Research Article
Volume 11:01, 2022

Journal of Integrative Oncology

ISSN: 2329-6771 Open Access

Combined TACE and Radiotherapy Treatment for Patients with Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

Pi-Yi Chang[1,2]*, Jen-I Hwang[3], Jau-Shin Hon[1] and Chen-Yang Cheng[4]

[1]*Department of Industrial Engineering and Enterprise Information, Tunghai University, Taichung, Taiwan*
[2]*Department of Radiology, Taichung Veterans General Hospital, Taichung, Taiwan*
[3]*Department of Radiology, Tung`s Taichung Metro Harbor Hospital, Taichung, Taiwan*
[4]*Department of Industrial Engineering and Management, Taipei, Taiwan*

Abstract

Objective: To evaluate the clinical effectiveness of a combined treatment consisting of local radiotherapy (external beam radiotherapy, "EBRT") and transarterial chemoembolization (TACE) for patients with advanced liver tumors with portal vein tumor thrombosis and to identify independent prognostic factors for such patients.

Patients and Methods: From March 2006 to December 2014, 96 patients with unresectable HCC complicated by PVTT were recruited as cases. All subjects received TACE and EBRT. Patient survival was estimated by Kaplan-Meier analysis. In multivariate analyses, the risk of patients' mortality was estimated by hazard ratio (HR) in Cox proportional hazard regression model.

Results: Mean overall patient survival was 14.8±0.9 months, with 1-year and 2-year survival rates of 40.6% and 14.6%, respectively. Multivariate analyses found that the number of TACE treatments (Hazard ratio [HR]:0.85; 95% confidence interval [CI]:0.75-0.96), maximum tumor diameter [HR: 1.10; 95% CI: 1.02-1.17], and post-TACE objective disease stabilization [HR:0.15; 95% CI:0.07-0.33] to be significantly associated with patient survival. The mean survival time was 22.1±0.97 months of subjects with objective responses to treatment.

Conclusion: Combined TACE and EBRT proved effective and safe for enhancing tumor control in HCC patients with PVTT and achieved a higher response rate and better patient response than single-agent modalities such as chemotherapy, sorafenib, or radiotherapy alone. In addition, only two factors – tumor diameter and the frequency of TACE treatment – were significantly associated with patient survival.

Keywords: Advanced HCC • Portal vein tumor thrombosis • TACE • Prognostic factors

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and a major cause of mortality. Portal vein tumor thrombosis (PVTT) arises in about 10%-40% of HCC patients, with lower rates being reported when HCC is diagnosed early, usually as a consequence of screening [1], and is apparent in up to 44% of patients at end of life [2]. The median survival time of patients with portal venous invasion is significantly reduced to 2-4 months if left untreated, as compared to 10-24 months without PVTT [3]. Optimal treatment for HCC with PVTT has not been established, and only a few randomized controlled trials have been conducted. Since PVTT compromises vascular supply to the liver, it is regarded as a contraindication to transarterial chemoembolization (TACE). However, a meta-analysis of 8 comparative studies confirmed the survival benefit of TACE for advanced HCC with PVTT, even with main portal vein obstruction [4].

Another potential therapeutic tool is radiation therapy (RT), which studies suggest can be effective in controlling the progression of HCC [5]. High-dose radiation can be safely delivered to liver tumors without serious complications, even in patients with PVTT. Although RT seems to provide an overall survival benefit, the prognostic influence of various factors is debatable.

Investigations into HCC co-treatment regimens of TACE with localized RT have demonstrated superior results over TACE alone [6]. In addition, a survival benefit has been reported in PVTT patients who were treated with TACE plus localized RT [7]. It has also been hypothesized that high-dose RT might lead to sustained local control and possible cure of localized HCC [8]. Promising outcomes have also been observed in patients with PVTT treated with radiotherapy. Thus, it seems to be reasonable to combine these two modalities: TACE to treat the tumor in the hepatic parenchyma and radiotherapy specifically targeting the PVTT.

This study evaluated the outcome and survival rate of advanced stage HCC patients with PVTT after combined treatment of TACE and local radiotherapy and sought to identify independent prognostic factors for patients with advanced HCC in a multivariate analysis.

Methodology

Patient selection

The present work is a retrospective study and was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CE17306A), waiving the requirement for informed consent. We searched patient records for primary hepatocellular carcinoma (ICD-9 155.0) from March 2006 to December 2014 and collected 255 subjects with advanced-stage HCC who received radiotherapy treatment. After accounting for patients who had also undergone TACE, 96 subjects were eligible.

Baseline patient data was collected upon initial cancer survey. Advanced HCC was defined as a hepatic lesion that was not eligible for curative treatment given the disease extent, or tumors that had recurred after local therapies.

***Address for Correspondence:** Pi-Yi Chang, Department of Industrial Engineering & Enterprise Information, Tunghai University, Taichung, Taiwan, Tel: + 0423594319112, E-mail: honjs@thu.edu.tw*

Received 31 December, 2021, Manuscript No. jio-21-49307; **Editor assigned:** 04 January, 2022, PreQC No. P-49307; **Reviewed:** 17 January, 2022, QC No. Q-49307; **Revised:** 22 January, 2022, Manuscript No. R-49307; **Published:** 31 January, 2022, DOI: 10.37421/2329-6771.2022.11.362

Exclusion criteria included patients without dynamic CT or MRI images prior to EBRT, who had not received combination treatment of TACE or had inferior vena cava invasion, or who lacked follow-up information after initial treatment. PVTT was classified into five grades, Vp0–Vp4, according to the guidelines established by the Liver Cancer Study Group of Japan (LCSGJ) [9].

