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Efficacy and toxicity of SBRT in advanced hepatocellular carcinoma with portal vein tumor thrombosis — a retrospective study

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ABSTRACT

Background: The purpose of this study was to evaluate the outcome of stereotactic body radiation therapy (SBRT) in patients of unresectable hepatocellular carcinoma (HCC) complicated with portal vein tumor thrombosis (PVTT) who are also unsuitable for other locoregional therapies.

Materials and methods: Between May 2018 and January 2020, twenty-nine patients with advanced unresectable HCCs, treated with SBRT, were enrolled in this retrospective audit. Patients of Child status A5-B7 and with healthy liver volume, ≥ 700 ccs were treated. Local control (LC), overall survival (OS), progression-free survival (PFS), PVTT opening rate, and effect of prognostic factors were analyzed.

Results: The median tumor diameter was 8.6 cm (5–14), and the median tumor volume was 275 cc (151–1196). The median SBRT dose prescription was 48 Gy in 6 fractions (32–50 Gy in 5–6 fractions). The median follow up was eight months (1–20), 1-year local control, progression-free survival, and overall survival were 95%, 53.4%, and 60%, respectively. Overall rate of grade III toxicity was less than 5%, and the most common toxicity was lymphocytopenia. Tumors of more than 350cc had worse OS and PFS when compared to tumors < 350 cc (median OS and PFS of tumors > 350 cc was 4 months and two months, p = .01 and .003, respectively). A total of fifteen patients progressed with the disease and the median time to progression was two months [1–4].

Conclusion: SBRT is safe and provides excellent local control in advanced HCC complicated with PVTT. The out of field failure pattern and time to failure in these patients highlights the need for adjuvant systemic therapy after completion of local treatment. Our data warrant the need for multimodality trials in this patient cohort.

Key words: hepatocellular carcinoma; SBRT; portal vein tumor thrombosis

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and is the second most common cause of cancer-related death [1, 2]. Its poor survival results from pre-existing chronic liver disease (CLD), comorbidities, and reduced rate of resectability [3]. Portal vein tumor thrombosis (PVTT) often complicates the management of HCC and is present in 35% to 50% of cases at the time of diagnosis. There is no universal consensus on how best to treat HCC with PVTT. The West

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considers it as a systemic disease and offers systemic therapy. Sorafenib has been the mainstay of systemic treatment for a long time and has resulted in modest survival benefits but a poor overall response rate and a high toxicity profile [4, 5]. More recently, immunotherapy has been introduced in a big way in the management of HCC [6]. There are many ongoing trials with nivolumab, ipilimumab, and atezolizumab that are addressing the issue of HCC with PVTT [7, 8]. The East, on the other hand, is more permissible of locoregional treatments along with systemic therapy. Recently, surgery has been found to be suitable for Vp1, and Vp2 PVTT, that is, Vp1, presence of a tumor thrombus distal to, but not in, the second-order branches of the portal vein; Vp2, presence of a tumor thrombus in the second-order branches of the portal vein [9]. Transarterial chemoembolization (TACE) or transarterial radio embolization (TARE) are options available for patients who refuse surgery or who are inoperable. Nevertheless, the prognosis of HCC with PVTT remains poor. Observation alone results in a median OS of two months; with sorafenib, it is 4 to 8 months [4, 10–12]. TACE has a better one-year OS when compared to conservative management, as reported in the meta-analysis by Xue et al. [13]. In their analysis, it was found that the pooled estimate for overall survival was significant (HR: 0.44; 95% CI: 0.34–0.57; z, 6.22; p = 0.000). The same was also confirmed in another meta-analysis by Leng et al. [14]. Surgical resection, in a few retrospective series, has shown promising results with median OS ranging between 6 to 30 months [15]. As PVTT is a contraindication for liver transplant, treatment strategies that target the recanalization of PVTT are required. Stereotactic body radiation therapy (SBRT) provides one such option. A Metanalysis by Rim et al. [16] concluded that SBRT is a safe treatment option that has a good response rate in treating HCC with PVTT. Our department conducted a retrospective study of unresectable HCC patients complicated with PVTT who had failed from other locoregional therapies.

Materials and methods

This retrospective review was approved by our internal review board, and informed consent was taken from all the patients who had undergone SBRT.

