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Lipiodol deposition in portal vein tumour thrombus predicts treatment outcome in HCC patients after transarterial chemoembolisation

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Abstract

Objective To study lipiodol deposition in portal vein tumour thrombus (PVTT) in predicting the treatment outcome of hepatocellular carcinoma (HCC) patients after transarterial chemoembolisation (TACE).

Methods We retrospectively reviewed data from 379 HCC patients with PVTT who underwent TACE as the initial treatment at Sun Yat-Sen University Cancer Center from January 2008 to December 2015. Patients were grouped by positive and negative lipiodol deposition based on the extent of lipiodol deposition in PVTT. The overall survival (OS) and progression-free survival (PFS) were compared between negative and positive lipiodol deposition groups; furthermore, the value of the combinatorial evaluation of tumour responses and lipiodol deposition in PVTT in predicting prognosis was analysed in subgroup patients with stable disease (SD) after TACE.

Results Of the 379 patients, 264 (69.7%) had negative and 115 (30.3%) had positive lipiodol deposition in PVTT after TACE. Multivariate analysis identified positive lipiodol deposition in PVTT as an independent prognostic factor for favourable OS ($p = 0.001$). The median OS and PFS of negative and positive lipiodol deposition groups were 4.70 vs. 8.97 months ($p = 0.001$) and 3.1 months vs. 5.8 months ($p < 0.001$). In subgroup patients, the median OS and PFS of negative and positive lipiodol deposition groups were 4.7 months vs. 10.5 months ($p < 0.001$) and 3.5 months vs. 7.0 months ($p < 0.001$), respectively.

Conclusions The patients with positive lipiodol deposition in PVTT had a longer OS than those with negative lipiodol deposition. Furthermore, the positive lipiodol deposition in PVTT can further differentiate HCC patients with favourable prognosis from SD patients.

Key Points

- *Lipiodol deposition in PVTT is a prognostic indicator for HCC patients after TACE treatment.*
- *Positive lipiodol deposition in PVTT is associated with a better prognosis.*

Keywords Hepatocellular carcinoma · Lipiodol · Chemoembolisation · Prognosis

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Abbreviations

ALBI	Albumin-Bilirubin
CI	Confidence interval
CR	Complete response
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
MR	Magnetic resonance
mRECIST	The Modified Response Evaluation Criteria in Solid Tumors
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PVTT	Portal vein tumour thrombus
SD	Stable disease
TACE	Transarterial chemoembolisation

Introduction

Liver cancer is the third leading cause of cancer death worldwide [1]. Approximately 70% of hepatocellular carcinoma (HCC) patients are diagnosed at an intermediate or advanced stage when curative treatments are no longer feasible. Unfortunately, the survival of patients with advanced HCC is still not satisfactory despite the advancements in treatment strategies such as targeted therapy, new chemotherapy regimens, and radioembolisation [2–4]. HCC has a propensity to easily invade the portal venous system resulting in intrahepatic metastasis and recurrence. Portal vein tumour thrombus (PVTT) plays a major role in the prognosis of patients with HCC [5, 6].

Studies have revealed that transarterial chemoembolisation (TACE) may still be a good choice for some HCC patients with PVTT who have adequate hepatic functional reserve and good performance status [7–11]. TACE offers better overall survival (OS) than systemic therapy or best supportive care [12, 13]. The Modified Response Evaluation Criteria in Solid Tumors [14] (mRECIST) criteria can reliably evaluate the treatment outcome of HCC patients after TACE and is, therefore, recommended for evaluating radiological responses of tumours [14–16]. However, because of difficulties in accurately and intuitively evaluating therapy responses in patients with PVTT based on intratumoural arterial enhancement, most patients cannot be discriminated after treatment of TACE and fall into the incomplete response (IR)/stable disease (SD) group in clinical practice. The main reason for this is that the lack of a reliable and easily used prognostic indicator for assessing the responses of patients with PVTT to TACE. Previous studies reported that the extent of lipiodol deposition in the primary tumour was a prognostic indicator for HCC patients after TACE treatment [17, 18]. However, these studies only evaluated the lipiodol deposition of primary tumours after TACE, not that of PVTT.

In this study, we aimed to investigate the lipiodol deposition of PVTT in predicting the outcomes of HCC patients after TACE using a large retrospective cohort. The lipiodol deposition in PVTT was used to assess the tumour response in combination with radiological responses of tumours.

Materials and methods

Patients

In total, 379 HCC patients with PVTT who received TACE as the initial treatment were identified at the Sun Yat-Sen University Cancer Center from January 2008 to December 2015. The diagnosis of HCC was based on clinical criteria from the European Association for the Study of the Liver and the American Association for the Study of Liver Disease [19, 20]. Diagnosis of PVTT was determined by two radiologists who had more than 10 years' experience in imaging diagnosis according to the follow imaging features of PVTT, including the following: (1) a low-attenuation mass within the portal vein; (2) the mass shows enhancement in the arterial phase on computed tomography (CT) or magnetic resonance (MR) imaging [7]. The extent of PVTT was classified according to Cheng's classification [21, 22]: type I, tumour thrombus in the segmental branches or smaller branches of the portal vein; type II, tumour thrombus involving the right/left portal vein; type III, tumour thrombus invading the main portal vein; and type IV, tumour thrombus invading the superior mesenteric vein.

The inclusion criteria were as follows: (a) patients between 18 and 75 years old; (b) any tumour size with PVTT; (c) TACE as the initial treatment; (d) patients did not receive tumour resection or organ transplantation after TACE; (e) Child-Pugh A or B liver function; and (f) Eastern Cooperative Oncology Group (ECOG) performance status is 0–2.