Technique

TACE: All the interventional procedures were performed via INNOVA 4100 IQ digital subtraction angiography (DSA) (GE Company, United States) by well-experienced interventional radiologists at the Department of Interventional Radiology. After a routine preoperative preparation, TACE was performed under local anesthesia. The right femoral artery was cannulated using a 6 Fr vascular sheath using Seldinger's technique. Selective angiography of the celiac artery and superior mesenteric artery was performed using a 4 Fr hepatic artery catheter, inserted through the vascular sheath. Maximum catheter selectivity of the hepatic artery and some hepatic branches was achieved using a 3 Fr microcatheter (Progreat, Terumo Corporation, Japan), with drug administration from the afferent branch to the tumor lesion. Drug dosages per procedure varied, ranging from 10–40 ml for ethiodized oil (LIPIODOL®, Guerbet, USA), 10–40 mg of doxorubicin (Pfizer Pharmaceuticals Ltd, USA), depending on the size of the tumor lesion and laboratory results. Lipiodol-chemotherapeutic agents were administered until stasis, minimizing reflux into non-target vessels. The injection was continued until near stasis was observed in the artery directly feeding the tumor (i.e., the contrast column should clear within 2–5 heartbeats). Gelatin sponge (Gelfoam, USP) cut into 1 × 1-mm particles was injected as a supplement when necessary. In the case of unilateral branch portal vein thrombosis, selective TACE for the feeding arteries of the tumor was performed. In cases where PVTT extended to the main portal vein, TACE was modified, e.g., by decreasing the amount of epirubicin hydrochloride or by not applying Gelfoam cubes. Additional TACE after the initiation of radiotherapy was allowed if adequate control of the intrahepatic tumor could not be maintained.

Local radiotherapy: External beam radiation were designed to include the gross therapy (EBRT) was delivered using a linear accelerator equipped with 10-15MV photon beams. Radiation portals tumor thrombosis in the main portal trunk and/or major branches on CT scan with 1.5-2 cm margin for daily set-up variation and the respiratory motion of the liver. The hepatic tumor was included only if the tumor was located adjacent to PVTT. The technique of external-beam radiation therapy used in our study was 3DCRT or intensity-modulated radiotherapy (IMRT), and the accepted radiotherapy planning was designed to preserve liver function and to protect the uninvolved liver. The median dose of radiation therapy was 45 Gy (range from 30 Gy to 56 Gy), with fraction size of 1.8-3Gy per day, 5 days per week.

Tumor assessment: Tumor assessments were made using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC, as developed by the American Association for the Study of Liver Diseases (AASLD) and shown in Table 1 [10]. Initial tumor assessments were made at between 4 to 8 weeks after treatment and continued at regular intervals until death.

Data processing and statistical analysis: Raw data was collected and archived via Microsoft Excel (2010) software. Data was decoded one by one, checked, and then entered into the Chinese version of SPSS for Windows 22.0 software package for statistical analysis. According to the purpose and hypotheses, appropriate statistical methods were used to test the hypothesis and examine differences between each variable, with $p < 0.05$ as the significant level of the analysis methods described below.

The difference in two-year overall survival between potential prognostic subgroups in patients treated with HCC was assessed using the Kaplan-Meier method and tested for statistical significance by the log-rank test, with $P < 0.05$ as the threshold for statistical significance.

Demographic data including age, sex, hepatitis virus status, treatment response and complications, were examined in the Cox proportional-hazards regression model to identify independent prognostic factors.

Results

The baseline characteristics are summarized in Table 2. A total of 96 patients (70 males and 26 females) with a mean age 60 ± 12.2 years (range, 53-69 years) were enrolled in the present study. Among these patients, the etiology of underlying liver disease included hepatitis B virus (HBV) in 40 patients (41.7%), hepatitis C virus (HCV) in 26 patients (27.1%), co-infection of hepatitis B (HBV) and hepatitis C (HCV) in 4 patients (4.2%), and non-B non-C hepatitis in 26 patients (27.1%). Median tumor diameter was 4.7 cm (range, 3.3-8.2 cm), while the mean number of TACE received by each patient from start of treatment was three (range, 2-6 times).

During the follow-up period, the mean overall patient survival ("OS") in advanced HCC patients was 14.8 ± 0.9 months (median 14.3 mo), with 1-year and 2-year survival rate were 40.6% and 14.6%, respectively (Figure 1).

Our univariate analyses are summarized in Table 3. During univariate

Table 1. Radiographic modified RECIST to assess tumor response.

mRECIST for HCC	Definition
CR (complete response)	The disappearance of any intratumor arterial enhancement in all targets lesions.
PR (partial response)	At least 30% decrease in the sum of one-dimensional diameters of a viable portion of the target lesions, with the baseline sum of the diameters as a reference.
SD (stable disease)	Any case that does not qualify for CR, PR or PD.
PD (progressive disease)	At least 20% increase in the sum of the diameters of viable target lesions, with the lowest sum of the diameters recorded since the treatment started as a reference.

