

Radiotherapy as valid modality for hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract

Although the current standard treatment for hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) is sorafenib, many previous studies have established the need for a reliable local modality for PVTT control, which is a major cause of liver function deterioration and metastasis. Additionally, there is growing evidence for the prognostic significance of PVTT classification according to the location of tumor thrombosis. Favorable outcomes can be obtained by applying local modalities, including surgery or transarterial chemoembolization, especially in second-order or distal branch PVTT. Rapid control of PVTT could maintain or improve liver function and reduce intrahepatic as well as distant metastasis. Radiotherapy (RT) is one of the main locoregional treatment modalities in oncologic fields, but has rarely been used in HCC because of concerns regarding hepatic toxicity. However, with the development of advanced techniques, RT has been increasingly applied in HCC management. Randomized studies have yet to definitively prove the benefit of RT, but several comparative studies have justified the application of RT in HCC. The value of RT is especially noticeable in HCC with PVTT; several prospective and retrospective studies have reported favorable outcomes, including a 40% to 60% objective response rate and median overall survival of 15 mo to 20 mo in responders. In this review, we evaluate the role of RT as an alternative local modality in HCC with PVTT.

Key words: Hepatocellular carcinoma; Portal vein tumor thrombosis; Radiotherapy; Local modality; Alternative

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Core tip: The optimal management of portal vein tumor thrombosis (PVTT), which can induce liver function deterioration and act as a source of metastasis, in patients with hepatocellular carcinoma (HCC) remains unclear. With growing evidence for the prognostic significance of PVTT classification and promising outcomes of local modalities in selected patients, the need for a reliable local modality of control is becoming increasingly apparent. In this review, the outcomes of radiotherapy as an alternative local modality for PVTT control in HCC are presented.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and second leading cause of cancer mortality worldwide^[1,2]. Despite remarkable improvements in the management of HCC, including antiviral agents^[3-5], adaptation of magnetic resonance imaging^[6] and major advances in local treatment modalities^[7-9], this disease remains a concerning health issue. The major issue in HCC management is that approximately 70% of newly diagnosed patients are not candidates for curative local treatment modalities^[10]; in particular, portal vein tumor thrombosis (PVTT), which is a common complication of HCC, is frequently an obstacle to the application of such modalities^[11].

PVTT is known to be present in approximately 30% to 40% of cases of advanced HCC^[10-12]. The association between PVTT and dismal outcomes has been confirmed by many studies^[13,14]. Because of the role of PVTT as the most powerful prognosticator in HCC, curative local modalities are not recommended for HCC with PVTT in the Barcelona Clinic Liver Cancer (BCLC) staging and treatment system^[15,16]. Nevertheless, local treatment modalities including surgical resection, trans-arterial chemoembolization (TACE), and radiotherapy (RT) are commonly applied in HCC with PVTT to obtain early and durable local control^[17,18].

RT is a key locoregional modality in oncology^[19]. It is minimally invasive and, unlike surgery, is not associated with pain or a long recovery period. In cancer patients with a relatively high risk of recurrence at other sites, as in those with oligo-metastatic disease, RT is generally preferred for obtaining local control over invasive surgical resection in order to avoid missing the optimal timing for systemic management^[20]. However, RT has played a very limited role in

past management of HCC, and is usually administered for palliation of symptoms related to extrahepatic metastasis, rather than for control of the primary liver tumor^[21]. The source of this limitation is the radiosensitive nature of the cirrhotic non-tumorous liver and related concern regarding the maintenance of clinical liver function, which is a main aim in HCC management^[22].

With the development of improved RT techniques and radiobiology, RT has recently been increasingly applied in HCC management. Although there is no definitive evidence for the role of RT, superior outcomes obtained by including RT in HCC management have been reported in several meta-analyses as well as many prospective and retrospective studies^[23-35]. Based on these favorable clinical outcomes of innovative RT techniques, liver-directed RT has been recommended for HCC patients who are not candidates for curative loco-regional modalities in the guidelines from the Korean Liver Cancer Study Group^[36] and the National Comprehensive Cancer Network^[37]. However, even though the use of RT in unresectable HCC is gradually increasing worldwide as a result of these recommendations^[38], RT is still not recommended by the BCLC system, which is the most widely used set of HCC management guidelines^[16].

In this review, we introduce the current status of RT in HCC and recently reported outcomes and discuss why the addition of RT is beneficial in HCC patients with PVTT.