The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Ethics Committee of the Sun Yat-Sen University Cancer Center. Written informed consents were obtained from patients before treatment.

Data collection

Clinical and laboratory parameters and radiological records were collected from all patients, including the following: sociodemographic data (age, sex, Eastern Cooperative Oncology Group performance status, HBV), the clinical characteristics of tumour (AFP, liver function, tumour feature: tumour size, tumour number, site of tumour, major vascular

invasion), and other adjuvant therapy. The Albumin-Bilirubin (ALBI) stage [23] and Child-Pugh stage were used to evaluate the liver function.

TACE procedure

The TACE protocol used in our centre was described as previously [24]. For all cases, TACE was performed by surgeons with more than 5 years of experience in interventional therapy for HCC. After local anaesthesia in patients, visceral angiography was routinely performed with a 5-F catheter (5F, Terumo Corporation; Yashiro Corporation) to assess tumour vascularity, vascular anatomy, and portal vein patency. After excluding the existence of an arteriovenous shunt based on visceral angiography, the tip of the catheter was advanced to the right or left hepatic artery, and a supersdistal super-selective catheterisation was then performed with a 2.9-F microcatheter (2.9F; Terumo Corporation) according to tumour distribution, tumour size, and tumour arterial supply. For all cases, the following chemotherapy regimen was used: carboplatin 300 mg (Bristol-Myers Squibb), epirubicin 50 mg (Pfizer), and mitomycin C 4–8 mg (Hisun Pharmaceutical). During the treatment procedure, carboplatin was first administered via hepatic artery infusion, and then a mixture of epirubicin, mitomycin C, and lipiodol 2–5 mL (Lipiodol Ultra-Fluide) was injected into the tumour for chemolipiodolisation. Then, pure lipiodol was injected into the arterial supply of the tumour until a substantial reduction in blood supply was achieved. Next, absorbable gelatine sponge particles (1 to 2 mm in diameter, Gelfoam) or polyvinyl alcohol particles (350 to 560 μm in diameter, Alicon Pharm SCT&TEC) were introduced to block the tumour feeding. Finally, angiography was performed to confirm lipiodol distribution and to exclude ectopic embolisation.

Follow-up and treatment

All patients received routine follow-up after the TACE. At each of these follow-ups, dynamic abdominal CT or MR and blood test including serum liver function tests and AFP were done. The lung is the most common extrahepatic site suffering from tumour metastasis, especially for patients with PVTT. Chest radiography was also carried out during every visit, and chest CT was performed every 6 months, especially when patients were suspected of lung metastasis, e.g. suspicious lumps in the lung during chest radiography or if corresponding respiratory symptoms appeared.

In our centre, repeated TACE was not recommended under the following circumstances: (1) tumour progression; (2) hepatic deterioration such as Child-Pugh C; (3) ECOG performance status > 2; or (4) patients' refusal of the next session of TACE. All the patients were recommended to undergo targeted treatment according to BCLC criteria recommendations; meanwhile, the preferences and economic conditions of patients were respected when the treatment decisions were determined. We defined OS time as the interval between the date of initial TACE and the date of death or the last follow-up date, and PFS time was defined as the interval between the date of initial TACE and the date of disease progression or death. This study was censored on January 1, 2017.

Radiological responses of tumours

The radiological responses of tumours were evaluated 4–6 weeks after TACE by two experienced radiologists (Dr. R.H. Zou and Dr. J.X. Shen) who have more than 10 years of experience on imaging diagnosis according to the mRECIST criteria [14], and any disagreement was resolved by consensus. The radiological responses of tumours were classified into the following four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Lipiodol deposition in PVTT

The extent of lipiodol deposition in PVTT was assessed by the same radiologists mentioned previously, and any disagreement was resolved by consensus. First, the PVTT was located through the CT imaging of portal phase. Then, the extent of lipiodol deposition in PVTT was assessed in non-contrast CT scan. The measurement of the longest lipiodol uptake diameter for PVTT was used to quantify the extent of lipiodol deposition in PVTT. We characterised the lipiodol deposition level as follows: none, no accumulation of lipiodol in PVTT; scattered, spots of lipiodol deposits in PVTT with diameters less than 1 mm; and massive, defined as clumps of lipiodol deposits in PVTT with diameters larger than 1 mm (Fig. 1). The survival of patients with no and scattered lipiodol deposits in PVTT did not differ significantly. Meanwhile, scattered lipiodol deposits < 1 mm diameter often may not be detected by conventional CT in clinical practice [25]. Therefore, we classified patients with no or scattered lipiodol deposits into the negative lipiodol deposition group and patients with massive lipiodol deposits in PVTT into the positive lipiodol deposition group.

To explore the clinical value of lipiodol deposition in PVTT in HCC patients after TACE, OS and PFS of the negative and positive lipiodol deposition groups were compared. The predictive power of the extent of lipiodol deposition in the subgroup patients with stable disease was further investigated. For patients with various PVTT stages, we also performed the subgroup analyses of OS in patients with negative and positive lipiodol deposition groups.

