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Original Article

Prognostic factors in cases of radiotherapy to portal vein tumor thrombus in advanced hepatocellular carcinoma: a 8-year retrospective study

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Abstract: For hepatocellular carcinoma (HCC) patients, Portal vein tumor thrombus (PVTT) is associated with an extremely poor prognosis. We retrospectively analyzed the clinical characteristics and the survival of 216 HCC with PVTT patients treated with radiotherapy (RT) between January 2007 and December 2014 using the Kaplan-Meier method and the Cox proportional hazard regression model. The median survival time (MST) was 11.2 months, and the 6 months, 1-year and 2-year overall survivals were 60.1%, 36.3%, and 11.9%, respectively. We found that the viral etiology, Child-Pugh classification, D-dimer, PVTT type, target areas, radiation dose, treatments after RT and RT response were independent prognostic factors for overall survival. Patients with more extensive tumor thrombus invasion associated with poorer survival (P<0.001, HR=2.083, 95% CI=1.621-3.034), and MSTs were 14.1 months, 12.0 months, and 4.5 months for PVTT of types II, III, and IV, respectively. Moreover, an objective response was observed in 113 patients (52.3%), in which 17 patients (7.9%) achieved CR, and significant survival differences were noted among the responder groups (P<0.001, HR=2.765, 95% CI=1.960-3.736). Furthermore, better survivals were also noted in the target areas included PVTT and entire HCC (P=0.031, HR=1.216, 95% CI=1.065-1.644) and in the combined treatments group after RT (P=0.006, HR=1.760, 95% CI=1.112-2.435). Only 2.8% of patients suffered from Grade 3 toxicities in this study. Therefore, RT is well-tolerated and effective treatment for PVTT in HCC patients. The combined treatment for the primary liver tumor after RT is indispensable.

Keywords: Hepatocellular carcinoma, portal vein tumor thrombus, radiotherapy, prognosis, survival

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide in men and the sixth in women, and the morbidity is highest in the East and South-East Asia and the Northern and Western Africa where hepatitis B virus is in endemic [1]. HCC, as a highly fatal cancer, has a great propensity to invade the portal venous system, which leads to the portal vein tumor thrombus (PVTT). PVTT was reportedly found in more than 40% of locally advanced HCC patients at diagnosis, which was associated with extremely poor prognosis [2, 3] with the median survival time (MST) was only 2.7-4.0 months under the best supportive care [2, 4, 5], and the Barcelona Clinic Liver Cancer (BCLC) staging system classifies HCC with PVTT as advanced HCC (BCLC stage C) [6]. The presence of portal vein tumor thrombus can reduce the portal blood flow, decrease the curative effect of transcatheter arterial chemoembolization (TACE) and the success rate of surgical resection.

There is no standard treatment for HCC and PVTT patients, but the presence of tumor thrombus is one of the indications for radiotherapy (RT) [7]. Recently, many reports have shown that RT is effective for survival in these patients [8, 9], and promising outcomes have also been observed in patients treated with RT [10-13]. RT can make the occluded portal vein recanalized by shrinking the tumor thrombus [14], and provide the possibility for additional local treatment, such as TACE [10], surgical resection [15]

