Unresectable Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: Sorafenib versus Radiotherapy

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Abstract:

Background: Hepatocellular carcinoma (HCC) patients associated with portal vein tumor thrombosis (PVTT) have less therapeutic options and carry a worse prognosis. Surgical and local treatments are contemplated only in a select few. Renewed interest has been established in radiotherapy (RTH) as a treatment modality in HCC but a direct comparison to systemic agents is lacking.

Methods: A retrospective comparative review of patients with unresectable HCC having PVTT that received sorafenib or RT. Overall survival and toxicity were compared between the two groups and analyses were performed.

Results: From 2018 - 2021 60 HCC with PVTT patients were equally divided between the two treatment arms. The two groups were well balanced with 90% being HCV positive, however a significant difference was observed for ECOG PS of 1 vs. 0 in the RTH and sorafenib arms respectively (80% vs. 50%; p=0.015). Likewise a significance in PVTT response was found in the RTH group vs. the systemic one (p=0.012). Median survival did not differ significantly between the sorafenib group (8 months) and the RT group (10 months; P = 0.258) and adverse events were equally encountered. A highly significant relation (p value <0.001) for AFP reduction and being a responder (achieving CR and PR) to either therapy in the tumor or thrombus was observed. The RTH group displayed significance relevant to the size (p = 0.029) and location (p value <0.001) of the thrombus; whilst the sorafenib group HBV negative cases fared better (p = 0.040).

Conclusions: RTH for unresectable HCC with PVTT is comparable to sorafenib. It provides a therapeutic option deserving further incorporation into the multidisciplinary care of these cases.

Keywords: Hepatocellular carcinoma, Portal venous tumor thrombosis, Radiotherapy (VMAT), Sorafenib

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Introduction:

The global burden of hepatic cancer continues to rise and is estimated to reach one million cases per annum by 2025. [1] HCC generally heralds a poor prognosis due to its late presentation, associated chronic liver disease and frequent recurrence after primary therapy. Moreover, in the setting of cirrhosis PVTT is a common finding and untreated portends a poor prognosis with a median survival shy of 3 months.[2] Though many agents have entered the scene, sorafenib remains in the first line armamentarium for treatment for over a decade in advanced HCC with a modest 2.8

month improvement in median overall survival (mOS).[3] Moreover sorafenib is widely available in most countries comparative to the newer drugs that are more resource challenging.[4]

Radiation-induced liver disease (RILD) was the major limiting factor to radiotherapy usage in hepatic tumors, fortunately advances in image guidance, acquisition and execution have rendered this a restriction of the past.[5] In fact, external beam radiation therapy (EBRT) and more hypofractionated stereotactic approaches are rapidly being adopted whenever permissible in many institutions adding to the multidisciplinary management of these tumors that require an intricate network of specialties to manage.[6]

In the PVTT setting established locoregional therapies comprising surgery, transarterial chemoembolization (TACE), transarterial radioembolization, are feasible in a select few though at a higher risk of complications notably hepatic ischemia. Conventionally fractionated radiotherapy (CFRT) in PVTT has demonstrated better outcomes in response and one year overall survival (OS) reaching 40.2% in some studies.[7–11]

Therefore this study aimed to present a comparison between IMRT and systemic therapy in the form of sorafenib in terms of clinical outcomes in HCC associated with PVTT.

Patients and Methods:

A retrospective collection of HCC cases having PVTT was performed at a private radiation facility and university hospital. The diagnosis of HCC was reached either pathologically or radiologically according to the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases(AASLD) guidelines.[12,13] Patients with HCC Child-Pugh classification A or B7 having an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and no extra-hepatic disease were selected. The main HCC had to be adjacent to the PVTT with no or minimal tumor in the remaining liver to meet eligibility. Contrast-enhanced computed tomography (CT) diagnosed PVTT by as intraluminal filling defect lesion for included cases. Multidisciplinary board reviews were noted for all participants to hold a final decision of being unresectable. Adequate laboratory cut offs were required. Ethical approval was granted from the corresponding local institutional facilities.