DISMAL PROGNOSTIC ROLE OF PVTT AND THE NEED FOR LOCAL MODALITIES

PVTT is present at diagnosis in approximately 30% to 40% of patients with advanced HCC^[11,12], and is one of the most important poor prognostic factors of HCC, with a reported median overall survival (OS) of 2.7 mo to 4.0 mo^[12,39].

There are several explanations for how PVTT results in dismal clinical outcomes. PVTT itself disturbs the portal blood supply in the normal liver and can therefore cause deterioration of liver function crucial to HCC management^[40]. Furthermore, local tumor progression can accelerate the deterioration of liver function. In addition, PVTT might act as a distributor of intrahepatic and extrahepatic metastasis^[41,42]. These possible unfavorable roles of PVTT were observed in our previous study evaluating the relationship between PVTT response and clinical outcomes in HCC patients with PVTT who were treated with TACE followed by RT^[43]. Elevation of Child-Pugh scores representing liver function deterioration was significantly more frequent in the non-responders than the responders of treatment. Moreover, the rates of intrahepatic and extrahepatic metastasis were significantly lower in responders.

Because of its well-known role as the most powerful

unfavorable prognosticator in HCC, the BCLC system does not recommend curative local modalities for patients with HCC with PVTT^[16]. Based on its survival benefit in two large prospective randomized phase III trials^[44,45], sorafenib, an oral multikinase inhibitor of platelet-derived growth factor receptor, vascular endothelial growth factor receptor and Raf, is the only standard treatment in these patients. However, physicians hesitate to use sorafenib in advanced but localized disease because of the disappointing objective response rate of 2% to 5% and extremely short median time to progression of 2.8 mo found in a study conducted in the Asia-Pacific region^[46]. A more reliable local modality that can rapidly control vascular invasion to the portal vein and thus maintain liver function while eliminating the source of metastasis is needed to improve clinical outcomes.

Furthermore, there is a wide spectrum of vascular invasion clinical manifestations of PVTT, and prognoses are clearly separated according to the extent of PVTT^[47-50]. PVTT can be classified into four categories as suggested by the Liver Cancer Study Group of Japan^[51] (Figure 1): the presence of tumor thrombus distal to the second-order branches of the portal vein is defined as Vp1, in the second-order branches of the portal vein as Vp2, in the first-order branches of the portal vein as Vp3, and in the main trunk or both first-order branches of the portal vein as Vp4. Although definitive evidence is lacking, customized treatments for HCC patients with PVTT according to PVTT classification combined with other recognized factors, such as liver function, performance status, tumor size and number, should be explored.

RESULTS OF OTHER LOCAL MODALITIES IN HCC WITH PVTT

The importance of local treatment modalities in the management of HCC cannot be overstated. Immediate methods of tumor elimination, such as surgical resection including liver transplantation (LT) and radiofrequency ablation (RFA), can prevent reductions in liver function by preventing tumor encroachment into the surrounding liver and removing the source of intra and/or extrahepatic metastasis^[52-55]. Long-term survival is achieved in approximately 60% to 70% of HCC patients treated with curative local modalities, but recurrence eventually occurs in more than half of patients, with the exception of those who undergo LT. However, the majority of patients are not candidates for curative local modalities, mainly due to tumor burden, and PVTT is a major obstacle to the application of curative local modalities^[10-12,39].

Notable survival rates of 20% to 40% 5 years after surgical resection were reported by the Liver Cancer Study Group of Japan, mainly in HCC patients with minor class Vp1 or Vp2PVTT^[56,57]. Although selection bias is inherent in those studies, the results indicate

that a proportion of patients might benefit from early elimination of the tumor and PVTT. Furthermore, some cases of long-term survival were reported after surgical resection of HCC with Vp3 or Vp4 PVTT^[58,59].

As an alternative local modality with proven efficacy, TACE is widely used in cases of large multinodular HCC^[60-62]. However, a complete response is rarely obtained and the duration of local control is unsatisfactory, especially for large tumors^[59]. Furthermore, because of the rationale for TACE, which is selective tumor embolization through the arterial blood supply of HCC, in contrast to the dual supply of the surrounding normal liver, TACE had previously been contraindicated in HCC with PVTT. Recent studies, however, have supported that TACE can be safely administered in these patients because of collateral circulation^[63,64]. In clinical practice, the super-selective method of TACE, with or without another modality, is one of the most frequently used treatments in HCC patients with PVTT^[48,65].