Table 2. Baseline characteristics of the study subjects.

Variables	Total (n=96)
Age (years)	60 ±12.2
Gender	
Male, n (%)	70 (72.9)
Female, n (%)	26 (27.1)
Hepatitis	
HBV only, n (%)	40 (41.7)
HCV only, n (%)	26 (27.1)
HBV+HCV, n (%)	4 (4.2)
Non-B non-C, n (%)	26 (27.1)
Tumor diameter (mm)	4.7 (3.3-8.2)
TACE times, n (range)	3 (2-6)

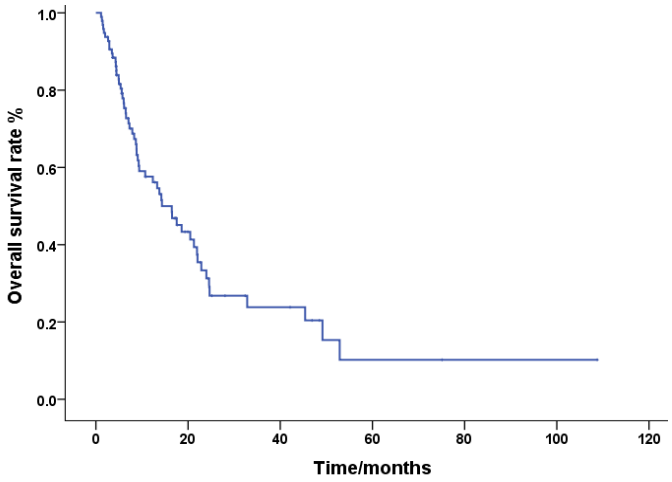

Figure 1. Cumulative overall survival of the advanced-stage HCC after TACE and radiotherapy.

Table 3. Multivariate analysis for overall survival among patients receiving TACE and radiotherapy.

		Univariate analysis			Multivariate analysis		
Variable	**Total(n=96)**	**HR**	**95%CI**	**P-value**	**HR**	**95%CI**	**P-value**
Age (year)	96	0.98	0.96-1.01	0.13	-	-	-
Gender							
Female	26	0.83	0.42-1.68	0.62	-	-	-
Male	70	-	-	-	-	-	-
Chronic viral hepatitis							
Non-B non-C	26	-	-	-	-	-	-
HBV only	40	0.95	0.50-1.83	0.89	-	-	-
HCV only	26	0.53	0.25-1.15	0.11	-	-	-
HBV+HCV	4	2.11	0.48-9.39	0.33	-	-	-
# of TACE treatments	96	0.74	0.63-0.88	<0.01**	0.85	0.75-0.96	0.01*
Tumor diameter	96	1.15	1.08-1.23	<0.01**	1.10	1.02-1.17	0.01*
Portal venous thrombosis							
Vp1	9	0.48	0.18-1.27	0.14	0.56	0.19-1.65	0.29
Vp2	27	0.29	0.13-0.64	0.01*	0.58	0.24-1.40	0.23
Vp3	40	0.50	0.25-1.01	0.05*	1.04	0.48-0.36	0.91
Vp4	20	-	-	-	-	-	-
TACE response							
Objective disease stabilization	36	0.15	0.08-0.32	<0.01**	0.15	0.07-0.33	<0.01**
Progression	60	-	-	-	-	-	-

analysis, it was found that subject age (HR: 0.98 95% CI=0.96-1.01; P = 0.13), gender (HR: 0.62 95% CI=0.42-1.68 P = 0.62), status of HBV (HR=0.95 95% CI = 0.50-1.83 P=0.89), HCV (HR=0.53 95% CI = 0.25-1.15 P=0.11) or concurrent HBV and HCV (HR=2.11 95% CI = 0.48-9.39 P=0.33) were not associated with overall patient mortality.

Tumor characteristics were also evaluated against mortality. A HR of 1.15 was found for maximum tumor diameter (95% CI = 1.08-1.23, P=<0.01), and severity of portal venous thrombosis in terms of Vp1-4 were also compared to mortality. Patients with Vp1 grade of PVTT had a HR of 0.48 (95% CI = 0.18-1.27, P=0.14), while HR is 0.29 for Vp2 (95% CI = 0.13-0.64, P=0.01) and 0.50 for Vp3 (95% CI = 0.25-1.01, P=0.05), respectively. An HR of 0.74 was calculated for number of TACE treatments (95% CI = 0.63-0.88, P=<0.01.), and achievement of objective disease stabilization ("ODS," defined as CR+PR+SD) had a HR of 0.15 (95% CI = 0.08-0.32, P=<0.01) in treatment responders.

After adjusting for confounders, multivariate analysis demonstrated that maximum tumor diameter (HR=1.10 95% CI = 1.02-1.17 P=0.01), number of TACE treatments (HR=0.85 95% CI = 0.75-0.96 P=0.01) and achievement of ODS after treatment (HR=0.15 95% CI = 0.07-0.33 P=<0.01) were significantly associated with patient survival. On the other hand, factors not significantly associated with mortality in patients with advanced HCC included PVTT of grade Vp1 (HR=0.56 95% CI = 0.19-1.65 P=0.29), Vp2 (HR=0.58 95% CI = 0.24-1.40 P=0.23) and Vp3 (HR=1.04 95% CI = 0.48-0.36 P=0.91).