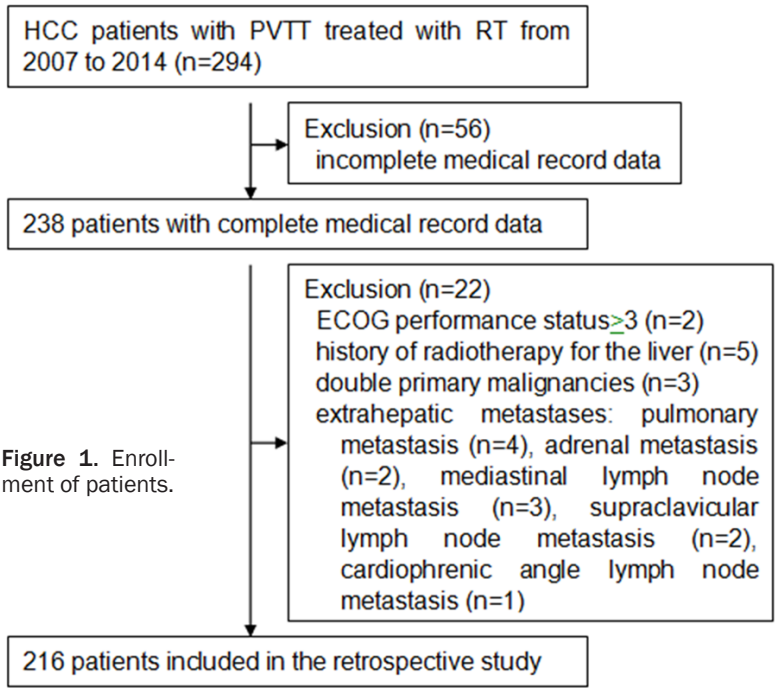

Figure 1. Enrollment of patients.

was approved by the Ethics Committee of the Shandong Cancer Hospital and Institute, and informed consent was obtained from all patients.

The diagnosis of HCC was based on the Chinese Criterions for Diagnosis, management, and treatment of hepatocellular carcinoma (V2011) [7], and the PVTT was confirmed by computed tomography (CT) scans or magnetic resonance imaging (MRI) scans on the basis of the following criteria: a low-attenuation intraluminal filling defect in the portal vein during the portal phase and an enhanced inner side of the filling defect during the arterial phase.

or radiofrequency ablation. The MST of these patients who were treated with RT was reported ranged from 6 months to 13 months, and so far there were no definite decisive factors about good prognosis.

In this retrospective study, we analyzed the survival of 216 HCC with PVTT patients who were treated with RT to seek the favorable prognostic factors, which could help us make rational treatment decision.

Materials and methods

Patients selection

In this study, we retrospectively reviewed 216 HCC with PVTT patients who were treated with RT admitted to Shandong Cancer Hospital and Institute between January 2007 and December 2014. Exclusion criteria for patients receiving radiotherapy included: liver function of Child-Pugh class C, Eastern Cooperative Oncology Group (ECOG) performance status of 3 or more, history of radiotherapy for the liver, history of second primary tumors, hepatic encephalopathy, extrahepatic metastases and no complete medical record data. The clinical features of the study population were investigated. The baseline characteristics were determined from review of the medical records. The clinical study

Based on the location and extent, PVTT was classified into 4 types according to Professor Cheng's classification method [16]. Type I: tumor thrombus involving segmental branches of portal vein or above; type II: tumor thrombus involving right/left portal vein; type III: tumor thrombus involving the main portal vein trunk; type IV: tumor thrombus involving the superior mesenteric vein or inferior vena cava.

Radiotherapy

Patients took supine position with both arms raised above the head and the head in a natural position under breath-holding in the expiratory phase. Respiratory motion of the liver was checked by fluoroscopy, and these data were used to determine the head-foot margin of planning target volume (PTV). The PVTT was defined as gross tumor volume (GTV), determined by dynamic enhanced CT with 3-mm continuous scans. Clinical tumor volume (CTV) included the PVTT and a 1 cm margin into the contiguous HCC in patients with huge and infiltrative HCC. In patients with small HCC, the CTV consisted of PVTT and the entire HCC. The PTV expanded from CTV with a 0.5- to 1-cm margin according to the respiratory movement of the liver. The whole and remnant liver, spinal cord, double kidneys, stomach, small intestine and colon were delineated and reconstructed three

Table 1. Baseline characteristics and survival of all patients by Log-rank test (*N*=216)