Surgical outcomes are generally reported to be superior to TACE in HCC with PVTT. Liu *et al.*^[66] reported superior outcomes of surgical resection compared to TACE in 108 pairs of matched patients selected using propensity score analysis. It is very hard to directly compare clinical outcomes between surgical resection and TACE because of the clear differences in patient and tumor characteristics, including liver function, performance status, and the extent of disease. Nevertheless, local control could enhance clinical outcomes in HCC with PVTT.

INTRODUCTION OF RT IN HCC

Historically, RT was not used in HCC management, especially for primary lesion of the liver. The main reason for the avoidance of RT in HCC was the low tolerance of liver tissue to RT exposure and concerns regarding radiation-induced liver disease (RILD), which typically presents as anicteric hepatomegaly and ascites 2-3 mo after RT^[22]. The pathology of radiation-induced liver damage shows changes similar to veno-occlusive disease, including endothelial swelling, terminal venule occlusion and sinusoidal congestion^[67]. RILD is a major concern in liver RT, because there is no established treatment and some patients will die of liver failure, although a few patients may recover^[68]. Recently, the incidence of classic RILD has decreased, but non-classic RILD (which appears with jaundice and marked elevation of serum transaminase) is still problematic in the application of RT in HCC^[69].

Because the treatment options for RILD are very limited, most investigations have focused on identifying predictive factors of RILD development^[69-74]. Factors related to RT planning, such as RT dose and liver volume, have been of particular interest. Mean liver dose was demonstrated by Dawson *et al.*^[71] to be a risk factor of RILD, and V20 Gy was suggested by Liang *et*