The overall survival rates for advanced HCC patients after combined treatment of TACE and EBRT within the 24-month study period are shown in Figure 2, according to the patient's treatment response. The mean survival time is 22.1 ± 0.97 months of subjects with objective response ("OR", defined as CR+PR) to treatment, with a significant difference between objective response, stable disease and progressive disease (*P*= 0.01).

Discussion

Sorafenib is currently the only therapy specifically recommended for HCC with PVTT in BCLC guidelines. However, the average median survival is only 8.1 months with common adverse events. In a 2009 sorafenib randomised trial with Asia-Pacific patients with advanced HCC, of the group that received sorafenib, at ≥ 4 weeks, none received a RECIST rating of CR, only 5 of 150 patients (3.3%) achieved an rating of PR, 81 achieved the nebulous SD rating (54%) and 46 received the negative PD rating (31%), for an OR rate of 3.3%, and objective and a median survival of 6.5 months [11]. Comparatively, our combined TACE + EBRT results showed an initial OR rate of 16.7% (16/96)

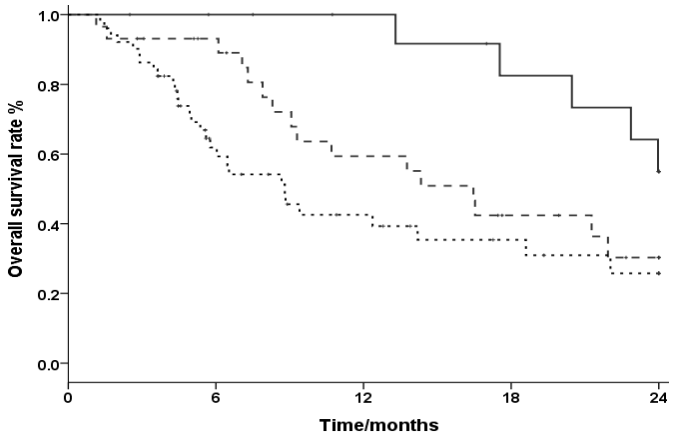

Figure 2. Cumulative overall survival of the advanced-stage HCC after TACE and radiotherapy.

and a mean survival rate of 14.8 ± 0.9 months in patients with advanced HCC, markedly longer than that shown in the sorafenib-only trial. Although a direct comparison between the two studies cannot be made, the better tumor response rates suggest better overall survival in patients with advanced HCC using our treatment.

Although PVTT is generally contraindicated for TACE, several groups have reported that subselective and superselective TACE can be performed safely in some patients with PVTT, and that it is associated with improved overall survival, provided they have good liver function and collateral blood flow around the obstructed portal vein [12]. Overall survival among PVTT patients treated with TACE in these studies ranged from 7.0 to 10.2 months. Luo J, et al. [13] prospectively treated 164 patients with PVTT with either lipiodol TACE or conservative treatment. Of the group receiving TACE (82 patients), at 4 weeks after treatment, none achieved a RECIST rating of CR, 19.5% achieved PR, and 43.9% achieved SD, for an OR of 19.5% and significantly prolonged 12- and 24- month survival rates (30.9% and 9.2% in the TACE group vs 3.8% and 0% in the conservative treatment group.). The benefit was consistent across patients with segmental and main PVTT [13]. Our analysis indicates that the presence of PVTT at the initial diagnosis of the HCC is not an absolute contraindication for TACE treatment, but patients must be selected carefully, with critical regard to their liver function. In Luo's study, patients with avascular or hypovascular tumors, diffuse-type HCC, evidence of hepatic decompensation (including ascites, esophageal, or gastric variceal bleeding or hepatic encephalopathy), severe underlying cardiac or renal diseases; or color Doppler showing PVTT with complete main portal vein obstruction without cavernous transformation were excluded. However, despite these rather stringent exclusion criteria and an initial OR of 19.5%, the survival rate of Luo's TACE-only series was significantly lower than that of the combined treatment (respectively, 30.9% *vs*. 40.6% at 12 months and 9.2% vs 14.6% at 24 months [13].

Advances in radiotherapy techniques have allowed selective delivery of increased radiation doses to tumors with minimal doses to normal tissue [14]. Yu SJ, et al. [15] appraised a number of retrospective studies that examined the use of these new technologies in selected patients accompanying PVTT and found a median OS of 6.7–11 months, and 1, 2, and 5-year survival rates 30%-40%, 20%-30%, and 5.1%-24%, respectively. However, upon examining these studies, we found that they often did not exclude patients who previously received TACE, so it was not feasible to determine response rates based on radiotherapy alone, as was also the case of Kim DY, et al [16]. Nakazawa T, et al. [17] did not find a significant difference in the median OS of sorafenib therapy *vs*. radiotherapy in unresectable HCC patients accompanying PVTT (Vp3 or Vp4), although it is worth noting that approximately 30% of both groups had previously received either TACE or transarterial infusion chemotherapy (TAI) (17). Similarly, Nakagawa *et al*. gave 52 HCC patients with PVTT targeted RT in effort to "re-actualize" transcatheter arterial embolization (TAE) for intrahepatic tumors. OR was seen 50% of patients at initial assessment, with a 1- and 2-year survival rate of 45.1% and 25.3% [18]. It is difficult to assess the effect of RT alone on non-resectable HCC, although as an adjunct treatment, the effects seem positive.