Clinical features	*N*. (%)	Log-rank test (*p* value)	Clinical features	*N*. (%)	Log-rank test (*p* value)
Gender		0.494	ALP		0.136
Male	160 (74.1)		≤150 U/L	175 (81.0)	
Female	56 (25.9)		>150 U/L	41 (19.0)	
Age		0.115	AFP		0.047
<53.6 years	108 (50.0)		<400 ng/ml	73 (33.8)	
≥53.6 years	108 (50.0)		≥400 ng/ml	143 (66.2)	
Viral etiology		0.004	TBIL		0.071
HBV(+) or HCV(+)	180 (83.3)		<34 μmol/L	157 (72.7)	
HBV and HCV(-)	36 (16.7)		≥34 μmol/L	59 (27.3)	
ECOG		0.012	γ-GGT		0.259
0-1	141 (65.3)		≤50 U/L	153 (70.8)	
2	75 (34.7)		>50 U/L	63 (29.2)	
Child-Pugh Class		0.006	ALB		0.098
A	185 (85.6)		≥35 g/L	137 (63.4)	
B	31 (14.4)		<35 g/L	79 (36.6)	
Cirrhosis		0.083	LDH		0.033
Positive	169 (78.2)		≤240 U/L	124 (57.4)	
Negative	47 (21.8)		>240 U/L	92 (42.6)	
Ascites		0.114	β2-M		0.423
Positive	67 (31.0)		≤1 ug/mL	89 (41.2)	
Negative	149 (69.0)		>1 ug/mL	127 (58.8)	
Splenomegaly		0.365	D-dimer		0.024
Positive	84 (38.9)		≤1 mg/L	35 (16.2)	
Negative	132 (61.1)		>1 mg/L	181 (83.8)	
Lymph node metastasis		0.268	PVTT type		<0.001
Positive	134 (62.0)		II	101 (46.7)	
Negative	82 (38.0)		III	82 (38.0)	
			IV	33 (15.3)	
ALT		0.347	Portal vein occlusion		0.109
≤80 U/L	154 (71.3)		Complete	42 (19.4)	
>80 U/L	62 (28.7)		Incomplete	172 (80.6)	
AST		0.642	AFP decrement		0.086
≤80 U/L	145 (67.1)		Positive	151 (69.9)	
>80 U/L	71 (32.9)		Negative	65 (30.1)	

dimensionally. All patients underwent 3-dimensional conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT) or image-guided radiotherapy (IGRT) planned with treatment planning system (ECLIPSE: v8.6, Varian Inc., Palo Alto, CA; PINNACLE: v8.0 m, Philips Medical, Cleveland, OH). The total prescribed dose was determined by the liver function, the volume of normal liver and the limited dose of stomach, kidneys, intestine. The general guideline was that no more than 50% of the normal liver was exposed to more than 30 Gy ($V_{30\ Gy}$<50%), and the mean dose of the liver should be less than 23 Gy for Child-Pugh class A and less than 6 Gy for Child-Pugh class B. A daily radiation dose of 1.8 to 3.0 Gy was administered to the PTV using 6-MV X-ray at 5 fractions per week to deliver a total dose of 36-60 Gy, which translated to a biologic effective dose (BED) of 47.8-72 Gy as the α/β=10. BED was calculated using a linear quadratic model to be equivalent to 2-Gy fraction treatments concerning acute effects on normal tissues and tumors.

Table 2. Treatments characteristics and survival by Log-rank test (*N*=216)

Clinical features	*N*. (%)	Log-rank test (*p* value)
Target areas		0.021
PVTT+ entire HCC	30 (13.9)	
PVTT	186 (86.1)	
Fraction dose		0.370
≤2 Gy	175 (81.0)	
>2 Gy	41 (19.0)	
Radiation dose		0.019
≥50 Gy	143 (66.2)	
<50 Gy	73 (33.8)	
Treatments before RT		0.081
Positive	121 (56.0)	
Negative	95 (44.0)	
Treatments after RT		0.015
RT-combined	168 (77.8)	
RT-alone	48 (22.2)	
RT response		0.008
CR	17 (7.9)	
PR	65 (30.1)	
VT	31 (14.3)	
NR	103 (47.7)	

Follow-up, evaluation of RT toxicity and response

The patients were followed 1-2 months after the completion of radiotherapy, and then every 3-months until death or the final follow-up date of December 2016. Each follow-up session of these HCC patients included a detailed history and physical examination, laboratory tests, abdominal Doppler ultrasonography and abdominal contrast-enhanced three-phase dynamic spiral CT or MRI. Laboratory tests included hematologic and biochemical analyses.