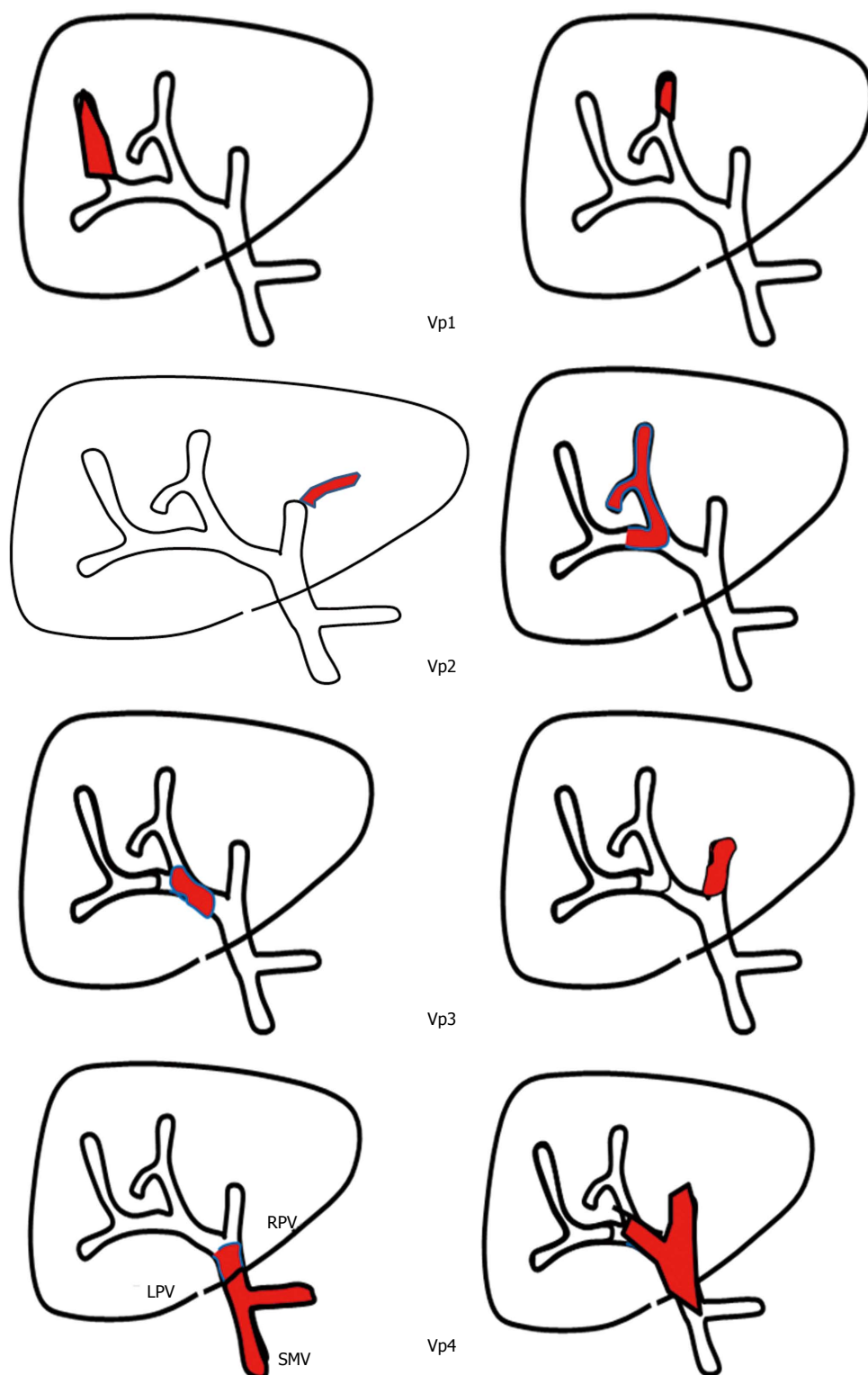


Figure 1 Classification of portal vein tumor thrombosis. PVTT is classified into four categories according to the site of tumor thrombus as suggested by the Liver Cancer Study Group of Japan. PVTT: Portal vein tumor thrombosis.

al^[74] to be a dosimetric predictor. Kim *et al*^[72] reported that grade 2 or higher radiation-induced hepatic toxicity was significantly related to the percentage of total normal liver volume exceeding 30 Gy irradiation. Our group reported that $V_{30\text{ Gy}}$ was a significant risk factor of Child-Pugh score elevation of two points

or greater^[69]. There is also a possibility of a higher incidence of liver function deterioration after RT in HCC combined PVTT than in the other, but the dosimetric factors of liver are more important, generally^[69,72].

With better information regarding RILD development and the application of computed tomography

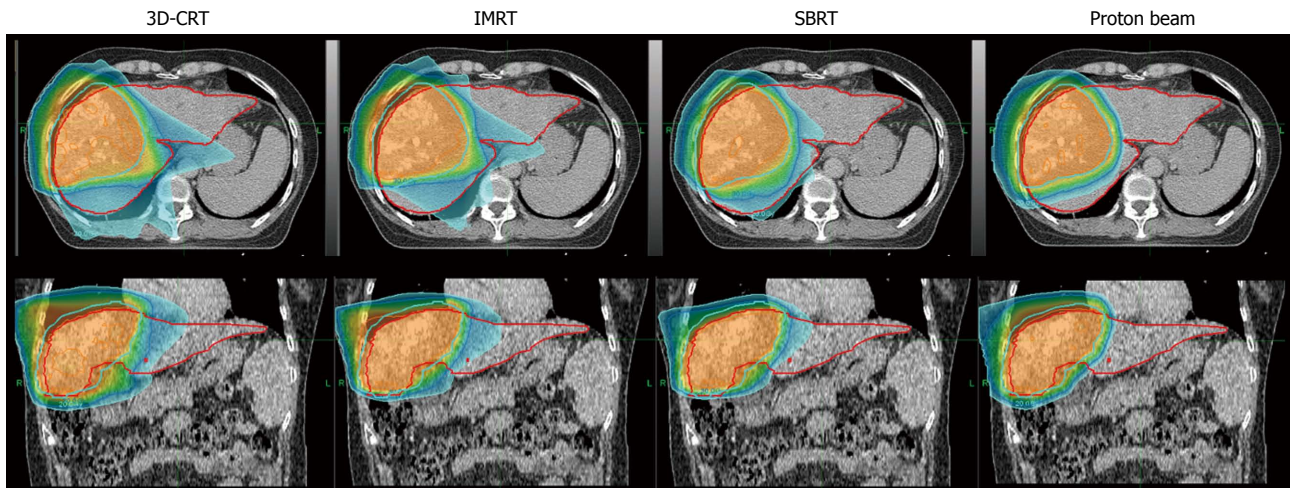


Figure 2 Radiation dose distribution according to radiotherapy technique. More conformal dose delivery to the main mass and tumor thrombosis with a reduced liver dose is achievable with 3D-CRT, IMRT, and SABR, as well as to an even greater extent with proton beam RT. 3D-CRT: Three-dimensional conformal RT; IMRT: Intensity-modulated RT; SABR: Stereotactic body ablative RT. RT: Radiotherapy technique.