In recent years, deliberately combining RT with TACE for liver tumors with PVTT has been found to be a feasible and effective approach [19]. Nagashima T [20] reported that 7 of 11 patients with HCC with PVTT showed partial response by this combined-modality treatment. According to a study by Chen SC, et al. [21], 5 of 10 patients showed complete response to such treatment and the rest showed a partial response, with a median survival time of 7.5 months. Recently, Cho JY, et al. [22] conducted a retrospective study comparing TACE combined with radiotherapy (n = 67) with sorafenib (n = 49) in 116 patients accompanying PVTT and demonstrated that overall survival in the TACE plus radiotherapy group was significantly prolonged over the sorafenib group (14.1 mo *vs*. 3.3 mo, P < 0.001). Even in the matched cohort by propensity score, the TACE combined with radiotherapy group demonstrated extended OS over the sorafenib group 6.7 mo *vs*. 3.1 mo, P < 0.001. In the present study, we found a mean survival time of 22.1 ± 0.97 months of subjects with an objective response (complete or partial response) to treatment, with significant differences between OR, SD, and PD (*P*= 0.01).

Figures 3 illustrate a representative case, a 53-year-old male patient with history of chronic hepatitis B, treated with TACE one month later after radiotherapy. Prior to treatment, the right major branch of the portal vein and bifurcation were completely obstructed due to tumor thrombosis. TACE was performed with injection of 40mg Epirubicin, 7 ml Lipiodol and some Gelfoam cubes. After this combined RT and TACE treatment, partial recanalization of the portal vein bifurcation was seen in follow-up imaging. Figures 4 and 5 illustrate another case of HCC in the liver S8 with right portal branch thrombosis. TACE through superselection of the right hepatic artery was performed and then combined with radiotherapy. The post-TACE follow-up DSA showed complete obliteration of tumor stains in the right lobe of liver. The MRI images at the three-month follow-up showed good response to the combined treatment.

Hepatic arterial infusion chemotherapy (HAIC) has been applied to treat advanced HCC patients with portal vein thrombosis. Theoretically, HAIC should show better effectiveness than systemic chemotherapy in advanced HCC because the infusion of the chemotherapeutic agents through the hepatic artery provides direct delivery of high concentrations of drugs to the arteries feeding the HCC. Recently, Nouso *et al*. evaluated the effectiveness of HAIC

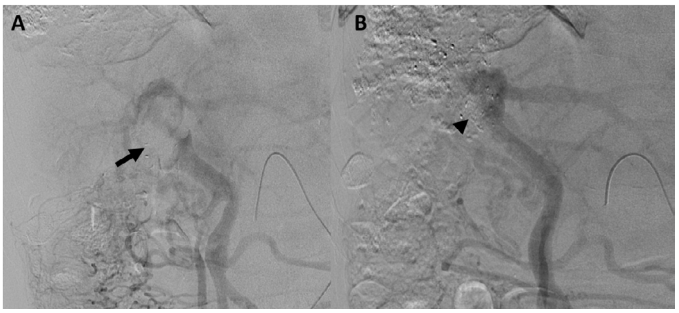

Figure 3. A case treated with radiotherapy after transcatheter arterial chemoembolization: a 53-year-old male patient with history of chronic hepatitis B who received TACE starting one month later after radiotherapy. **A)** Before treatment, compete obstruction of the right major branch of the portal vein and bifurcation (Black arrow) and **B)** After treatment, partial recanalization of the bifurcation was seen (Black arrowhead).

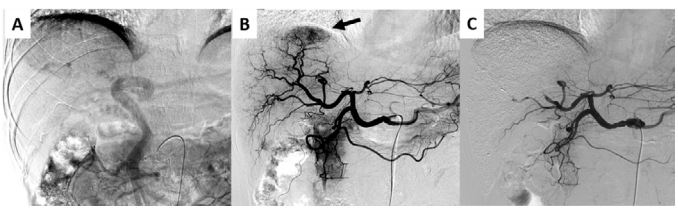

Figure 4. HCC in liver S8. **A)** Thrombosis of right portal branch was noted, **B)** Hypervascular tumor stain was noted over S8 of liver (black arrow) and **C)** The post-TACE follow-up DSA showed complete obliteration of tumor stains in the right lobe of liver.

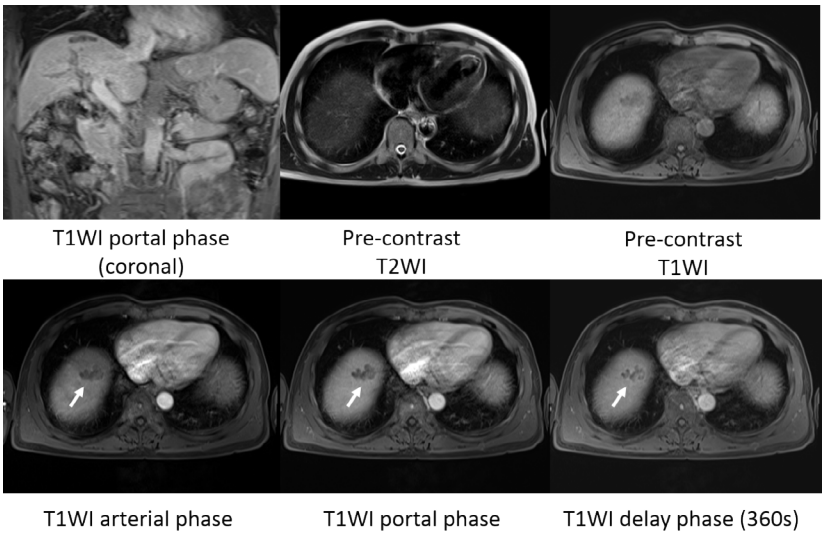

Figure 5. Post follow up MRI images showed good response without hypervascular tumor (white arrows).