Radiation therapy group

A Volumetric modulated arc therapy (VMAT) - technique allowed the precise delivery with CT planning fusion with PET and MRI to define radiation fields target volume. In addition to the main HCC, the hepatic vascular invasion was irradiated along with it, if it was directly involved and this comprised the gross tumor volume (GTV). Other multiple nodules were not always included in the GTV (prerequisite to be absent or minimal). The clinical target volume (CTV) was a 0.5-cm margin expansion of the GTV whilst the planning target volume (PTV) was a further 1 to 1.5cm added margin to the CTV in anterior–posterior and cranio-caudal margins respectively.

Rapid ARC was planned according to preliminary guidelines to ensure that the normal liver volume was irradiated along with the tumor and dose constraints were followed as per table 1. A dose of 1.8 Gy per fraction was administered with 6- or 10-MV linear accelerator using up to four-ARCs arrangement with five fractions per week to a dose of 45 Gy. Patients were assessed weekly during the RT period using cone beam CT (CBCT) for position evaluation with relevance to PTV uncertainties for onboard *correction.*

Sorafenib group

The standard dose of sorafenib, 400 mg twice daily (800 mg/day) was initiated for this cohort. In case of an AE ≥2 reduction or interruption were pursued and therapy resumed upon recovery to at least a grade 1 AE. Reductions were one dose level (400mg/day) or two (400mg/day every other day). Treatment continued till progression or unacceptable toxicity.

Overall survival (OS) was the primary aim and AEs the secondary aim with a comparison between the two study groups. OS rates of patients who underwent radiotherapy or sorafenib were calculated from the date of diagnosis of macroscopic hepatic vascular invasion. Treatment response was according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria[15]. AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), v.5.0.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences, version 20.0 IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) and a P value of less than 0.05 was considered statistically significant. Pearson Chi-square ($\chi 2$) test or Fisher's exact test were used to analyze categorical variables. Survival rates were estimated using the Kaplan-Meier method. Log rank test was used to compare survival rates between study groups.

Table 1: Dose constraints of organs at risk (OARs)

Organ at risk	Whole – organ tissue tolerance	Range of maximum	Partial volume dose limits (% volume at dose in Gy)
Liver	30 Gy	30-35 Gy	33% V35
Kidneys	23Gy	20-22GY	10% V18-50% V20
Stomach	50Gy	45-54Gy	2% V50 - 10 % V45
Spinal Cord	47Gy	45-50Gy	10% V45
Small Intestine (duodenum)	40Gy	30-54 Gy (60Gy)	10 % V45-25% V55 (33 % V45)

Reference: [14]

Results:

From June 2018 to April 2021 60 HCC with PVTT patients were equally divided between the two treatment arms. Patient characteristics are shown in Table 2. The median age of the included patients was 55 years (range: 43 – 68 years; interquartile range: 52 – 58 years). Initial patient characteristics were comparable, however a significant difference was observed for ECOG PS of 1 vs. 0 in the radiotherapy and sorafenib arms respectively (80% vs. 50%; p=0.015). Similarly a significance in PVTT response was found in the radiation group vs. the systemic one (p=0.012).

Radiation techniques were mostly VMAT (70 %). The median GTV volume was 21.8 cc (range 9.9 cc - 54.2 cc) for the 30 patients. The mean biological equivalent dose (BED) as α/β ratio of 10 was 50 Gy. The mean of mean liver dose kept less than 30Gy for the rest of the uninvolved remaining liver. Figures 1 and 2 demonstrate radiotherapy distribution in a case with its corresponding dose volume histogram (DVH).

The median follow-up time was 9.5 (IQR 7-13) months. At least 3 months of systemic therapy were administered with a median time on sorafenib of 7 months. The number of patients alive by the study closure were 22(36.7%), with the median survival of 10 months (95% CI 8.448-11.552) and 8 months (95% CI 8.448-11.552) in the RTH and sorafenib groups respectively and this was not significant(p= 0.258).(Fig 3)

Analysis of the two groups (see table 3) found a highly significant relation (p value <0.001) for AFP reduction and being a responder (achieving CR and PR) to either therapy in the tumor or thrombus. The RTH group displayed significance relevant to the size (p = 0.029) and location (p value <0.001) of the thrombus; whilst the sorafenib group HBV negative cases fared better (p = 0.040).