Table 1 Systematic meta-analyses evaluating the efficacy of radiotherapy in hepatocellular carcinoma

Ref.	Subject	Study aim	n	CR OR	P value	3 yr OS OR	P value
Meng <i>et al</i> ^[24]	5 RCT, 12 CCT	TACE + RT <i>vs</i> TACE	1370	2.58	< 0.001	2.75	< 0.001
Liao <i>et al</i> ^[25]	10 RCT, 18 non-RCT	TACE + RT <i>vs</i> TACE	1223	-	-	2.53	0.001
Huo <i>et al</i> ^[30]	11 RCT, 14 non-RCT	TACE + RT <i>vs</i> TACE	2577	2.73	< 0.001	1.91	< 0.001
	PVTT subgroup		-	2.38	< 0.001	2.22	< 0.001

CCT: Non-randomized controlled clinical trial; CR: Complete response; OS: Overall survival; PVTT: Portal vein tumor thrombosis; RCT: Randomized controlled trial; TACE: Trans-arterial chemoembolization. RT: Radiotherapy technique.

(CT) to RT planning, higher RT doses for local tumor control can be administered with an acceptable RILD risk level^[73,75-77]. Further innovative RT technologies, including three-dimensional conformal RT (3D-CRT)^[78], intensity-modulated RT (IMRT)^[79], stereotactic body ablative RT (SABR)^[80] and particle beam therapies^[81], have been introduced and actively applied in HCC management (Figure 2). Additionally, image-guided RT^[82], which is used as a supportive/supplementary method with other precision RT techniques, is also standard RT practice. These biological and technical developments have enabled delivery of higher-dose RT with improved precision and better conformation and without an increased probability of normal tissue complications. With these rapid developments in techniques and radiobiology, RT has become an accepted tool in the management of HCC^[77].

APPLICATION OF RT IN HCC

Although evidence from well-designed randomized trials on the role of RT is still needed, several comparative studies have justified the application of RT in HCC management. The results of three systematic meta-analyses of randomized and non-randomized trials are displayed in Table 1^[24,25,30]. In all three reports, the addition of RT to TACE showed

a significant survival benefit over TACE alone, with an OR of 1.91 to 2.75 for 3-year OS rates. The complete response (CR) rate was also significantly higher in the TACE plus RT group with an OR of 2.58 to 2.73, and a similar effect was observed in the PVTT subgroup (OR = 2.38)^[30].

Several comparative reports presented the efficacy of RT compared to other treatment modalities in HCC, and a summary of these studies is displayed in Table 2^[23,26-28,31,33-35,83]. In the retrospective cohort study of Eun *et al*^[83], RT showed a clear survival benefit in advanced HCC over best supportive care (median OS 45.9 mo *vs* 4.8 mo, $P < 0.001$). Yoon *et al*^[35] compared concurrent chemoradiotherapy (CCRT) and other treatment modalities, including surgery, RFA and TACE, in locally advanced HCC using a propensity score matching technique and showed that CCRT yielded significantly longer-term OS than other modalities (median OS 11.4 mo *vs* 6.6 mo, $P = 0.02$).

Two studies compared RT with or without TACE to sorafenib as the current standard treatment in patients with BCLC stage C disease including PVTT, and both showed a positive effect of RT on survival^[27,28]. Moreover, TACE with RT also led to a significant survival advantage in HCC with PVTT in a comparative study using propensity score matching^[33]. Cho *et al*^[27] reported that OS was significantly higher in the RT

Table 2 Comparative studies evaluating the effectiveness of radiotherapy in unresectable advanced hepatocellular carcinoma

Ref.	Subject	Study aim	n	1 yr PFS	OS	P value
Eun <i>et al</i> ^[83]	BCLC C/D	RT vs BSC	29 vs 18	-	45.9 vs 4.8	< 0.001
Yoon <i>et al</i> ^[35]	Locally advanced	CCRT vs others	106 vs 106	-	11.4 vs 6.6	0.02
Cho <i>et al</i> ^[27]	BCLC C	TACE + RT vs sorafenib	67 vs 49	-	14.1 vs 3.3	< 0.001
Nakazawa <i>et al</i> ^[28]	HCC with PVTT	RT vs sorafenib	28 vs 28	-	10.9 vs 4.8	0.002
Li <i>et al</i> ^[33]	HCC with PVTT	TACE + RT vs TACE	108 vs 108	-	10.9 vs 4.1	< 0.001
Guo <i>et al</i> ^[23]	Large HCC	TACE + RT vs TACE	89 vs 76	-	1-yr (%) 64.0 vs 39.9	< 0.001
Tang <i>et al</i> ^[26]	HCC with PVTT	RT vs surgery	185 vs 186	32.3% vs 42.2%	1-yr (%) 51.6 vs 40.1	0.03
Shiozawa <i>et al</i> ^[31]	≤ 5-cm solitary HCC	SABR vs RFA	35 vs 38	86.1% vs 85.6%	1-yr (%) 95.2 vs 100	0.08
Wahl <i>et al</i> ^[34]	Inoperable localized	SABR vs RFA	63 vs 161	LC 97.4% vs 83.6%	1-yr (%) 74.1 vs 69.6	NS

