed that hepatic resection was beneficial for patients with segmental PVTT (Vp1), and provided better outcomes than TACE/SIRT or sorafenib. These findings suggest that for well-selected patients with minor PVTT, resection may be an appropriate alternative therapeutic option when deemed oncologically reasonable.

Supporting information

S1 Checklist. STROBE statement—Checklist of items that should be included in reports of observational studies.

(DOC)

S1 Fig. Kaplan Meier curves for the different portal vein thrombosis cohorts. A = Vp1, B = Vp2, C = Vp3, D = Vp4. TACE, Transarterial chemoembolization; SIRT, Selective internal
radiation therapy; BSC, Best supportive care.

Acknowledgments
This study contains data that are part of the doctoral thesis of one of the authors (VS). AMK and VS contributed equally to this study.

Author Contributions
Conceptualization: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Christoph Düber, Hauke Lang, Arndt Weinmann.

Data curation: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Sebastian Schotten, Irene Schmidtmann, Arndt Weinmann.

Formal analysis: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Felix Hahn, Irene Schmidtmann, Jan Bernd Hinrichs, Arndt Weinmann.

Funding acquisition: Aline Mähringer-Kunz, Christoph Düber, Peter Robert Galle, Hauke Lang.

Investigation: Aline Mähringer-Kunz, Sebastian Schotten.

Methodology: Aline Mähringer-Kunz, Roman Kloeckner, Irene Schmidtmann, Jan Bernd Hinrichs, Arndt Weinmann.

Project administration: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Sebastian Schotten, Arndt Weinmann.

Resources: Aline Mähringer-Kunz, Christoph Düber, Peter Robert Galle, Hauke Lang, Arndt Weinmann.

Software: Aline Mähringer-Kunz, Roman Kloeckner, Felix Hahn, Irene Schmidtmann, Jan Bernd Hinrichs, Arndt Weinmann.

Supervision: Aline Mähringer-Kunz, Roman Kloeckner, Sebastian Schotten, Peter Robert Galle, Hauke Lang.

Validation: Aline Mähringer-Kunz, Roman Kloeckner, Sebastian Schotten, Felix Hahn, Irene Schmidtmann, Jan Bernd Hinrichs.

Visualization: Aline Mähringer-Kunz, Felix Hahn.

Writing – original draft: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Arndt Weinmann.

Writing – review & editing: Aline Mähringer-Kunz, Verena Steinle, Roman Kloeckner, Sebastian Schotten, Felix Hahn, Irene Schmidtmann, Jan Bernd Hinrichs, Christoph Düber, Peter Robert Galle, Hauke Lang, Arndt Weinmann.

References
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394–424. https://doi.org/10.3322/caac.21492 PMID: 30207593

2. Cheung TK, Lai CL, Wong BC, Fung J, Yuen MF. Clinical features, biochemical parameters, and virological profiles of patients with hepatocellular carcinoma in Hong Kong. Aliment Pharmacol Ther. 2006; 24:573–583. https://doi.org/10.1111/j.1365-2036.2006.03029.x PMID: 16907890
3. Kudo M, Izumi N, Ichida T, Ku Y, Kokudo N, Sakamoto M, et al. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res. 2016; 46:372–390. https://doi.org/10.1111/hepr.12697 PMID: 26970231

4. Mähringer-Kunz A, Steinele V, Duber C, Weinmann A, Koch S, Schmidtmann I, et al. Extent of portal vein tumour thrombosis in patients with hepatocellular carcinoma: The more, the worse? Liver Int. 2019; 39:324–331. https://doi.org/10.1111/liv.13988 PMID: 30318826

5. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999; 19:329–338. https://doi.org/10.1055/s-2007-1007122 PMID: 10518312

6. European Association for the Study of the Liver (EASL). Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018; 69:182–236. https://doi.org/10.1016/j.jhep.2018.03.019 PMID: 29628281

7. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018; 68:723–750. https://doi.org/10.1002/hep.29913 PMID: 29624699

8. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391(10127):1301–14. https://doi.org/10.1016/S0140-6736(18)30010-2 PMID: 29307467

9. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378–390. https://doi.org/10.1056/NEJMoa0708857 PMID: 18650514

10. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10:25–34. https://doi.org/10.1016/S1470-2045(08)70285-7 PMID: 19095497

11. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015; 35:2155–2166. https://doi.org/10.1111/liv.12818 PMID: 25752327

12. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. Ann Surg. 2013; 257:929–937. https://doi.org/10.1097/SLA.0b013e31828329b8 PMID: 23426336

13. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016; 65:938–943. https://doi.org/10.1016/j.jhep.2016.05.044 PMID: 27266618

14. Zhang ZY, Dong KS, Zhang EL, Zhang LW, Chen XP, Dong HH. Resection might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: A systematic review and meta-analysis. Medicine (Baltimore). 2019; 98:e18362. https://doi.org/10.1097/MD.00000000000018362 PMID: 31852141

15. Ye HH, Ye JZ, Xie ZB, Peng YC, Chen J, Ma L, et al. Comprehensive treatments for hepatocellular carcinoma with tumor thrombus in major portal vein. World J Gastroenterol. 2016; 7; 22:3632–3643. https://doi.org/10.3748/wjg.v22.i3.3632 PMID: 27035855

16. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenvrucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007; 370:1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X PMID: 18064739

17. Weinmann A, Koch S, Niederle IM, Schulze-Bergkamen H, Konig J, Hoppe-Lotichius M, et al. Trends in epidemiology, treatment, and survival of hepatocellular carcinoma patients between 1998 and 2009: an analysis of 1066 cases of a German HCC Registry. J Clin Gastroenterol. 2014; 48:279–289. https://doi.org/10.1097/MCG.0b013e318283a793 PMID: 24045276