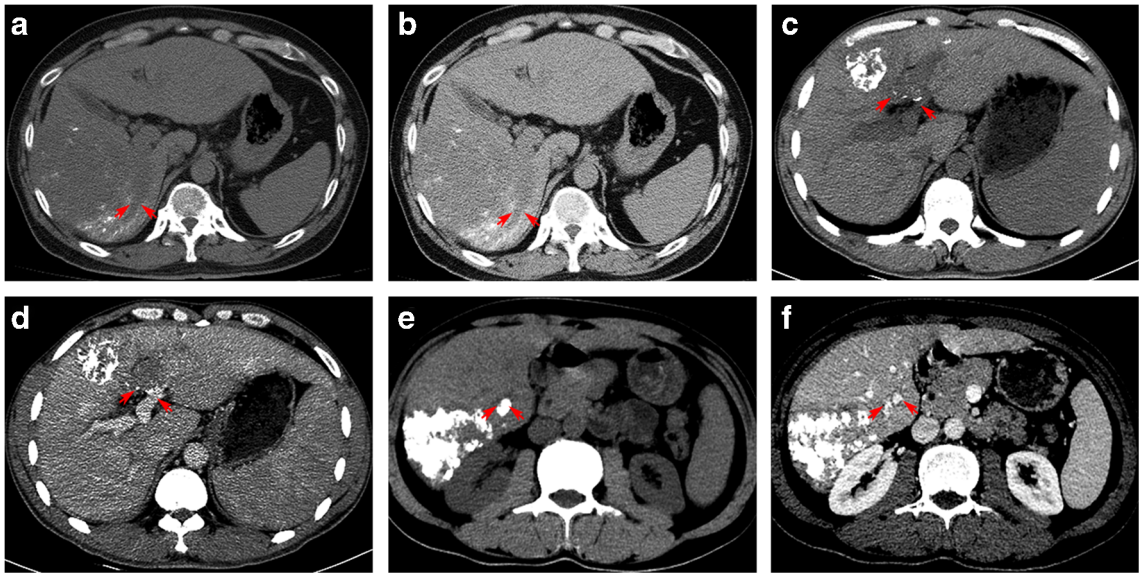

Fig. 1 Extent of lipiodol deposition in PVTT based on CT images after TACE for HCC patients with PVTT. CT scans obtained in three HCC patients during follow-up after treatment. Scans obtained during the arterial (**a**, **c**, **e**) and venous (**b**, **d**, **f**) phases. **a**, **b** None, indicating the absence of lipiodol deposits in PVTT; **c**, **d** scattered, indicating spots of lipiodol deposits in PVTT with diameters < 1 mm; **e**, **f** massive, indicating clumps of lipiodol deposits in PVTT with diameters ≥ 1 mm. Patients with no and scattered lipiodol deposits in PVTT were classified into the negative lipiodol deposition group, and patients with massive lipiodol deposits in PVTT were classified into the positive lipiodol deposition group

Statistical analysis

Categorical variables are shown as descriptive values, and continuous variables are reported as the means (standard deviations) or medians (interquartile ranges). For all patients, continuous variables between two treatment groups were compared using Student's *t* test or the Mann-Whitney *U* test; binary and ordinal categorical variables were compared using the chi-square test and Kruskal-Wallis test, respectively. The Kaplan-Meier method and log-rank test were used to respectively estimate and compare OS and PFS. Median survivals and the corresponding 95% confidence intervals (CIs) were reported. Univariate analysis was performed to select factors predictive of OS and PFS. The variables with p values < 0.1 in univariate analyses and variables reported by previous studies to predict patient survival were used for a multivariate analysis. Multivariate analyses were performed using Cox proportional hazards models. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp.). All p value calculations were two sided, and p values < 0.05 were considered statistically significant.

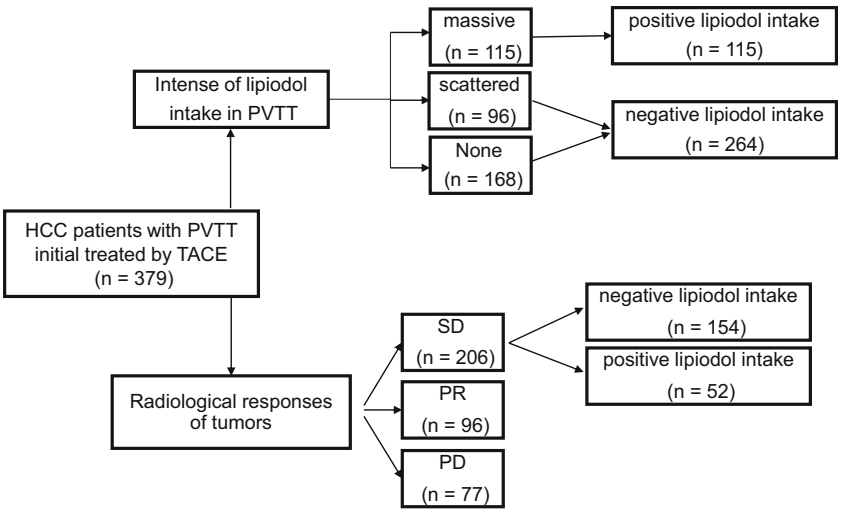

Fig. 2 Flowchart of the study: study population and study design. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation; PVTT, portal vein tumour thrombus; PR, partial response; SD, stable disease; PD, progressive disease

Results

Patients

A total of 379 HCC patients with PVTT who underwent TACE as the initial treatment at the Sun Yat-Sen University Cancer Center from January 2008 to December 2015 were included in our study. The study design is illustrated in Fig. 2. In this study, 168 (44.3%) patients had no lipiodol deposits, 96 (25.3%) had scattered lipiodol deposits, and 115 (30.3%) had massive lipiodol deposits. Thus, 264 (69.7%) patients were classified into the negative lipiodol deposition group, and 115 (30.3%) patients were classified into the positive lipiodol deposition group (Table 1). Additionally, 50 patients (13.2%) had lung metastasis, and 40 (10.6%) patients were diagnosed with lymphatic metastasis based on CT or MR imaging prior to TACE. Thirty-three patients had received sorafenib therapy. The clinical characteristics of patients with negative and positive lipiodol deposition in PVTT asre listed in Table 2.