BCLC: Barcelona Clinic Liver Cancer; BCS: Best supportive care; CCRT: Concurrent chemoradiotherapy; HCC: Hepatocellular carcinoma; NS: Not significant; OS: Overall survival; PFS: Progression-free survival; PVTT: Portal vein tumor thrombosis; RFA: Radiofrequency ablation; RT: Radiotherapy; SABR: Stereotactic body radiotherapy; TACE: Trans-catheter arterial chemoembolization.

Table 3 Prospective and retrospective studies applying radiotherapy with or without transcatheter arterial chemo-embolization in hepatocellular carcinoma with portal vein tumor thrombosis

Ref.	Year	Design	Treatment	No.	OR	Median survival, mo		P value
						OR (+)	OR (-)	
Tazawa <i>et al</i> ^[90]	2001	Retrospective	TACE + RT	24	50.0%	9.7	3.8	< 0.001
Yamada <i>et al</i> ^[91]	2003	Prospective	TACE + RT	19	57.9%	15.4	4.6	0.16
Kim <i>et al</i> ^[87]	2005	Retrospective	RT	59	45.8%	10.7	5.3	0.05
Nakazawa <i>et al</i> ^[89]	2007	Retrospective	RT	32	48.0%	13.8	7.0	0.01
Zeng <i>et al</i> ^[94]	2008	Retrospective	RT	136	57.6%	19.5 (CR) 10.2 (PR)	7.2 (SD) 3.5 (PD)	< 0.001
Yu <i>et al</i> ^[93]	2011	Retrospective	RT ± TACE	281	53.8%	22.0	5.0	< 0.001
Yoon <i>et al</i> ^[92]	2012	Retrospective	TACE + RT	412	39.6%	19.4	7.0	< 0.001
Kim <i>et al</i> ^[88]	2014	Retrospective	TACE + RT	59	51.0%	NR	7.0	< 0.001

CR: Complete response; NR: Not reported; OR: Objective response; PD: Progressive disease; PR: Partial response; SD: Stable disease.

group in a propensity score-matched cohort (median OS 8.9 mo vs 3.1 mo, $P < 0.001$), as well as in all cohorts (median OS 14.1 mo vs 3.3 mo, $P < 0.001$). Tang *et al*^[26] also compared surgical resection to RT in 371 patients with resectable HCC with PVTT and reported a median 2.3-mo survival advantage with RT when compared to resection ($P = 0.03$), with comparable progression-free survival.

The popularity of SABR, also known as stereotactic body RT, has recently increased in RT for HCC^[29,31,32,34,84]. Two studies compared SABR and RFA, which is one of standard local modalities, and both showed that local control with SABR was comparable or even higher for larger tumors (≥ 2 cm) with similar OS in early HCC^[31,34]. Although differences in characteristics originating from the retrospective design were compensated for in these studies, the results should be interpreted with caution.

TECHNIQUES AND CLINICAL OUTCOMES OF RT IN HCC WITH PVTT

Clinical outcomes of 3D-CRT and IMRT

The basis of modern RT is 3D-CRT, which involves conformal radiation delivery based on 3-D anatomical information and dose distribution using CT simu-

lation^[85]. More innovative RT techniques, which will be introduced in the following sections, are based on 3D-CRT planning. IMRT, for example, makes it possible to deliver an even more conformal RT dose using non-uniform inverse-planned intensity-modulated beams^[79,86]. Several techniques, such as tomotherapy and arc-therapy, are classified as IMRT. Theoretically, a dose increased from that used with 3D-CRT could be safely delivered in HCC using these approaches.

There are numerous reports regarding 3D-CRT with or without TACE for locally advanced HCC with Vp3-4 PVTT, and most of these studies yielded a favorable objective response rate of 40% to 60% and promising OS of 8 mo to 11 mo^[87-94]. Representative studies of RT with or without TACE are summarized in Table 3. Although there are some discrepancies in clinical outcomes that are probably related to differences in patient and tumor characteristics, a greater than 40% objective response rate was obtained in all studies. In addition, excellent median survival outcomes of more than 12 mo are also reported in treatment responders.