From May 2018 to January 2020, twenty-nine advanced unresectable HCC patients having failed from prior locoregional and systemic therapy were retrospectively reviewed. Patients with a normal liver volume of more than 700 cc and with Eastern Co-operative Oncology Group (ECOG) performance status of 0–2 were treated with SBRT. SBRT was not offered or deferred in patients who had a total bilirubin level of more than 3 mg/dL, child B8 or higher, ECOG higher than 2, acute viral hepatitis, platelets less than 50,000, AST/ALT levels of more than five times the normal upper limit, PT/INR > 2.2, albumin < 2.8 gm/dL and previous liver-directed radiation. SBRT was delivered four weeks after TACE and seven days after stopping sorafenib.

Patients characteristics is presented in Table 1.

SBRT treatment planning

In our department, all eligible patients undergo respiratory coaching and assessment 4–6 days before CT simulation. Patients who are capable of breath-hold SBRT are treated in normal expiratory breath-hold (NEBH) and the ones who are not competent, are treated with abdomen compression along with our novel protocol of synchronized 4DCT simulation [17]. All Cases were planned using the MONACO treatment planning system from Elekta, Sweden using the volumetric modulated arc therapy (VMAT) technique as it is dosimetrically superior to dynamic conformal arc [18].

NEBH technique

We acquire a CT in NEBH using Anzai Version 6.0, Japan during CT simulation for obtaining and indexing a breath-hold four phase-contrast CT. Intra- and inter-breath-hold liver movements are calculated by taking CT scans at various time points, and the same is incorporated in the internal target volume (ITV). An arterial, late arterial, porto-venous, and delayed phase CT scans are taken at 20, 30, 40 seconds, and 5 minutes, respectively, after administration of the contrast injection. The delayed phase CT is used to delineate all organs at risk (OARs), and perform dose calculation. The gross tumor volume (GTV) or clinical target volume (CTV) is contoured using information from all the four phases of the acquired CT and is then transferred to the delayed phase CT. An ITV is generated by calculating the difference in

Table 1. Patient characteristics

Patient characteristic	N (%) [total patients —29]
Age (median)	56 (25–74)
Sex	
Male	24 (83)
Female	5 (17)
ECOG	
0-1	23 (76)
2	6 (24)
BCLC	
A	0
B	0
C	29 (100)
Child	
A5	15 (51)
A6	13 (44)
B7	1 (4)
PVTT	
Vp2	6 (20)
Vp3	11 (36)
Vp4	12 (41)
CLD cause	
Hepatitis B	12 (41.5)
NASH	4 (14)
Hepatitis C	6 (20.5)
Ethanol	6 (20.5)
No CLD	1 (3.5)
Previous treatment	
TACE and sorafenib	11 (38)
Sorafenib only	9 (31)
Ablation and TACE	9 (31)

ECOG — Eastern Co-operative Oncology Group; BCLC — Barcelona Clinic Liver cancer staging; PVTT — portal vein tumor thrombosis; CLD — chronic liver disease; NASH — non-alcoholic steatohepatitis; TACE — transarterial chemoembolization

the liver position from all the acquired CTs. A department-specific 5 mm planning target volume (PTV) is given on top of the ITV on which the final planning and dose calculation takes place. The dose constraints and other planning parameters used in optimization are provided in the Supplementary File — Table S1. The treatment plan is accepted when 95% of the PTV receives a minimum of 95% of the prescribed dose. The dose prescription varied case by case according to the presence of normal liver in each patient. The dose varied from 35 Gy to 54 Gy in 5 to 6 fractions, refer to the Supplementary File — Table S2 for treatment details. In the treatment room, we place the Anzai version 6.0 pressure belt on the same indexed location with the same pressure parameters, and a breath-hold 3DCBCT is acquired. We use the liver boundaries to match the liver, which acts as a surrogate for the tumor. OARs are also kept in mind during the match process, and if an OAR comes inside the high dose PTV then the patient is repositioned. The treatment beam is gated in breath-hold using the Anzai system.