Adverse events are shown in table 4. No treatment-related grade 5 toxicity was reported. Only 2 patients developed a grade 3 hepatic toxicity, namely hyperbilirubinemia in either group and resolved with conservative management. For the RTH cohort the majority of gastrointestinal side effects occurred during treatment.

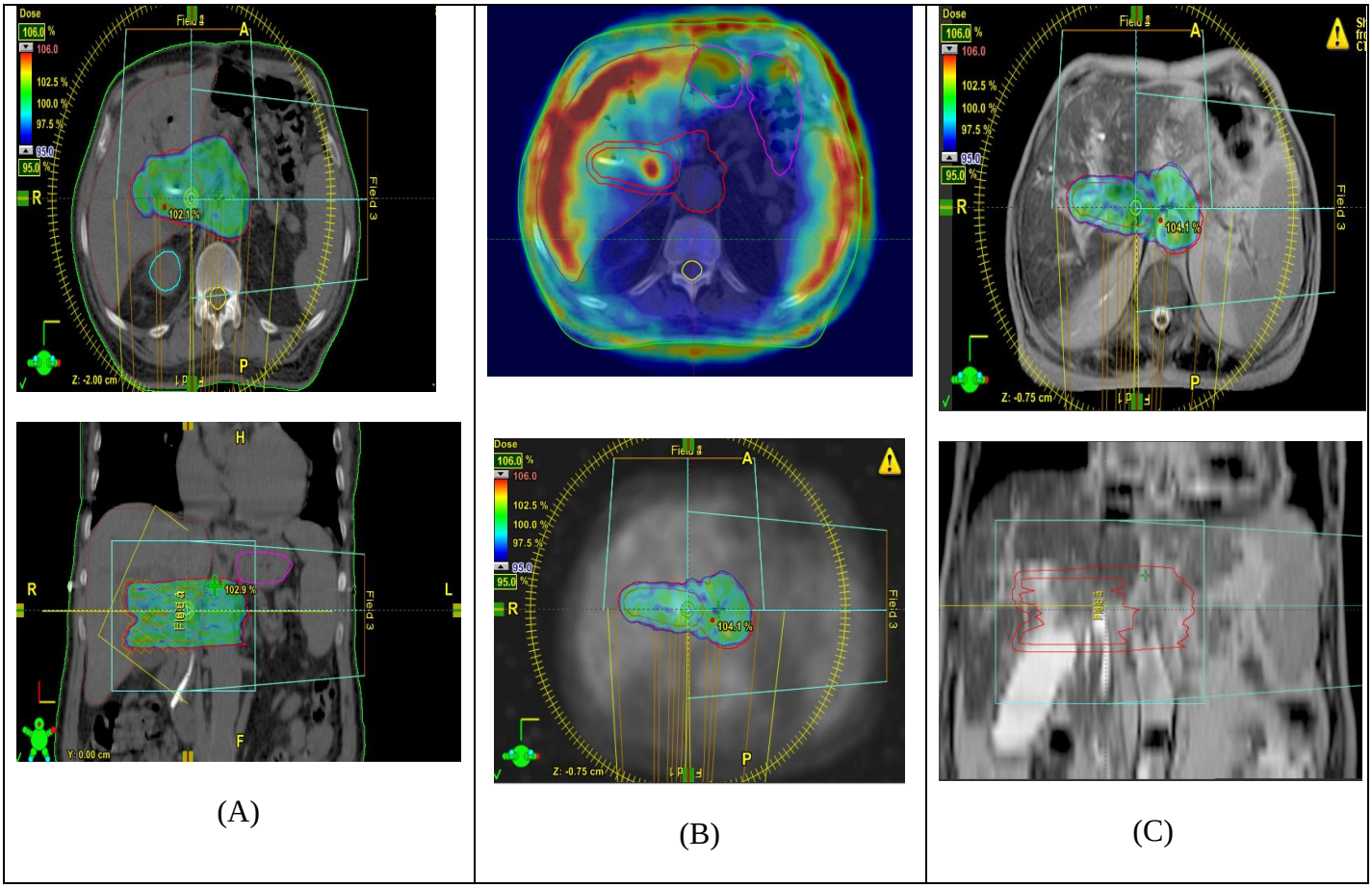
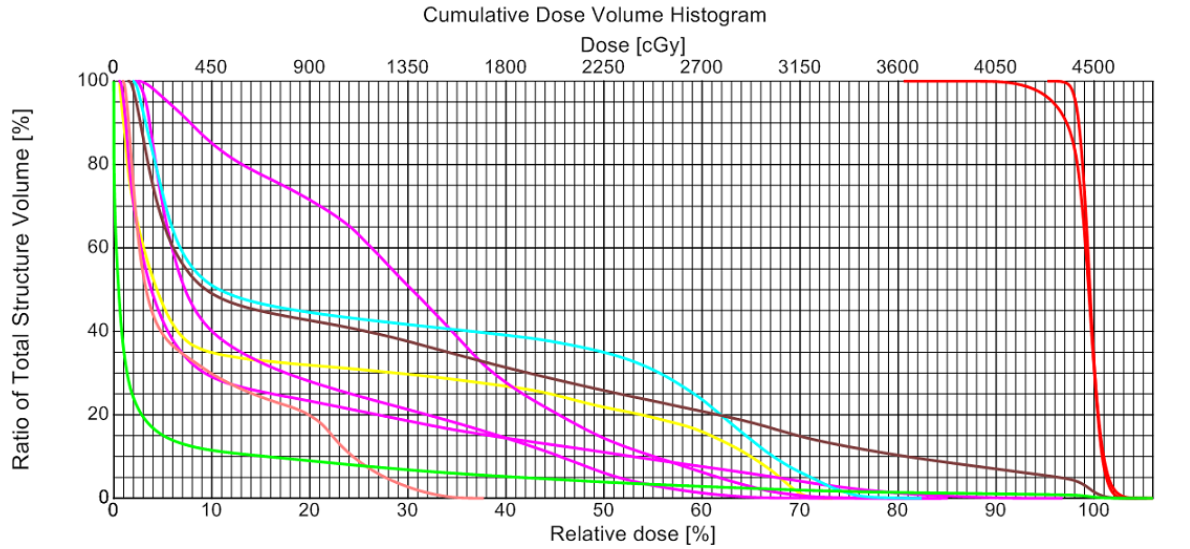