Radiological responses of tumours

In the present study, a mean of 1.5 TACE sessions (range, 1–7 sessions; total, 589 sessions) was performed, and a total of 121 patients received the second session of TACE. The median volume of lipiodol was 20.0 (20.0 ± 6.9) mL in the first session of TACE. A total of 54.4% ($n = 206$) of the patients maintained SD, while 25.3% ($n = 96$) exhibited PR, and 20.3% ($n = 77$) exhibited PD after the first TACE session (Table 3).

Survival analysis

Univariate analyses of all potential predictive covariates of OS and PFS are presented in Table 4. Tumour size > 10 cm ($p = 0.007$), AFP level > 200 ng/mL ($p = 0.005$), negative lipiodol deposition ($p < 0.001$), absent radiological tumour response ($p = 0.001$), and absence of treatment with sorafenib ($p = 0.038$) were associated with unfavourable OS. Indeed, lipiodol deposition in PVTT (hazard ratio (HR) = 0.619; 95% CI, 0.473–0.811; $p = 0.001$), AFP level > 200 ng/mL (HR = 1.178; 95% CI, 1.031–1.346; $p = 0.007$), radiological responses of tumours (HR = 0.714; 95% CI, 0.543–0.938; $p = 0.014$), and treatment with sorafenib (HR = 0.603; 95% CI, 0.401–0.909; $p = 0.008$) were identified as independent prognostic factors for OS (Table 4).

Next, OS and PFS were compared between patients with negative and positive lipiodol deposition in PVTT. Interestingly, OS and PFS were better in the positive lipiodol deposition group than in the negative lipiodol deposition group (Fig. 3). The median OS and PFS in patients with negative and positive deposition were 4.7 vs. 9.0 months (HR = 0.569, 95% CI 0.441–0.733, $p = 0.001$; Fig. 3b) and 3.1 months vs. 5.8 months (HR = 0.577, 95% CI 0.454–0.732, $p < 0.001$, Fig. 3c), respectively.

We conducted a subgroup analysis to explore the outcome results in various stages of portal vein thrombosis. OS was

Table 1 Clinical characteristic of all patients pre-TACE

Variable	HCC patients with PVTT		
		$N = 379$	%
Age (year)	Median ± SD	51.0 ± 10.08	Range (41–56)
Sex	Male	365	96.3
	Female	14	3.7
HBV	Absent	40	10.6
	Present	339	89.4
Child-Pugh stage	A	337	88.9
	B	42	11.1
ALBI grade	1	154	40.6
	2	222	58.6
	3	3	0.8
Tumour size (cm)	Median ± SD	10.2 ± 3.5	
	< 5	27	7.1
	5–10	154	40.6
	≥ 10	198	52.2
PVTT stage	I	71	18.7
	II	175	46.2
	III	119	31.4
	IV	14	3.7
Lipiodol intake in PVTT	None	168	44.3
	Spot	96	25.3
	Mass	115	30.3
Tumour number	Unifocal	254	67.0
	Multifocal	125	33.0
Alpha fetoprotein	≤ 200	101	26.6
	> 200	278	73.4
Lung metastasis	Absent	329	86.8
	Present	50	13.2
Lymphatic metastasis	Absent	339	89.4
	Present	40	10.6
Times of TACE	1	219	57.8
	2	121	31.9
	3 or more	39	10.3
Sorafenib	Absent	346	91.3
	Present	33	8.7
Anti-virus treatment	Absent	246	64.9
	Present	93	24.5
	NA	40	10.6
Tumour response	Absent	283	74.7
	Present	96	25.3

TACE, transarterial chemoembolisation; *HCC*, hepatocellular carcinoma; *PVTT*, portal vein tumour thrombus; *HBV*, hepatitis B virus; *ALBI*, the Albumin-Bilirubin grade

Table 2 Characteristics of patients with positive and negative lipiodol deposition in PVTT before TACE

Variables	All patients		*p*
	Positive group ($n = 115$)	Negative group ($n = 264$)	
Gender (M/F)	106/9	259/5	0.012
Age (year)	51 (42–58)	47 (40–56)	0.066
Hepatitis B (%)	102 (88.70%)	237 (89.80%)	0.720
WBC (10^9/L)	6.60 (5.30–8.40)	6.90 (5.73–8.20)	0.514
RBC (10^9/L)	4.50 (4.11–4.96)	4.63 (4.19–5.16)	0.121
HB (g/L)	136.00 (125.00–150.00)	139.00 (128.00–139.00)	0.088
PLT (10^9/L)	189.00 (130.00–239.00)	184.00 (130.45–243.68)	0.848
ALT (U/L)	43.00 (30.10–64.00)	51.60 (35.13–75.70)	0.212
AST (U/L)	59.90 (45.60–91.30)	79.45 (55.53–121.70)	0.195
GGT (U/L)	175.80 (99.20–270.80)	220.00 (143.33–332.67)	0.217
ALB (g/L)	39.20 (36.30–41.80)	38.70 (35.80–42.13)	0.529
TBIL (μmol/L)	16.00 (11.50–20.30)	16.95 (12.73–23.30)	0.383
Creatine (μmol/L)	73.10 (64.70–81.07)	71.70 (64.50–78.58)	0.272
PT (s)	12.40 (11.70–13.40)	12.50 (11.80–13.30)	0.294
AFP (ng/mL)			
≤ 200	35 (30.40%)	66 (25.0%)	
> 200	80 (69.60%)	198 (75.0%)	0.343
Tumour size (cm)	10.10 (8.00–12.50)	10.75 (8.60–13.00)	0.427
Tumour number			
Solitary	79 (68.70%)	175 (66.30%)	
Multifocal	36 (31.30%)	89 (33.70%)	0.628
Lung metastasis	13 (11.30%)	37 (14.00%)	0.514
Lymphatic metastasis	14 (12.2%)	226 (9.80%)	0.586
Times of TACE			
1	66 (57.40%)	153 (58.00%)	
2	35 (30.40%)	86 (32.60%)	
≥ 3	14 (12.20%)	25 (9.40%)	0.746
Child-Pugh stage			
A	108 (93.90%)	229 (86.70%)	
B	7 (6.10%)	35 (13.30%)	0.116
Sorafenib	9 (7.80%)	24 (9.10%)	0.843
Anti-virus treatment	34 (29.60%)	59 (22.30%)	0.153
ABIL grade			
1	54 (47.00%)	100 (37.90%)	
2	60 (52.20%)	162 (61.40%)	
3	1 (0.90%)	2 (0.80%)	0.248