18. Catalano OA, Choy G, Zhu A, Hahn PF, Sahani DV. Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging. Radiology. 2010; 254:154–162. https://doi.org/10.1148/radiol.09090304 PMID: 20032150

19. The general rules for the clinical and pathological study of primary liver cancer. Liver Cancer Study Group of Japan. Jpn J Surg. 1989; 19:98–129. https://doi.org/10.1007/BF02471576 PMID: 2659865

20. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010; 33:41–52. https://doi.org/10.1007/s00270-009-9711-7 PMID: 19908093

21. Lencioni R, de Baere T, Burrel M, Caridi JG, Lammer J, Malagari K, et al. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations.
22. Kloeckner R, Weinmann A, Prinz F, Pinto dos Santos D, Ruckes C, Dueber C, et al. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer. 2015; 15:465. https://doi.org/10.1186/s12885-015-1480-x PMID: 26059447

23. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013; 32:3388–3414. https://doi.org/10.1002/sim.5753 PMID: 23508673

24. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria; 2016. https://www.R-project.org/, accessed 2019/2020.

25. Statistical Analysis System, Software developed by SAS, Institute for advanced analytics [Internet]. Cary, NC, accessed 2019/2020.

26. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014; 3:458–468. https://doi.org/10.1159/000343875 PMID: 26280007

27. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017; 11:317–370. https://doi.org/10.1007/s12072-017-9799-9 PMID: 28620797

28. Korean Liver Cancer Study G, National Cancer Center K. 2014 KLCSG-NCC Korea Practice Guideline for the Management of Hepatocellular Carcinoma. Gut Liver. 2015; 9:267–317. https://doi.org/10.5009/gnl14460 PMID: 25918260

29. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014; 146:1691–1700 e3. https://doi.org/10.1053/j.gastro.2014.02.032 PMID: 24583061

30. Roayaie S, Jibara G, Taouli B, Schwartz M. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol. 2013; 20:3754–3760. https://doi.org/10.1245/s10434-013-0240-9 PMID: 23884750

31. Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol. 2010; 17:2073–2080. https://doi.org/10.1245/s10434-010-0940-4 PMID: 20131013

32. Liang L, Chen TH, Li C, Xing H, Han J, Wang MD, et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. HPB (Oxford). 2018; 20:1119–1129. https://doi.org/10.1016/j.hpb.2018.06.1804 PMID: 30056066

33. Xue TC, Xie XY, Zhang L, Yin X, Zhang BH, Ren ZG. Transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a meta-analysis. BMC Gastroenterol. 2013; 13:60. https://doi.org/10.1186/1471-230X-13-30 PMID: 23566041

34. Leng JJ, Xu YZ, Dong JH. Efficacy of transarterial chemoembolization for hepatocellular carcinoma with portal vein thrombosis: a meta-analysis. ANZ J Surg. 2016 Oct; 86:816–820. https://doi.org/10.1111/ans.12803 PMID: 25088384

35. Silva JP, Berger NG, Tsai S, Christians KK, Clarke CN, Mogal H, et al. Transarterial chemoembolization in hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. HPB (Oxford). 2017; 19:659–666. https://doi.org/10.1111/1471-230X.13360 PMID: 28552299

36. Zhang XP, Wang K, Li N, Zhong CQ, Wei XB, Cheng YQ, et al. Survival benefit of hepatic resection versus transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombus: a systematic review and meta-analysis. BMC Cancer. 2017; 17:902. https://doi.org/10.1186/s12885-017-3895-z PMID: 29282010

37. Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol. 2011; 18:413–420. https://doi.org/10.1245/s10434-010-1321-z PMID: 20839057

38. Niu ZJ, Ma YL, Kang P, Ou SQ, Meng ZB, Li ZK, et al. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. Med Oncol. 2012; 29:2992–2997. https://doi.org/10.1007/s12032-011-0145-0 PMID: 22200992

39. Chung GE, Lee JH, Kim HY, Hwang SY, Kim JS, Chung JW, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology. 2011; 258:627–634. https://doi.org/10.1148/radiol.10101088 PMID: 21273224
40. Lv WF, Liu KC, Lu D, Zhou CZ, Cheng DL, Xiao JK, et al. Transarterial chemoembolization for hepatocellular carcinoma combined with portal vein tumor thrombosis. Cancer Manag Res. 2018; 10:4719–4726. https://doi.org/10.2147/CMA.S166527 PMID: 30410405

41. Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol. 2012; 57:821–829. https://doi.org/10.1016/j.jhep.2012.06.014 PMID: 22727733

42. Ganem D, Prince AM. Hepatitis B virus infection—natural history and clinical consequences. N Engl J Med. 2004; 350:1118–1129. https://doi.org/10.1056/NEJMra031087 PMID: 15014185

43. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018; 391:1163–1173. https://doi.org/10.1016/S0140-6736(18)30207-1 PMID: 29433850

44. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 389:56–66. https://doi.org/10.1016/S0140-6736(16)32453-9 PMID: 27932229

45. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med. 2018; 379:54–63. https://doi.org/10.1056/NEJMoa1717002 PMID: 29972759

46. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018; 19:940–952. https://doi.org/10.1016/S1470-2045(18)30351-6 PMID: 29875066

47. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382:1894–1905. https://doi.org/10.1056/NEJMoa1915745 PMID: 32402160