Laboratory tests were evaluated weekly during the treatment and 4 weeks after the completion of RT. Adverse effects related to RT were scored using the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0) [17]. RILD was defined as anicteric non-malignant ascites, elevation of alkaline phosphatase (ALP) levels to more than two-fold pretreatment values in the absence of documented progressive disease [18].

Response of PVTT to RT was evaluated by contrast-enhanced CT or MR imaging. The most significant change in images was regarded as the treatment response by comparing with the initial value at the beginning of RT. The overall tumor response was defined according to the treatment responses proposed by Dr. Huang in 2008 [19], which were classified according to image comparisons as follows: no response (NR); partial response (PR): thrombus regression, which was a volumetric reduction of the largest diameter reduced by >30% in images, PR portal vein collapse, which was a total regression of thrombus without portal flow restoration by Doppler ultrasonography, and recanalization, which was blood flow detected in the portal area without volumetric thrombus reduction in Doppler ultrasonography; vascular transformation (VT), either cavernous transformation or collateral circulation; complete response(CR), complete disappearance of tumor thrombus. The patients lost follow-up were classified as "missing" (MS). The objective response was based on the combined number of patients with CR, PR and VT. α-Fetoprotein (AFP) value was tested at 4 weeks after radiotherapy.

Statistical analyses

All statistical analyses were performed by using SPSS statistical package, version 17.0 (SPSS Inc., Chicago, Il). All patients were included in the survival analysis. Patients who underwent at least one follow-up imaging assessment were evaluable for treatment response. The endpoint was overall survival, who was estimated from the date of PVTT diagnosed to death or last follow-up. Survival curves were calculated by the Kaplan-Meier method. Univariate analyses were performed by Log-rank test. Variables with a *p* value of less than 0.05 in the univariate analysis were entered into the multivariate analysis. The multivariate analysis was performed by Cox proportional hazard regression model. The statistical significance level was set at $P<0.05$.

Results

Patient characteristics and survival analysis

A total of 294 HCC patients with PVTT treated with RT during the study period. 78 patients who met the exclusion criteria were excluded from the study. Finally, 216 patients were included in this retrospective study (**Figure 1**).

Table 3. Cox regression of independent prognostic factors associated with overall survival

Parameter	*p* value	HR (95% CI)
Viral etiology (HBV and HCV-/HBV+ or HCV+)	0.026	1.415 (1.166~1.914)
Child-Pugh class (A/B)	0.002	1.985 (1.460~2.134)
D-dimer (≤1 mg/L/>1 mg/L)	0.005	1.781 (1.421~2.232)
PVTT type (II vs. III vs. IV)	<0.001	2.083 (1.621~3.034)
Target areas (PVTT+ entire HCC/PVTT)	0.031	1.216 (1.065~1.644)
Radiation dose (≥50 Gy/<50 Gy)	0.028	1.342 (1.124~1.951)
RT response (CR vs. PR vs. VT vs. NR)	<0.001	2.765 (1.960~3.736)
Treatments after RT (RT-combined vs. RT-alone)	0.006	1.760 (1.112~2.435)

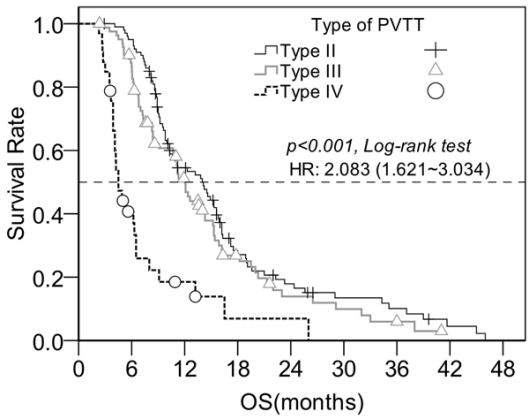

Figure 2. Kaplan-Meier curves for OS among the three different types of PVTT.