WBC, white blood cell; *RBC*, red blood cell; *HB*, haemoglobin; *PLT*, platelet; *ALT*, alanine transaminase; *AST*, aspartate aminotransferase; *GGT*, gamma-glutamyl transpeptidase; *ALB*, albumin; *TBIL*, total bilirubin; *PT*, prothrombin time; *CRP*, C-reactive protein; *INR*, international normalised ratio; *AFP*, alpha fetoprotein; *PVTT*, portal vein tumour thrombus; *TACE*, transcatheter arterial chemoembolisation; *BCLC*, Barcelona Clinical Liver Cancer; *ABIL*, Albumin-Bilirubin

similar between the negative and positive lipiodol deposition groups for PVTT stage I patients ($p = 0.749$), whereas OS was better in the positive lipiodol deposition group than in the negative lipiodol deposition group for PVTT stage II ($p = 0.0024$) and III + IV ($p = 0.0002$) patients. The median OS was 9.2 vs. 10.5 months, 4.9 vs. 8.2 months, and 4.3 vs. 8.5 months.

The predictive value of lipiodol deposition in PVTT in SD patients

In this study, a significant number of patients exhibited SD according to radiological tumour response. To analyse the predictive power of the extent of lipiodol deposition in PVTT and the radiological tumour response, we further

Table 3 Efficacy outcomes rated as per the mRECIST criteria

Outcomes	*N* (%)
Complete response (CR)	0 (0)
Partial response (PR)	96 (25.3)
Stable disease (SD)	206 (54.4)
Progressive disease (PD)	77 (20.3)
Three-month PFS rate (%)	206 (66.0)
Six-month PFS rate (%)	50.0
Median PFS (months)	6.0
Median OS (months)	6.0
One-year OS rate (%)	21.0
Two-year OS rate (%)	10.0

mRECIST, the Modified Response Evaluation Criteria in Solid Tumors

analysed the prognosis of patients with SD. For this purpose, the SD group patients were classified into a negative subgroup ($n = 154$) and a positive subgroup ($n = 52$). The median OS values of the negative and positive subgroups were 4.7 months and 10.5 months, respectively ($p < 0.001$; Fig. 4a). Additionally, the median PFS values of the negative and positive subgroups were 3.5 months and 7.0 months, respectively ($p < 0.001$; Fig. 4b).

Discussion

The main result of our study is that in patients with PVTT, lipiodol deposition within the tumour-in-vein after TACE was associated with an improved survival. Approximately 8 to 30.6% of patients have PVTT when they are diagnosed with HCC [26, 27]. Thus, PVTT is an important unfavourable prognostic factor and plays a major role in HCC treatment [4]. Currently, TACE has been proven to be effective in HCC patients with PVTT [11, 26, 28, 29], and its use is being gradually accepted in clinical practice. Two studies have reported that the extent of lipiodol deposition in PVTT is a prognostic factor for HCC patients after TACE; however, the main research objectives of both studies were not the correlation with lipiodol deposition in PVTT and prognosis [11, 26]. To the best of our knowledge, this study is the first to use the extent of lipiodol deposition in PVTT to assess the prognosis of HCC patients with PVTT after TACE. In this study, we investigated the relationship between lipiodol deposition in PVTT and survival after TACE. Patients were classified into the negative lipiodol deposition group and the positive lipiodol deposition group based on the extent of lipiodol deposition in PVTT. Survival analysis showed that patients with positive lipiodol deposition in PVTT had better OS and PFS than patients with negative lipiodol deposition. Additionally, combined with the mRECIST criteria and lipiodol deposition in PVTT could further stratify patients in the SD group into two groups with different prognosis.

Previous studies indicated that the extent of lipiodol deposition in the liver tumour correlated well with the treatment outcome, and tumour haemodynamics correlated with the extent of lipiodol deposition in tumour [17, 18, 30, 31]. The reason for these results was the blockage of tumour blood flow, which further resulted in complete necrosis of hepatic tumour. In our study, patients who had lipiodol deposition in PVTT were shown to have significantly better OS and PFS compared with patients with no lipiodol deposition. We speculate that the prolongation of survival and time to progression in patients with positive lipiodol in PVTT was associated with the PVTT inflow occlusion. The extent of lipiodol deposition in PVTT may be related to the extent of blood supply blockage. Therefore, the extent of lipiodol deposition in PVTT can be considered an effective predictor for HCC patients with PVTT.