Table 4. Comparing various treatment strategies for hepatocellular carcinoma patients accompanying portal vein tumor thrombosis.

Modality	Source	RECIST, mRECIST, or EASL	SD/NR	OR (CR+PR)	ODS (CR+PR+SD)	PD	Median Survival Time	12-month /24-month survivability (%)
Sorafenib	Cheng 2009	RECIST	54%	3.3%	57.3%	31.0%	6.5 months	NR
TARE with Y90 microspheres	Sangro 2011	RECIST	NR	NR	77.0%	NR	11 months	NR
Surgical Resection	Shi 2010	N/A (did not exclude prev TACE)	N/A	N/A	N/A	N/A	10.1 - 18.1 months (branch vs. main portal involvement)	13.3%/4.7% (12/36 months)
HAIC with cisplatin	Nouso 2015	EASL	23.60%	40.5%	64.1%	23.7%	7.9 months	NR
TACE	Luo 2011	RECIST	43.90%	19.5%	63.4%	36.6%	7 - 10.2 months	30.99%/3.8%
Radiotherapy	Yu 2015	N/A (did not exclude other prior treatments)	N/A	N/A	N/A	N/A	6.7 - 11 months (as an adjunct treatment)	30-40%/20-30% (as an adjunct treatment)
TACE + Radiotherapy	Present Study	mRECIST	30%	16.70%	46.70%	53.1%	14.3 months	40.6%/14.6%

of 5-FU and cisplatin for advanced HCC in a nationwide survey in Japan. The outcome of 476 patients with HCC who underwent HAIC was compared with 1,466 patients who did not receive active therapy. In this study, at the time of initial tumor assessment, 4% achieved an EASL CR rating, 36.5% achieved PR (≥ 50% tumor reduction, differing from RECIST/mRECIST), 23.6% achieved SD, and 27.2% received PD, with an OR of 40.5% and leaving 8.7% "undefined." In a propensity score-matched analysis, median survival in patients who received HAIC was longer than that in patients who received only supportive care (14.0 *vs.* 5.2 mo, respectively, P < 0.0001) [23]. However, the study also noted that in cases of Child-Pugh A/B disease with portal vein tumor thrombus, the median survival times dropped to 7.9 months *vs.* 3.1 months.

Transarterial radioembolization (TARE) uses yttrium-90 microspheres for treating HCC in the following scenarios: down-staging/bridging to transplantation or resection, advanced disease, and HCC with portal vein thrombosis. In a review paper, Sangro *et al.* reported that the improvement of median survival with intermediate- to advanced-stage HCC and the median survival was 3.2-41.6 months, with objective response rates from 20%-77% [24]. However, the longest survival times and highest objective response rates were from studies where PVTT explicitly excluded [25,26] or where TARE was part of a downstaging strategy and subsequent transplants were not excluded from the survival data [27]. Limiting Sangro *et al.* to those papers which specifically studied radioembolization with PVTT, the median survival range dropped to 3.2-11 months [24], with one small study (n=20) reporting a 2-month ODS rate (CR + PR + SD) of 77%, which dropped to 57% at 6 months [28]. TARE has been proven to be more well-tolerated and associated with favorable overall survival. Moreover, there is increasing evidence that TARE can be delivered safely and effectively in suitable HCC patients with PVTT, with several studies reporting median OS rates of approximately 10 months following the procedure in these patients [29]. However, it comes at a cost approximately 550% more than the combined TACE+EBRT treatment with comparatively similar results.

We compared our EBRT + TACE results against the treatment modalities discussed above, and in general, found that our co-treatment compared very favorably against them. In all cases, patients in our RT + TACE study showed higher rates of overall response (OR, defined as CR + PR from the mRECIST scale) the other treatments, except for TARE. However, TARE is at present prohibitively expensive and not widely available in Taiwan. Our findings are summarized in Table 4.

In multivariate analysis, our results showed that only two factors – tumor diameter and the frequency of TACE treatment – were significantly associated with the risk factors for patient survival. Although the analysis showed that achievement of objective disease stabilization after treatment was also significantly associated with patient survival, the low hazard ratio and confidence intervals lead us to discount its importance. Our findings also show that the degree of PVTT and the type of hepatitis did not actually significantly contribute to mortality risk. It is reasonable to suppose that patients who had larger tumors would eventually experience worse outcomes, as theoretically, a higher degree of PVTT should show a worse prognosis. However, our analysis showed that the obstruction level of the portal vein was not associated with the therapeutic outcome. This may suggest that radiotherapy combined with multiple interventions of TACE could attain an overall better outcome, regardless of the severity of the PVTT. Our study provides information to recognize the factors that can affect survival and design tailored treatment for advanced HCC in the future. Understanding these factors may help identify optimal treatment regimens and establish more detailed treatment guidelines in patients with HCC with PVTT.