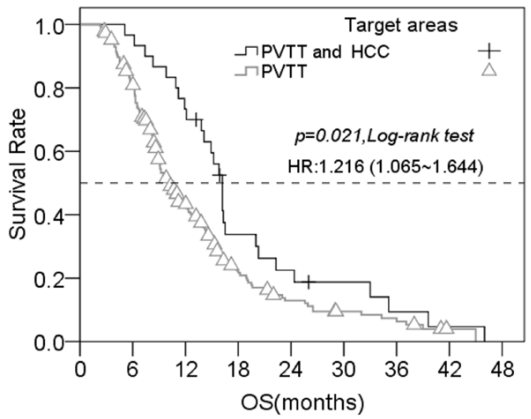

Figure 3. Kaplan-Meier curves for OS of the different target areas.

All patients were classified as advanced HCC (BCLC stage C) [6], according to the BCLC Staging System. Detailed baseline patient characteristics are shown in **Table 1**. The 6 months, 1 year and 2 years overall survivals (OS) were 60.1%, 36.3%, and 11.9%, respectively, and the MST was 11.2 months. 74.1% of these patients were male, and the median age was 53.6 years old (range: 30-76 years old). 172 patients were HBsAg positive (172/216, 79.6%), and 8 patients were HCV-Ab positive (8/216, 3.7%).

Tables 1 and **2** also show the results of log-rank test for survivals of various clinical features. On univariate analysis, Viral etiology, ECOG performance status, Child-Pugh classification, AFP, lactate dehydrogenase (LDH), D-dimer, PVTT type, target areas, radiation dose, treatments after RT and RT response were revealed as significant prognostic factors. Multivariate analysis further confirmed that viral etiology, Child-Pugh classification, D-dimer, PVTT type, target areas, radiation dose, treatments after RT and RT response were independent prognostic factors for overall survival. **Table 3** shows the results of Cox proportional hazards regression.

Survival difference among the PVTT type and target area

Based on the classification of PVTT described by Professor Cheng [16], the MSTs of type II (101/216, 46.7%), type III (82/216, 38.0%), and type IV (33/216, 15.3%) were 14.1 months, 12.0 months and 4.5 months, and the 1-year overall survival rates were 61.1%, 39.4% and 14.9%, respectively. The statistically significant survival advantage was observed in the patients between different types of PVTT (P<0.001, **Figure 2**), multivariate analysis also showed that the PVTT type was a significant independent prognostic factor for survival (P<0.001, HR=2.083, 95% CI=1.621-3.034). There was no patient with PVTT of type I treated with RT.

The MST of target areas included PVTT and entire HCC (30/216, 13.9%) was 16.2 months, which was longer than that only included the PVTT (186/216, 86.1%) of 10.3 months (P=0.021, **Figure 3**). The univariate and multivariate analysis both showed that target areas were significant independent prognostic factor