Synchronized contrast 4DCT

We use our novel protocol to take an arterial enhancing, and a delayed phase 4DCT along with abdomen compression for patients incapable of performing a department desired breath-hold pattern; details of the same are available elsewhere [17]. 4DCT is done after confirming that the movement of the liver is less than 1cm by using fluoroscopy. The target is contoured on all phases of the 4DCT by using information from the arterial and delayed phases, and an ITV is generated. The delayed phase 4DCT is used for contouring OARs and dose calculation. A department-specific 5 mm PTV is generated for planning. In the treatment room, the patient is positioned with Vaclok, abdomen compression belt, and the Anzai pressure belt. A 4DCBCT (cone beam CT) is acquired to confirm the patient's treatment position and liver motion. The Anzai pressure belt is used to monitor the breathing during radiation delivery, and similar respiratory cycle parameters generated during CT simulation are reproduced during treatment delivery. In case a change is detected in the breathing cycle during delivery, the beam is automatically stopped. Figure S1 in the Supplementary File shows a patient set up with an abdomen and chest compression pre-SBRT.

Toxicity assessment and follow-up

Liver function tests were carried out during radiation to monitor any acute treatment-related toxicity. Along with the LFTs, complete blood chemistry and kidney function tests were done at each follow up for toxicity assessment. Toxicity was graded using common toxicity criteria and adverse events version 5.0. The first follow up after SBRT was at one month and after that every two months until death. The response assessment was

carried out at three months using tumor markers [alpha-fetoprotein (AFP) or protein induced by vitamin K absence-(PIVKA)] for a biochemical response (biochemical response was defined as a reduction of tumor markers by 50% or more from the baseline) [19] and PET CT or MRI for a radiological response; response assessment was done using mRECIST criteria version 1.1. A baseline MRI was also done at one-month post-SBRT to understand any RT changes in the liver and to differentiate from tumor progression during the response assessment at three months. Progression within 1 cm of the treated volume was considered as in-field failure. Any new lesions appearing outside the treated volume were considered as out of field failure. Only the index lesion was calculated to estimate local control. Any distant metastases were also considered as an event for progression-free survival.

Statistical analysis

Kaplan-Meier method was used to generate the local control (LC), progression-free survival (PFS), and overall survival (OS). As only the index lesion was evaluated for LC, the competing risk model was not used. The log-rank test was used for group comparisons. Univariate analysis with hazard ratio (HR) and 95% confidence interval (estimated by Cox proportional hazards regression) was used to correlate tumor and patient-related factors to LC, PFS, and OS. Factors that were found to be significant in univariate analysis were applied to the multivariate Cox proportional hazards regression. $p < 0.05$ was considered as statistically significant. The median time to tumor progression, OS and PFS were also calculated. All calculations were done using SPSS version 23.

Results

After evaluating the twenty-nine patients treated between May 2018 and March 2020, it was found that the median largest tumor diameter was 8.6cm, median GTV was 275 cc, the normal liver volume was 1302 cc, Median biological effective dose (BED) to the PTV was 86.4 Gy, the median dose to the normal liver was 13.6 Gy. Detailed results are available in the Supplementary File — Table S2. After doing a cox proportional analysis for all patients and tumor factors, only GTV was significantly associated with a poor outcome. Patients with GTV of more than 350 cc had a poor prognosis. The remaining details of patient and tumor characteristics are available in Table 1 and Table S2. Risk factor assessment and their respective p-values are presented in the Supplementary File — Table S3.

At a median follow up of 6 months (1–20 months), the median overall survival (OS) and progression-free survival (PFS) was 15 months and five months, respectively. The 1-year OS, PFS, and Local control (LC) was 53.4%, 31%, and 96%, respectively (corresponding Kaplan Meir Curves can be found in Figure 1). The overall response rate assessed by Modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria 1.1 at three months was 90%, with complete response seen in 45% and partial response in 45% cases. Biochemical response at three months (which was defined as a more than 50 percent reduction in baseline or normalization of tumor marker levels) was 80% (Supplementary File — Table S5). There were a total of 15 progression events, out of which 14 were out of the field, and one was both infield and distant. Out of the 14 out-of-field events, four were distant only, and six were out-of-field liver-only failures