The mRECIST criteria were proposed as an assessment of the efficacy of TACE in HCC patients based on tissue enhancement [14], which involves a combinatorial evaluation of intrahepatic lesion responses and unmeasurable PVTT responses. However, PVTT responses may not be measured accurately and objectively based on intratumoural arterial enhancement in clinical practice. The main reason is that PVTT cannot withdraw significantly within several weeks after TACE, regardless of whether TACE treatment is effective against PVTT. Moreover, the small change in PVTT enhancement cannot be detected by radiologists, meaning that we cannot obtain accurate evaluation results of PVTT in clinical practice. Therefore, the use of mRECIST criteria is sometimes of limited value in assessment prognosis of HCC patients with PVTT after TACE. On the other hand, in clinical practice, few patients can achieve CR in the presence of PVTT after TACE, and most patients are thus classified into the SD group. As reported by previous studies, up to 70% of HCC patients with PVTT have SD after TACE therapy; moreover, approximately 54.4% of patients with PVTT had SD in our series. The distribution of patients was highly imbalanced, an issue that also indicates that the mRECIST criteria cannot accurately stratify those patients with SD. To address this problem, the combination of lipiodol deposition in PVTT and radiological responses of tumours was introduced to further differentiate the SD subgroup patients in this study. The patients with SD were divided into negative and positive lipiodol deposition in the PVTT subgroup (154 vs. 52). Patients with positive lipiodol deposition in PVTT had a longer median survival and PFS than patients with negative lipiodol deposition in PVTT (median OS 10.5 months vs. 4.7 months, median PFS 7.0 months vs. 3.5 months). Therefore, the evaluation of lipiodol deposition in PVTT will help to select more appropriate patients with PVTT to undergo TACE.

Table 4 Univariate and multivariate analyses of the clinical factors in relation to overall survival

Variable			Univariate analysis		Multivariate analysis		
		N	Median OS (95% CI)	*p* value	HR	Median (95% CI)	*p* value
Age (years)	< 55	59	5.83 (4.29–7.37)				
	≥ 55	320	6.03 (5.20–6.86)	0.294			
Sex	Male	365	8.23 (5.76–10.70)				
	Female	14	5.83 (5.07–6.59)	0.444			
Tumour number	Unifocal	146	6.63 (5.07–8.19)				
	Multifocal	233	5.8 (4.92–6.69)	0.175			
Child-Pugh stage	A	337	6.07 (5.39–6.75)				
	B	42	4.30 (2.52–6.08)	0.189			
ALBI grade	1	157	6.00 (5.34–6.66)				
	2–3	225	5.30 (3.37–7.23)	0.797			
Tumour size (cm)	< 10	181	7.00 (5.70–8.30)				
	≥ 10	198	4.67 (3.83–5.51)	0.007			
HBV	Absent	40	5.83 (2.62–9.04)				
	Present	339	5.97 (5.23–6.71)	0.875			
PVTT stage	I	71	7.27 (5.50–9.04)				
	II	175	5.83 (4.76–6.90)				
	III	119	5.40 (4.08–6.72)				
	IV	14	9.90 (4.57–15.23)	0.601			
Anti-virus	Absent	246	5.70 (4.88–6.52)				
	Present	93	6.57 (5.93–7.21)				
	NA	40	6.43 (2.25–10.61)	0.873			
Treatment with sorafenib	Absent	346	5.80 (5.15–6.45)				
	present	33	8.43 (6.86–10.00)	0.038	0.603	0.401–0.909	0.016
Alpha fetoprotein	< 200	101	8.07 (5.92–10.22)				
	≥ 200	278	5.07 (4.25–5.89)	0.005	1.178	1.031–1.346	0.016
Radiologic tumour response	Absent	283	4.73 (3.94–5.53)				
	Present	96	7.63 (6.64–8.62)	0.001	0.714	0.543–0.938	0.016
Lipiodol deposition in PVTT	Absent	264	4.70 (4.13–5.27)				
	Present	115	8.97 (6.81–11.13)	0.001	0.619	0.473–0.811	0.001
Lung metastasis	Absent	329	6.07 (5.38–6.76)				
	Present	50	4.27 (3.08–5.46)	0.092	1.102	0.778–1.561	0.584
Lymphatic metastasis	Absent	339	6.17 (5.47–6.87)				
	Present	40	5.07 (3.68–6.46)	0.771			

PVTT, portal vein tumour thrombus; *HBV*, hepatitis B virus; *ALBI*: the Albumin-Bilirubin grade

The extension of PVTT is known to affect patients' prognosis [32, 33]. We conducted a subgroup analysis to explore the outcome results in various stages of portal vein thrombosis. For the PVTT stages II and III + IV (Supplementary Fig. 2B and C), the positive lipiodol deposition group had better OS than the negative deposition group. For the PVTT stage I, the OS between negative and positive deposition groups was not significantly different, but we observed a trend towards better OS with the positive lipiodol deposition group than with the negative lipiodol deposition group. We speculated that these results were affected by the following factors: (a) The small sample size (36 vs. 22). The effect of portal vein invasion on the overall survival of patients with PVTT stage I is relatively small compared with stages II and III. We could speculate that the difference might be statistically significant in a larger sample size of subgroup patients. (b) Although the technical improvements in imaging techniques, the misdiagnosis of PVTT grade I is sometimes inevitable. Therefore, we think lipiodol deposition in PVTT is a reliable prognostic indicator for patients with various PVTT stages after TACE treatment.