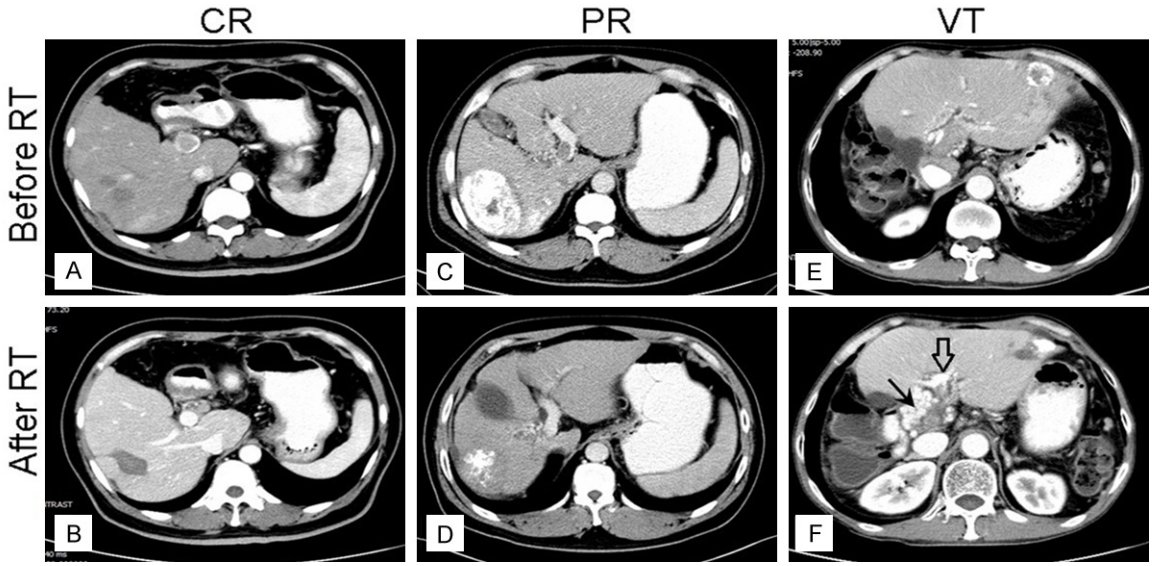

Figure 4. Serial computed tomography scans showed changes in images of the tumor thrombus area. A, B. There was a PVTT in the main trunk of portal vein. The thrombus completely disappeared after radiotherapy, and complete response (CR) was achieved. C, D. Tumor thrombus involved the right branch and the main trunk of portal vein, and the thrombus regressed after radiotherapy, partial response (PR) was achieved. E, F. The obvious cavernous transformation after radiotherapy (black arrow) was observed, which was classified as vascular transformation (VT) together with the partial recanalization (black hollow arrow) of portal vein.

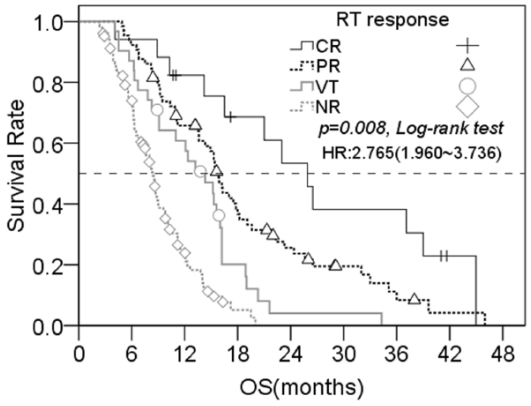

Figure 5. Kaplan-Meier curves for OS among the CR, PR, VT, NR groups.

for survival (*P*=0.031, HR=1.216, 95% CI= 1.065-1.644).

PVTT response after RT

During the four to eight weeks following up after the completion of the RT, an objective response was observed in 113 patients (52.3%) according to the treatment responses of PVTT proposed by Dr. Huang [19]. Of the 113 patients, 17 patients (7.9%) achieved CR, 65 patients (30.1%) achieved PR composed of 41 patients with thrombus regression (19.0%), 16 patients with portal vein collapse (7.4%) and 8 patients with recanalization (3.7%), 31 patients (14.3%) had VT, with cavernous transformation (23/216, 10.6%) and collateral circulation (8/216, 3.7%). **Figure 4** shows examples of follow-up CT images in patients who achieved CR, PR and VT. The MSTs were 25.9 months, 15.8 months, 14.3 months and 8.0 months for the CR, PR, VT and NR group, respectively. The survival curves for the various response groups are shown in **Figure 5** (*P*=0.008). Statistically significant differences were found among the responder groups (*P*<0.001, HR=2.765, 95% CI=1.960-3.736). There was no person grouped into MS group, because the 56 patients without complete medical record data to evaluate the efficacy were excluded. AFP decrement was observed in 151 patients (69.9%) at four weeks follow up after RT, but the differences in the decrement didn't show statistical significance (*P*=0.086).