We thereby recommend a first-line combined treatment consisting of EBRT for PVTT and TACE for liver tumor, which our data suggests could reach a higher response rate (objective response rate, 16.7%) and median survival (14.3 months) than single-modality treatments by themselves, including hepatectomy, systemic chemotherapy, sorafenib, and HAIC.

However, some issues must be addressed. Firstly, based on this study, the response of PVTT after TACE and radiotherapy is difficult to determine, because of the tumor configuration and PVTT region. HCC can be assessed by mRECIST criteria, which means that only the hypervascular part of treated HCC should be measured, but there is no proper radiologic response guideline for the portal thrombus for determining a more objective response to radiotherapy. We can only assess response by measuring size reduction of PVTT compared with initial size; however, substantial portions of responding HCC with PVTT showed the disappearance of contrast enhancement without an actual reduction in tumor and thrombus size, followed by no increase in thrombus size during long-term follow-up (28).

Secondly, thirty-three patients in our study received various treatments before and after TACE, including Sorafenib, RFA, and surgery. It is possible that these treatments could have influenced our study results, but that is impossible to assess with only the data that is at hand.

Other limitations: this was a retrospective study, not a randomized control prospective study. In addition, although many studies have reported the use of TACE in patients with HCC, certain issues remain unresolved, such as a lack of regarding the ideal chemo-embolic regimen, procedure end points, the degree of vascular stasis to be achieved, and the ideal time interval between treatment sessions. Another limitation is that the fractionated radiation dose might have influenced the PVTT response to RT due to the wide range of biologic properties of HCC, but a standard dose fractionation schedule has not yet been established for RT for HCC with PVTT. Finally, the sample size was too small to postulate the benefits of TACE in patients with PV thrombosis. Further investigation, long-term follow-up, and prospective clinical trials are warranted.

Conclusion

Combining radiotherapy and TACE for hepatocellular carcinoma with PVTT was found to be an effective treatment regimen, which achieved a higher response rate and better patient outcome as compared with single-agent modalities, such as systemic chemotherapy, sorafenib, radiotherapy or HAIC.

Our findings also suggest that, in patients diagnosed with advanced HCC, continuous application of TACE treatment results in better response and increased survival rate, regardless of the severity of portal vein tumor obstruction, and that tumor size is directly related to overall survival, making both valuable prognostic indicators.