Our study has some limitations. First, the potential bias in patient selection could not be completely avoided, as this is a retrospective study performed at a single centre. The treatment strategies for HCC patients with PVTT vary greatly across

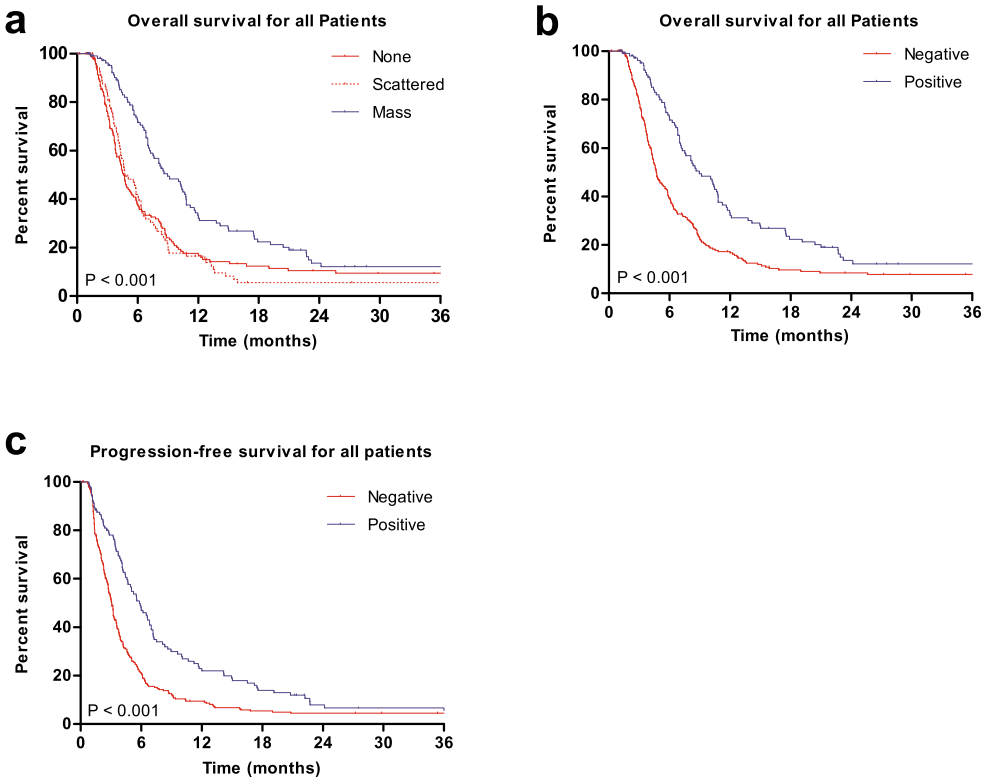

Fig. 3 Prognostic significance of lipiodol deposition in PVTT. **a** Overall survival (OS) of patients with none, scattered, or massive lipiodol deposits in PVTT. The median OS for patients with none, scattered, or massive lipiodol deposits in PVTT was 4.6 months, 4.73 months, and 8.97 months, respectively (log-rank test, $p < 0.001$); **b** OS of groups with negative and positive lipiodol deposition in PVTT. The median overall survival times for patients with negative and positive lipiodol deposition in PVTT were 4.7 months and 8.97 months, respectively (log-rank test, $p < 0.001$); **c** progression-free survival (PFS) of groups with negative and positive lipiodol deposition in PVTT. The median PFS times for patients with negative and positive lipiodol deposition in PVTT were 3.1 months and 5.8 months, respectively (log-rank test, $p < 0.001$)

centres. In our centre, the plan for the treatment of HCC patients with PVTT was usually determined by a multidisciplinary team according to the physical condition of the patient, such as liver function, tumour burden, general health, and patient preference. To reduce selection bias, we recruited patients in strict accordance with the inclusion criteria. Second, we did not evaluate the safety of TACE in HCC patients with PVTT; however, the main aim of this study was to evaluate the value of lipiodol deposition in PVTT in determining the prognosis of HCC patients with PVTT. Third, lipiodol deposition in PVTT could not be discerned from the primary tumour in most patients due to two-dimensional nature of the angiography imaging, which limits us to explore the correlation between lipiodol uptake on angiography and on CT. We will overcome previous difficulties of assessing lipiodol uptake in PVTT by three-dimensional imaging reconstruction in the future. Finally, this is a single-centre study; therefore, the findings may not be consistent with the results obtained in other centres and geographic regions. To obtain more generalisable results, an independent external validation database may be necessary. Thus, our findings should be interpreted in light of these limitations.

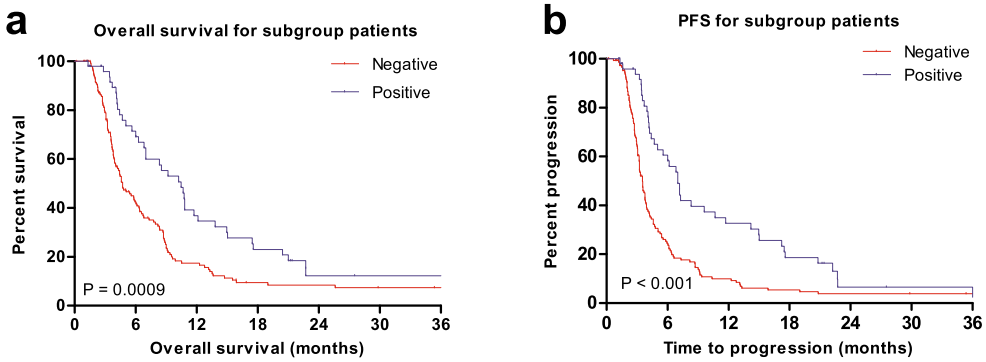

Fig. 4 Prognostic significance of lipiodol deposition in PVTT in subgroups of patients with SD after TACE. **a** OS and PFS of subgroups of patients with SD after TACE based on lipiodol deposition in PVTT. The median OS times for patients with negative and positive lipiodol deposition in PVTT were 4.73 months and 10.47 months, respectively (log-rank test, $p = 0.0009$). **b** PFS of groups with negative and positive lipiodol deposition in PVTT. The median PFS times for patients with negative and positive lipiodol deposition in PVTT were 3.5 months and 7.0 months, respectively (log-rank test, $p < 0.001$). The stratified based on the combinatorial evaluation of the intrahepatic lesion responses and extent of lipiodol deposition in PVTT

In conclusion, this study demonstrates that lipiodol deposition in PVTT is a favourable prognostic factor for HCC patients and can help assess the tumour response after TACE in clinical practice.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Yunfei Yuan.