Previous and Post-RT treatments

Of the study population, 56.0% (n=121) patients accepted treatments for the primary tumor before radiotherapy after the diagnosis of PVTT, such as TACE, TACI, PEI, RFA and surgi-

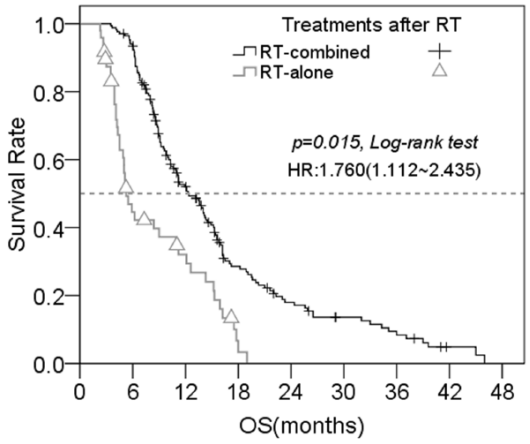

Figure 6. Kaplan-Meier curves for OS between the two different post-RT treatments groups.

cal resection, but it did not show a statistically significant effect on OS. Log-rank test showed no significant survival benefit between patients with and without treatment before radiotherapy, but univariate and multivariate analysis all observed the statistically significant survival advantage in patients who underwent combined treatments after the beginning of radiotherapy (P=0.006, HR=1.760, 95% CI=1.112-2.435). Better survival was noted in the combined group after RT than in the RT-alone group (MST, 12.3 *vs*. 5.3 months, p=0.015, **Figure 6**), and the combined treatments included sorafenib, chemotherapy, TACE, PEI, RFA, hepatectomy and re-irradiation.

Radiation-related toxicity

Acute toxicities classified as Grade 1 or 2 were noted in 82% (177/216) of patients, such as anicteric ascites, fatigue, anorexia, nausea, ALP increase and total bilirubin (TBIL) increase. In total, 2.8% (6/216) patients suffered from Grade 3 toxicities after RT. Five patients (2.3%) developed RILD, no radiation-related hepatic failure or treatment-related death was observed.

Discussion

The natural history of HCC with PVTT patients is dismal (approximately 2.7-4 months) without anti-tumor therapy [2, 4, 5]. Portal invasion in HCC promotes intrahepatic dissemination and decreases blood supply to the normal liver, finally causes portal hypertension resulting in the rupture of collateral vessels, hepatic encephalopathy, ascites and the deterioration of liver function which leads to the failure of treatments [20, 21]. Therefore, the prognosis of HCC patients with PVTT is extremely poor.

Standard treatment strategy have not been established in these patients [22]. Although sorafenib has become the standard treatment for patients with BCLC stage C in the BCLC treatment algorithm [6], its therapeutic efficacy is reduced in patients with PVTT [23]. RT is a better first-line therapy than sorafenib in patients who have advanced unresectable HCC with PVTT [24], with a better survival noted (MST: 10.9 mo *vs*. 4.8 mo). In the treatment of the HCC patients with PVTT, RT plays a critical role [25].

Most of the staging or prognostic systems, such as the Tumor-Node-Metastasis (TNM) stage, Barcelona Clinic Liver Cancer (BCLC) guideline, Cancer of the Liver Italian Program (CLIP) [26], and Japan Integrated Staging (JIS) [27] use PVTT as an important prognostic parameter, but they are not available to estimate the prognosis of HCC with PVTT patients, especially not applicable for patients treated with RT [27]. In 2009, Huang *et al.* [19] published the ECOG performance status, radiation dose, ascites, AFP, albumin, and HBsAg as the risk factors for 326 HCC patients with PVTT who were treated with RT, but there were so many "missing" patients (155/326, 47.5%), which reduced the reliability of data. In 2011, Yu *et al.* [25] proposed a Prognostic index of RT for PVTT of HCC (PITH) scoring system in prognostic assessment of patients with HCC and PVTT treated with RT, which included ECOG performance status, Child-Pugh class, multiple tumors, main PVTT, complete portal vein occlusion, lymph node metastasis, and primary tumor size. Although the PITH scoring system was well correlated with the OS, it only used seven pre-treatment factors and ignored the effect of radiotherapy on the prognosis. Yoon *et al.* [14] showed that the significant independent variables associated with OS in HCC and PVTT patients included advanced tumor stage, AFP, degree of PVTT, and response to radiotherapy, but the patients into group were treated with RT and TACE. Bae *et al.* [28] revealed that changes in Child-Pugh score and response to RT were statistically significant factors of survival, but