References

1. Chueng TK, CL Lai, BCY Wong, J Fung, and MF Yuen. "Clinical Features, Biochemical Parameters, and Virological Profiles of Patients with Hepatocellular Carcinoma in Hong Kong." *Aliment Pharmacol Ther* 24(2006): 573-583.
2. Pirisi, Mario, Claudio Avellini, Carlo Fabris and Cathryn Scott, et al. "Portal Vein Thrombosis in Hepatocellular Carcinoma: Age and Sex Distribution in an Autopsy Study." *J Cancer Res Clin Oncol* 124(1998): 397–400.
3. Xi, Mian, Li-Zhang, Lei Zhao, Qiao-Qiao Li and Su-Ping Guo, et al. "Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis." *PloS One* 8(2013): e63864.
4. Xue, Tong-Chun, Xiao-Ying Xie, Lan Zhang and Xin Yin, et al. "Transarterial Chemoembolization for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Meta-Analysis." *BMC Gastroenterol* 13(2013): 60.
5. Robertson JM, TS Lawrence, LM Dworzanin and JC Andrews, et al. "Treatment of Primary Hepatobiliary Cancers with Conformal Radiation Therapy and Regional Chemotherapy." *J Clin Oncol* 11(1993): 1286-1293.
6. Meng, Mao-Bin, Yao-Li Cui, You Lu and Bin She, et al. "Transcatheter Arterial Chemoembolization in Combination with Radiotherapy for Unresectable Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis." *Radiother Oncol* 92(2009): 184–194.
7. Yoon, Sang Min, Young-Suk Lim, Hyung-Jin Won and Jong Hoon Kim, et al. "Radiotherapy Plus Transarterial Chemoembolization for Hepatocellular Carcinoma Invading the Portal Vein: Long-term Patient Outcomes." *Int J Radiat Oncol Biol Phy* 82(2012): 2004–2011.
8. Cheng, Jason-Chia-Hsien, Vincent Chuang, Skye Hongiun-Cheng and Andrew Huang, et al. "Local Radiotherapy with or without Transcatheter Arterial Chemoembolization for Patients with Unresectable Hepatocellular Carcinoma." *Int J Radiat Oncol Biol Phys* 47(2000): 435-442.
9. Katagiri, Satoshi, Masakazu Yamamoto. "Multidisciplinary Treatments for Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombus." *Surg Today* 44(2014): 219–226.
10. Lencioni, Riccardo, Josep Llovet. "Modified RECIST (MRECIST) Assessment for Hepatocellular Carcinoma." *Liver Dis* 30(2010): 52–60.
11. Cheng, Ann-Lii, Yoon-Koo Kang, Zhendong Chen and Chao-Jung Tsao, et al. "Efficacy and Safety of Sorafenib in Patients in the Asia-Pacific Region with Advanced Hepatocellular Carcinoma: A Phase III Randomised, Double-Blind, Placebo-Controlled Trial." *Lancet Oncol* 10(2009): 25-34.
12. Pinter, Matthias, Florian Hucke, Ivo Graziadei and Wolfgang Vogel, et al. "Advanced-stage Hepatocellular Carcinoma: Transarterial Chemoembolization *vs.* Sorafenib." *Radiol* 263(2012): 590–599.
13. Luo, Jun, Rong-Ping Guo, Eric-Ch Lai and Yao-Jun Zhang, et al. "Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Prospective Comparative Study." *Ann Surg Oncol* 18(2011): 413-420.
14. Hawkins, Maria, Laura Dawson. "Radiation Therapy for Hepatocellular Carcinoma: From Palliation to Cure." *Cancer* 106(2006): 1653-1663.
15. Yu, Su-Jong, Yoon Jun-Kim. "Effective Treatment Strategies Other than Sorafenib for the Patients with Advanced Hepatocellular Carcinoma Invading Portal Vein." *World J Hepatol* 7(2015): 1551-1561.
16. Kim, Dae-Yong, Won Park, Do Hoon-Lim and Joon Hyoek-Lee, et al. "Three-Dimensional Conformal Radiotherapy for Portal Vein Thrombosis of Hepatocellular Carcinoma." *Cancer* 103(2005): 2419–2426.
17. Nakazawa, Takahide, Hisashi Hidaka, Akitaka Shibuya and Yusuke Okuwaki, et al. "Overall Survival in Response to Sorafenib *vs.* Radiotherapy in Unresectable Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis: Propensity Score Analysis." *BMC Gastroenterol* 14(2014): 84.
18. Nakagawa, Keiichi, Hideomi Yamashita, Kenshiro Shiraishi and Naoki Nakamura, et al. "Radiation Therapy for Portal Venous Invasion by Hepatocellular Carcinoma." *World J Gastroenterol* 11(2005): 7237–7241.
19. Yamada, Kazunari, Kenta Izaki, Koji Sugimoto and Hiroshi Mayahara, et al. "Prospective Trial of Combined Transcatheter Arterial Chemoembolization and Three-dimensional Conformal Radiotherapy for Portal Vein Tumor Thrombus in Patients with Unresectable Hepatocellular Carcinoma." *Int J Radiat Oncol Biol Phy* 57(2003): 113–119.
20. Nagashima, Tohru. "The Study on Radiotherapy for Hepatocellular Carcinoma." *Nihon Igaku Hoshasen Gakkai Zasshi. Nippon Acta Radiol* 49(1989): 1141–1151.
21. Chen, Shinn-Cherng, Shi-Long Lian, Wen-Yu Chang. "The Effect of External Radiotherapy in Treatment of Portal Vein Invasion in Hepatocellular Carcinoma." *Cancer Chemother Pharmacol* 33(1994): 124-127.
22. Cho, Ju-Yeon, Yong-Han Paik, Hee-Chul Park and Jeong-Il Yu, et al. "The Feasibility of Combined Transcatheter Arterial Chemoembolization and Radiotherapy for Advanced Hepatocellular Carcinoma." *Liver Int* 34(2014): 795-801.
23. Nouso K, K Miyahara, Daisuke Uchida and K Kuwaki, et al. "Effect of Hepatic Arterial Infusion Chemotherapy of 5-Fluorouracil and Cisplatin for Advanced Hepatocellular Carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan." *British J Cancer* 109(2013): 1904–1907.
24. Sangro, Bruno, Riad Salem, Andrew Kennedy and Douglas Coldwell. "Radioembolization for Hepatocellular Carcinoma: A Review of the Evidence and Treatment Recommendations." *Am J Clin Oncol* 34(2011): 422-431.
25. Riaz A, RJ Lewandowski, RK Ryu and L Kulik, et al. "Abstract No. 215: [R/F]

Chemoembolization *vs.* Radioembolization: Comparison of Toxicity, Imaging Response and Long-Term Outcomes in 100 TACE vs 104 Y90 Patients." *J Vascular Interv Radiol* 20(2009): S83.

26. Scanlon T, A Riaz, L Kulik and RJ Lewandowski, et al. "Abstract No. 195: Treatment of Solitary HCC: Comparison of TACE and Y90 Radioembolization." *J Vascular Interv Radiol* 20(2009): S75–576.
27. Lewandowski RJ, LM Kulik, A Riaz and S Senthilnathan, et al. "A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization *vs.* Radioembolization." *Am J Transplant* 9(2009): 1920–1928.
28. Inarrairaegui M, KG Thurston, M Rodriguez and A Martinez-Cuesta, et al. "Radioembolization Using Resin Microspheres in Patients with Hepatocellular Carcinoma and Portal Vein Thrombosis." *Hepatol* 50(2009): 1105.
29. Kooby, David, Vasili Egnatashvili, Swetha Srinivasan and Abbas Chamsuddin, et al. "Comparison of Yttrium-90 Radioembolization and Transcatheter Arterial Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma." *J Vasc Interv Radiol* 21(2010): 224-230.

How to cite this article: Pi-Yi Chang, Jen-I Hwang, Jau-Shin Hon and Chen-Yang Cheng. "Combined TACE and Radiotherapy Treatment for Patients with Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis." J Integr Oncol 11 (2022): 518.