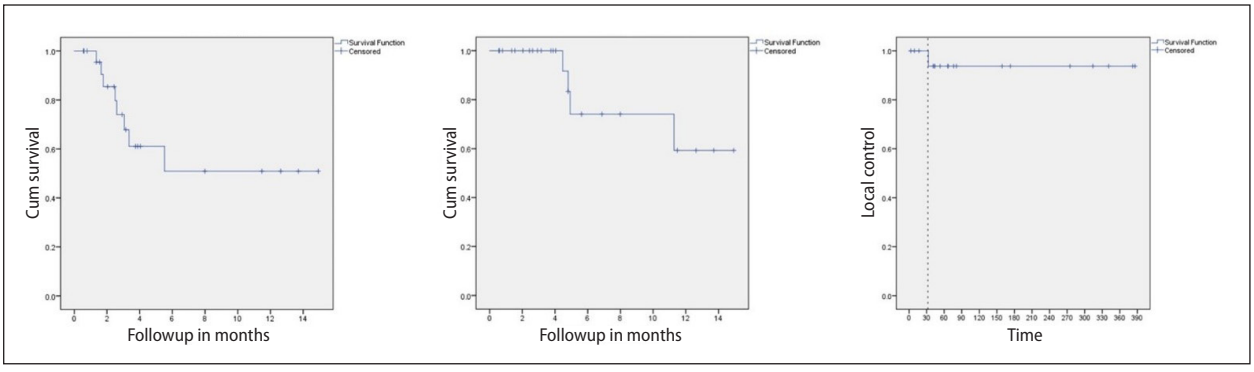

Figure 1. Kaplan-Meier curves, progression-free survival (PFS), overall survival (OS), and local control (LC) at one year

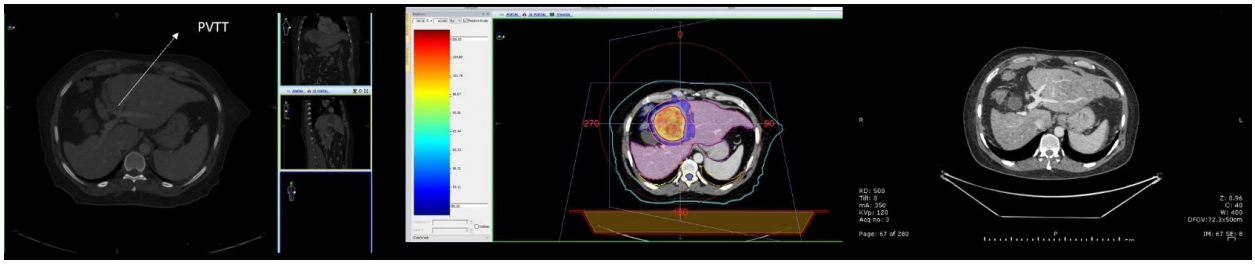

Figure 2. Portal vein recanalization. **A.** The pr-SBRT scan with portal vein tumor thrombosis (PVTT) involving the confluence of the portal veins, the same thrombus was extending into the main portal vein a Vp4 thrombus; **B.** The isodose distribution of a full arc the volumetric modulated arc therapy (VMAT) plan; **C.** Contrast-enhanced computed tomography (CECT) at the same level showing a complete resolution 6 months post stereotactic body radiation therapy (SBRT). This patient underwent a liver transplant and is disease free

(progression within 1 cm of the treated volume was considered as in-field failure, and outside that margin, as out of field). Four events were both distant and out of field. The median time to progression was 2 months (1–6 months), and all progression events occurred within six months, post-SBRT in our patient population.

Complete recanalization of the portal vein occurred in two patients. Both of them underwent a liver transplant and are currently disease-free. Hence, the complete recanalization rate in our patient population was 7%, and a partial response radiological response to the PVTT was seen in twenty-three of the twenty-nine patients (80%). A stable or progressive PVTT was seen in four patients. Figure 2 shows the complete recanalization of the portal vein.

Toxicity

In general, SBRT delivered to this advanced stage patient population was well tolerated. All toxicities were graded via common toxicity criteria version 5.0 (CTC v5.0). The most common toxicity was hematological in the form of lymphocytopenia. Fifty-five percent of cases had grade 1 to 2 lymphocytopenia, and twenty-eight percent cases developed grade 3 lymphocytopenia. Grade I–II nausea vomiting was seen in 53% cases, grade III–V liver enzyme elevation was seen only in 2 cases (7%). Ten patients developed worsening of the Child-Pugh score by more than two at a median follow up of 6 months, but all these patients also had progressive disease. One patient decompensated and developed grade I hepatic encephalopathy during radiation but later recovered with conservative management. None of the cases developed duodenal ulceration radiation pneumonitis or classical radiation-induced liver disease. Further details on toxicity are available in Table 2.