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from patients in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108
2. Yoshidome H, Takeuchi D, Kimura F et al (2011) Treatment strategy for hepatocellular carcinoma with major portal vein or inferior vena cava invasion: a single institution experience. J Am Coll Surg 212:796–803
3. Han K, Kim JH, Ko GY, Gwon DI, Sung KB (2016) Treatment of hepatocellular carcinoma with portal venous tumor thrombosis: a comprehensive review. World J Gastroenterol 22:407–416
4. Lin DX, Zhang QY, Li X, Ye QW, Lin F, Li LL (2011) An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. J Cancer Res Clin Oncol 137:139–149
5. Sun JX, Shi J, Li N et al (2016) Portal vein tumor thrombus is a bottleneck in the treatment of hepatocellular carcinoma. Cancer Biol Med 13:452–458
6. Zhang ZM, Lai EC, Zhang C et al (2015) The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. Int J Surg 20:8–16
7. Cheng S, Chen M, Cai J (2017) Chinese expert consensus on multidisciplinary diagnosis and treatment of hepatocellular carcinoma with portal vein tumor thrombus: 2016 edition. Oncotarget 8:8867–8876
8. Zhang XB, Wang JH, Yan ZP, Qian S, Du SS, Zeng ZC (2009) Hepatocellular carcinoma with main portal vein tumor thrombus: treatment with 3-dimensional conformal radiotherapy after portal vein stenting and transarterial chemoembolization. Cancer 115:1245–1252
9. Zhang YF, Guo RP, Zou RH et al (2016) Efficacy and safety of preoperative chemoembolization for resectable hepatocellular carcinoma with portal vein invasion: a prospective comparative study. Eur Radiol 26:2078–2088
10. Kim HC, Chung JW, Lee W, Jae HJ, Park JH (2005) Recognizing extrahepatic collateral vessels that supply hepatocellular carcinoma to avoid complications of transcatheter arterial chemoembolization. Radiographics 25:S25–S39
11. Chung GE, Lee JH, Kim HY et al (2011) Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 258:627–634
12. Niu Z, Ma Y, Kang P et al (2012) Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. Med Oncol 29:2992–2997
13. Wu FX, Chen J, Bai T et al (2017) The safety and efficacy of transarterial chemoembolization combined with sorafenib and sorafenib mono-therapy in patients with BCLC stage B/C hepatocellular carcinoma. BMC Cancer 17:645
14. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liv Dis 35:52–60
15. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer (2012) EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908–943
16. Shim JH, Lee HC, Kim S et al (2012) Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 262:708–718
17. Yang L, Zhang XM, Zhou XP et al (2010) Correlation between tumor perfusion and lipiodol deposition in hepatocellular carcinoma after transarterial chemoembolization. J Vasc Interv Radiol 21:1841–1846
18. Monsky WL, Kim I, Loh S et al (2010) Semiautomated segmentation for volumetric analysis of intratumoral ethiodol uptake and subsequent tumor necrosis after chemoembolization. AJR Am J Roentgenol 195:1220–1230
19. Bruix J, Sherman M, Practice Guidelines Committee, American Association for the Study of Liver Diseases (2005) Management of hepatocellular carcinoma. Hepatology 42:1208–1236
20. Bruix J, Sherman M, Llovet JM et al (2001) Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 35:421–430
21. Shi J, Lai EC, Li N et al (2011) A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 18:74–80
22. Shuqun C, Mengchao W, Han C et al (2007) Tumor thrombus types influence the prognosis of hepatocellular carcinoma with the tumor thrombi in the portal vein. Hepatogastroenterology 54:499–502
23. Johnson PJ, Berhane S, Kagebayashi C et al (2014) Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol 33:550–558
24. Peng ZW, Zhang YJ, Chen MS et al (2013) Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 31:426–432

25. Pourmorteza A, Symons R, Sandfort V et al (2016) Abdominal imaging with contrast-enhanced photon-counting CT: first human experience. Radiology 279:239–245
26. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY (1997) The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. Cancer 79:2087–2094
27. Kuo YH, Lu SN, Chen CL et al (2010) Hepatocellular carcinoma surveillance and appropriate treatment options improve survival for patients with liver cirrhosis. Eur J Cancer 46:744–751
28. Pinter M, Hucke F, Graziadei I et al (2012) Advanced-stage hepatocellular carcinoma: transarterial chemoembolization versus sorafenib. Radiology 263:590–599
29. Luo J, Guo RP, Lai EC et al (2011) Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 18: 413–420
30. Choi BI, Kim HC, Han JK et al (1992) Therapeutic effect of transcatheter oily chemoembolization therapy for encapsulated nodular hepatocellular carcinoma: CT and pathologic findings. Radiology 182:709–713
31. Catalano O, Esposito M, Sandomenico F, Nunziata A, Siani A (2000) Multiphasic helical computerized tomography of hepatocarcinoma. Assessment after chemoembolization. Radiol Med 99:456–460
32. Lau WY, Sangro B, Chen PJ et al (2013) Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. Oncology 84:311–318
33. Mazzaferro V, Sposito C, Bhoori S et al (2013) Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology 57:1826–1837