Clinical outcomes of SABR

Although there is no clear definition of SABR, it is generally defined as extremely conformal and accurate delivery of a larger single fraction size with relatively little

fractionation, such as one to five fractions^[95,96]. Recently, SABR has been one of the most enthusiastically applied and best-studied areas of RT application, especially in the treatment of HCC^[31,34,80,84,97-100]. The number of prospective SABR study protocols for subjects with HCC with or without PVTT registered on Clinicaltrials.gov has dramatically increased since 2008.

Kang *et al.*^[101] reported an objective response of greater than 85% with median OS of 12 mo to 15 mo in a retrospective study of SABR with or without TACE involving 101 patients with HCC with PVTT. Prospective phase I and II trials of more than 100 HCC patients with tumor thrombosis showed a 1-year local control rate of 87% (95%CI: 79%-93%) after SABR and a 2-year local control rate of more than 50%, with median OS of 17.0 mo (95%CI: 10.4-21.3 mo)^[84]. Based on the favorable results of these large prospective trials, SABR is now recommended for unresectable HCC in the National Comprehensive Cancer Network guidelines^[37] and a randomized phase III prospective trial evaluating the addition of SABR to the current standard treatment of sorafenib in locally advanced HCC including PVTT is ongoing^[102].

Clinical outcomes of particle beam RT

Based mainly on the superior radiation dose distribution, the application of particle beam RT, mainly consisting of proton or carbon ions, is increasing^[103-109]. In addition, particle beams show a relative insensitivity to hypoxia, which is the main reason for the resistance of cancer cells to other RT techniques, and these theoretically enhanced biological effects of particle beam RT have been confirmed in some studies^[106]. Use of particle beam therapy in HCC has attracted a great deal of attention because of its exceptional ability to spare normal organs including the surrounding liver. Favorable outcomes of particle beam therapy in HCC have been reported by several groups, and a meta-analysis demonstrated that particle beam therapy enhanced survival outcomes as well as reducing toxicity when compared with 3D-CRT and SABR^[110,111].

Sugahara *et al.*^[112] reported a median OS of 22 months with 91% local control and without grade III or higher late toxicity after proton beam RT in 35 HCC patients with PVTT. Lee *et al.*^[113] reported a median OS of 13.2 mo with a 55.6% objective response rate without severe toxicity in HCC with PVTT.

Although the application of carbon ion specifically to HCC with PVTT has not yet been documented, several reports reported promising outcomes of 90% to 100% local control and 22% to 35% 5-year OS in HCC patients including combined with PVTT. These results were similar to those of proton beam RT. Komatsu *et al.*^[114] reported that carbon ion and proton therapies for HCC show comparable local control (93%, carbon ion; 90.2%, proton) and 5-year survival rates (36.3%, carbon ion; 38%, proton).

SELECTION OF LOCAL MODALITIES IN PVTT

As mentioned above, the wide variety of clinical outcomes of PVTT reflects not only the extent of PVTT, but also other factors^[13,14,39,47-50]. Previously, our group reported a prognostic model in HCC with PVTT treated with RT that clearly stratified patient survival outcomes based on other validated prognostic models of HCC^[93]. In addition, our prognostic model was validated by another independent data set from a multicenter cohort^[115].

A comparative study evaluating surgical resection vs conformal RT combined with TACE for resectable HCC with PVTT including more than 50% Vp3 or Vp4 cases showed a significant survival advantage in the TACE and RT group vs the surgical group (median 12.3 mo vs 10.0 mo, $P = 0.03$)^[26]. In our unpublished analysis comparing surgical resection vs TACE followed by RT in HCC with Vp1/2 PVTT, the OS of patients that underwent surgical resection was slightly higher in cases with small tumor size (< 3 cm), solitary tumor and low α -fetoprotein level (< 200 ng/mL), although statistical significance was not reached.

The detrimental role of PVTT as an obstacle to liver function maintenance and a source of metastasis indicates that valid local modalities based on PVTT extent, clinical liver function and tumor extent are urgently needed to improve clinical outcomes for HCC. Suggested local modalities for control of HCC with PVTT according to PVTT classification and/or disease extent are displayed in Figure 3, although prospective studies are still needed on the role of these modalities in the treatment of HCC. Large, prospective, randomized, controlled studies evaluating local treatment modalities and survival outcomes compared to the current standard treatment of sorafenib should be performed.