Discussion

In the current study, SBRT to the tumor and the thrombus was generally given to the patients who had exhausted all other locoregional treatment options. Most of them had failed on either TACE or RFA or were unresectable due to advanced macrovascular invasion. Only two out of the twenty-nine patients of HCC with PVTT were treated with upfront SBRT. The median tumor diameter and median GTV volume in our study were 8.6 cm and 275 cc, respectively. This is much higher than previously published studies [19–21] and comparable to a recently published Indian data [22]. Still, we were able to achieve an ORR of 90%, with a respectable CR of 45% at 3 months. This compares favorably to other published data where ORR varying from 25.2%, Huang et al. [23] to 93%, Matsuo et al. [24] have been quoted. In the past poor response to radiotherapy, Barcelona Clinic Liver cancer staging (BCLC) stage, tumor volume more than 350 cc, Child-Pugh status, and radiation dose have been associated as poor prognostic factors, yet in our study, only gross tumor volume of more than 350 cc was associated with poor survival and progression, none of the other risk factors were found to be significant. SBRT achieved an excellent local control of 96% in this patient cohort. The six months and one year PFS was 37% and 31%, respectively, with a median PFS of 5 months. The most common form of progression was out of field, with the liver being the most common site. This reflects the underlying

Table 2. Toxicity (worst grade of toxicity from treatment to 3 months follow-up)

CTC Toxicity and grade	No of patients — 29	%
Nausea and vomiting		
0	12	41
1–2	17	59
3–5	0	
Liver enzymes		
0–2	27	93
3–5	2	7
Bilirubin		
0–2	27	93
3–5	2	7
Anemia		
0	27	93
1–5	2	7
Lymphocytopenia		
0	4	14
1–2	16	55
3–5	9	31
Thrombocytopenia		
0	10	34.5
1–2	19	65.5
3–5	0	
Fatigue		
0–2	11	38
3–5	0	0
Radiation dermatitis		
0–1	10	34.5
2–5	0	0
Abdomen pain		
0–2	6	20
Abdomen distension		
0–2	7	24
Duodenal ulceration	0	0
Radiation pneumonitis	0	0

CTC — common toxicity criteria

chronic inflammation in the liver, which is probably carcinogenic. The most common distant site involved with metastasis was the lung (seven out of the twenty-nine cases).

Interestingly, the median time to progression in patients of HCC with PVTT is quite short, and all progression events took place within six months. Similar results were also noted by Shui et al. [25] where all progression events occurred within six months of SBRT, and the median time to progression was 3 months, though, in that study, SBRT was used as the first treatment. Even Chopra et al. noted that post-SBRT the most common form of progression is an out-of-field failure and quoted a distant relapse rate of 34% among the twenty-five analyzed patients. We experienced a similar distant relapse rate of 27% and a liver relapse of 34%. This pattern of failure post SBRT signifies the efficacy of SBRT in controlling the local disease but also reflects the aggressive nature of HCC with PVTT and the presence of metastatic/micrometastatic disease in cases of PVTT [26]. After assessing the patterns of failure and time to progression, it appears that patients with PVTT might benefit from multimodality treatment where systemic treatment should be started within one month of completion of local treatment. Systemic treatment alone results in a dismal median OS of 4–6 months with an ORR of 3.3% [10] in Asians. Even though close to 50% of the patients progressed within six months of SBRT, the other 50% did not. Because of that, we had a promising six month and one year OS of 83% and 54%, respectively, with a median OS of 15 months. The survival in this study was at the upper end of that reported in the literature (Tab. 4) [21, 22, 24, 25, 27] even when these patients were provided with SBRT as a treatment option at last. As we restarted sorafenib 8–12 weeks after SBRT, we believe this might be the reason for early distant progression in some cases. In the future, we will require trials that start systemic treatment within one month of SBRT or any other locoregional treatment.