the small patient group only contained 47 patients with PVTT or hepatic vein thrombus (HVT) in HCC.

In our study, we systematically analyzed almost all clinical data before and after RT, and the 56 "missing" patients without complete medical record data to evaluate the efficacy were excluded. Firstly, We found the pre-treatment factors including viral etiology, Child-Pugh classification, D-dimer and PVTT type as the the risk factors for OS, which were easy to collect before RT. Patients infected with hepatitis [29] may have a relatively higher risk of ongoing hepatocarcinogenesis [30] and more aggressive progression of associated liver dysfunction, resulting in a poorer outcome. Child-Pugh classification is an important indicator of liver reserve function [7], and good liver reserve function is the foundation for treatment, indicates a good prognosis. Except the direct portal invasion, pro-coagulant cytokine production by neoplastic cells is also responsible for portal vein tumor thrombus [31], which can lead to the rise of D-dimer. D-dimer, as a sensitive indicator of high coagulation state [32], had been reported for many times to be related to the prognosis and malignancy of tumor [33-35], and in this study we also found that D-dimer was an independent prognostic factor for OS in HCC with PVTT patients. In addition, a statistically significant survival advantage was observed in the patients between different types of PVTT and the tumor thrombus of type II had a longer survival time than type III and type IV. There was no patient with PVTT of type I treated with RT in our study, because surgical resection is the absolute indication for type I patients. PVTT classification was based on the location and extent, and the wider the tumor thrombus invasion, the shorter survival time, therefore, the treatment of tumor thrombus is primary for HCC with PVTT patients.

Moreover, we found that radiation dose and RT response were also the significantly independent prognostic factors for survival. The dose of more than 50 Gy is a radical dose for tumor, and the survival benefit was found between the prescribed dose more than 50 Gy and less than 50 Gy. Reducing the tumor thrombus can delay the intravascular tumor growth and the deterioration of liver function by preserving adequate portal flow, as well as by facilitating the subsequent treatment of the primary tumor [12, 36]. In this study, the significant survival benefits were found among the responder groups, which is not similar to the previous report [19]. The objective response rate was promising 52.3%, composed of the patients with CR, PR and VT. Furthermore, we also discovered that the target areas and the treatments after RT affected the overall survival. However the RT in HCC with PVTT patients mainly targeted the portal vein invasion site. Even if the PVTT got controlled, the primary liver tumor is still active, and treatment to the primary liver tumor is crucial [19]. In this retrospective study, the survival status of patients whose target areas included the PVTT and entire HCC was superior to the patients whose target areas only included the PVTT, which revealed the importance of the treatment to primary liver tumor. It was also confirmed from the survival advantage in the patients who underwent combined HCC treatments after the beginning of radiotherapy. All the values indicated the importance of combination treatments after radiotherapy, and the combined treatments will gain the greater benefits.

In conclusion, these results indicated that the HCC and PVTT patients treated with RT with HBV/HCV(-), Child-Pugh class A, normal D-dimer, and PVTT type II showed good prognosis. Appropriately increasing radiation dose and improving the response of radiotherapy could also effectively improve the survival, and the combined treatment for the primary liver tumor is indispensable. This study might help us make rational treatment decision and avoid unnecessary treatments and costs. Prospective, randomized trial is desirable to confirmed the appropriate prognostic evaluation factors for patients with HCC and PVTT treated with RT in the future.

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Disclosure of conflict of interest

None.

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