LIMITATIONS OF RT

Although RT has shown promising results including favorable treatment response and survival rates in HCC with PVTT, treatment decisions regarding RT should be made cautiously because of several remaining limitations^[116].

Liver function is one of the most important factors determining the method and purpose of HCC management^[16], and is a key concern when considering RT. In patients with a Child-Pugh score ≥ 8 , liver-directed RT is not generally recommended. Thus, there have been few studies in which RT was applied in those patients^[36,37]. Culleton *et al.*^[117] reported a prospective study of SABR outcomes in patients with Child-Pugh class B or C HCC, and significantly lower survival was detected in patients with a Child-Pugh score ≥ 8 (9.9 mo in those with scores of 7 vs 2.8 mo with scores of 8 or higher, $P = 0.01$). In another prospective

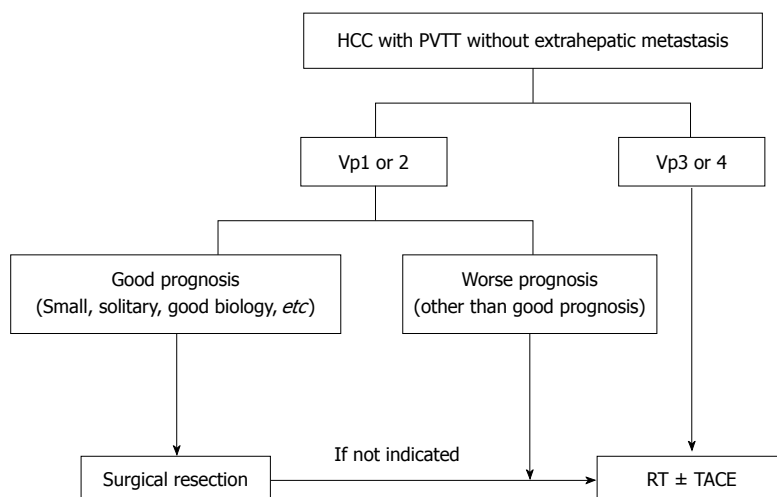


Figure 3 Suggested local treatment modalities for hepatocellular carcinoma with portal vein tumor thrombosis according to portal vein tumor thrombosis classification. To rapidly eliminate tumor thrombosis, RT with or without TACE could be considered, except in the case of technically resectable Vp1/2 disease with a favorable prognosis. HCC: Hepatocellular carcinoma; PVTT: Portal vein tumor thrombosis; RT: Radiotherapy; TACE: Trans-arterial chemoembolization.

phase I study of SABR for HCC, 3 of 11 patients with Child-Pugh class B disease developed grade III hepatic toxicity, while none of the 17 patients with Child-Pugh class A disease did^[98]. A significantly higher incidence of grade II or higher liver toxicity in patients with Child-Pugh class B disease was reaffirmed by a large retrospective SABR study (36.0% vs 11.9% of Child-Pugh class A patients)^[118].

Another important obstacle to RT application in HCC is the radiation susceptibility of the bowel, including the stomach and duodenum. The positive correlation between the incidence of symptomatic bowel toxicity and RT dose/bowel volume has been confirmed in several studies^[119–121]. Our group also reported that liver function deterioration is related to a higher incidence of symptomatic bowel toxicity^[122].

Before applying RT in HCC, these unresolved obstacles need to be considered. Although promising outcomes were achieved in HCC patients with poor liver function (Child-Pugh class C) or adjacent to the bowel in small studies using particle beam RT^[123–125], in these high-risk patients the use of RT should be carefully restricted or limited to prospective clinical trials.

While acceptable local control using RT in HCC has been reported, especially with SABR, frequent intrahepatic recurrence remains an unresolved issue^[88,126–128]. Several studies have suggested that RT may induce intrahepatic metastasis *via* viral reactivation^[129,130] and/or expression of vascular endothelial growth factor^[131]. With the development and optimal application of antiviral agents and targeted agents like sorafenib, intrahepatic recurrence might be minimized after RT^[3–5,131,132]. Further studies on combination treatment with RT are needed.

CONCLUSION

Considering the role of PVTT in liver function deterioration and metastasis, a reliable local modality for early control of PVTT is urgently needed. Because there is considerable variation in patient prognosis, customized application of local modalities including surgical resection and TACE should be based on the extent of the main mass and/or PVTT. With recent technological advances, RT could be an effective local modality for HCC control, especially for patients with HCC combined with PVTT.

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