We did not experience any case of classical radiation induced liver disease (RILD). We observed an increase in child score by more than two in ten patients, though these cases also had progressive disease. No patient with a non-progressive disease had an increase of CP score at three months. One patient developed hepatic decompensation during SBRT after receiving 40 Gy in 4 fractions. He had developed grade I hepatic encephalopathy. The patient recovered in a week, and further radiation was abandoned. He ended up with a complete response and is still alive. Our patient population received a median tumor dose of 86.4 Gy BED with a mean normal liver dose of 14 Gy resulting in a toxicity profile that compares favorably with the published literature [16]. The most common toxicity observed was lymphocytopenia, with grade 3 toxicity seen

Table 3. Blood changes post stereotactic body radiation therapy (SBRT) (average) in heavily pre-treated cases of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT)

Test	Baseline	During RT	1 month	3 months
Total bilirubin [mg/dL]	1.16	1.22	1.44	1.8
Direct bilirubin [mg/dL]	0.35	0.34	0.52	0.72
ALP [IU/L]	203	200	178	247
ALT [IU/L]	52.3	52.2	53.7	60
AST [IU/L]	81	67	65	68
Albumin [g/dL]	3.4	3.35	3.3	3.1
Protein [g/dL]	7.4	7.2	7.2	7.3
ALC [thou/cc]	1.3	0.66	1	1.1
ANC [thou/cc]	3.9	5.5	4.4	3.9
AFP [ng/mL]	8159	10104	2462	2017
PIVKA [mAU/mL]	30979	9433	4236	4161

ALP — alkaline phosphatase; ALT — alanine aminotransferase; AST — aspartate aminotransferase; ALC — absolute lymphocyte count; ANC — absolute neutrophil count; AFP — alpha-fetoprotein; PIVKA — protein induced by vitamin K absence; RT — radiotherapy

Table 4. A summary of a few studies on hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) treated with stereotactic body radiation therapy (SBRT)

First author, year	Patients	Median tumor size	% of PVT patients	RT dose (EQD2) [Gy]	Overall survival rate (%)		Median survival (months)	Response criteria	Response rate			
					1 year	2 years			CR	PR	OR	LC
Matsuo, 2013	27	1.5	37	62.5	56	11	N/A	WHO	67	71	93	N/A
Matsuo et al. 2015 [24]	16	5.5	44	50.4	38	19	N/A	WHO	62	62	81	N/A
Kang et al. 2014 [21]	34	4.5	32	60	58	29.4	17	WHO	20.5	52.9	73.4	85.2
Jang et al. 2016 [20]	37	6	39	60	54	27	15	WHO	16	54	70	86
Xi et al. 2013 [19]	41	Thrombus	100	48	50	13	N/A	mRECIST	39	75	92	N/A
Lo et al. 2017 [5]	23	3.4	54	71.2	18.7	N/A	N/A	mRECIST	N/A	N/A	N/A	N/A
Chopra et al. 2019 [22]	21	9.8	42	47	51	15	11	RECIST	N/A	N/A	N/A	90
Liu et al. [31][7]	96	3.8	21	71	71 (BCLC B and C)		23	mRECIST	N/A	N/A	N/A	94
Present study	29	8.6	100	70	54	N/A	15	mRecist	35	52	87	95

PVT — portal vein tumor thrombosis; RT — radiotherapy; EQD2 — equivalent dose in 2Gy fractions; CR — complete response; PR — partial response; OR — overall response; LC — local control; WHO — World Health Organization; RECIST — Response Evaluation Criteria in Solid Tumors; mRECIST — Modified Response Evaluation Criteria in Solid Tumors; NA — non available

in 26% of the patients. We hypothesize that high dose per fraction radiation results in direct cell kill of lymphocytes in the highly vascular liver, and there is inadvertent splenic radiation, which might kill the resting splenic lymphocytes in the enlarged spleens of CLD patients. Various studies on pancreatic radiation [28] and liver SBRT [29, 30] have reported the same. A summary of a few studies on HCC with PVTT treated with SBRT is seen in the discussion (Tab. 4) [19–22, 24, 31].

This review carries the general limitations of a retrospective study. Different treatments were given to the patient before SBRT, and this may result in a varied patient population. Two patients ended up having a liver transplant as the portal vein completely recanalized, and this could represent a source of bias for the presented data. A well designed prospective study is warranted to validate the results.

Nevertheless, this study provides a detailed account of the treatment of HCC with PVTT using SBRT by a linear accelerator. It also describes the nature of progression, survival, and toxicity profile in advanced cases of HCC having large tumors and failing from conventional forms of treatment.

Conclusion

SBRT in advanced cases of HCC with PVTT results in excellent local control, survival, and toxicity profile. The short median time to progression and out-of-field failures point towards a systemic disease and warrant early adjuvant systemic treatment. Further multimodality trials that incorporate systemic treatment with SBRT or other locoregional therapies are necessary.

Conflict of interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article. There is no conflict of interest.

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