Figure 1. Radiation dose distribution according to radiotherapy technique. More conformal dose delivery to the main mass and tumor thrombosis with a reduced liver dose is achievable with VMAT technique, display distribution for CT for planning and calculation (A) PET image fusion (B) and MRI image fusion (C)



Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
Spinal Cord	Approved	100.0 / 99.9	45.0 cm³	0.6 %	73.3 %	20.0 %	1.1 %	4.4 %	25.4 %
Small intesttine	Approved	100.0 / 100.0	421.1 cm³	2.4 %	84.4 %	30.8 %	36.0 %	30.4 %	16.9 %
avoidance	Approved	100.0 / 100.0	6838.8 cm³	0.5 %	96.8 %	14.6 %	1.4 %	3.8 %	21.5 %
stomach	Approved	100.0 / 100.0	230.2 cm³	2.1 %	85.1 %	16.2 %	3.7 %	7.3 %	16.5 %
PTV	Approved	100.0 / 100.0	336.3 cm³	80.6 %	106.0 %	99.2 %	99.5 %	99.4 %	1.8 %
BODY	Approved	100.0 / 100.0	39001.5 cm³	0.0 %	106.0 %	5.8 %	0.0 %	0.5 %	16.1 %
CTV	Approved	100.0 / 100.0	101.7 cm³	95.2 %	104.4 %	99.6 %	99.6 %	99.6 %	1.0 %
Rt Kidney	Approved	100.0 / 100.0	138.5 cm³	1.9 %	82.4 %	29.0 %	2.9 %	10.8 %	27.2 %
Lt Kidney	Approved	100.0 / 100.0	134.6 cm³	0.9 %	37.8 %	8.6 %	1.8 %	3.3 %	9.3 %
Liver	Approved	100.0 / 100.0	1828.0 cm³	1.4 %	105.4 %	28.8 %	2.8 %	9.4 %	31.4 %

Figure 2. The DVH for PTV coverage and OAR dose

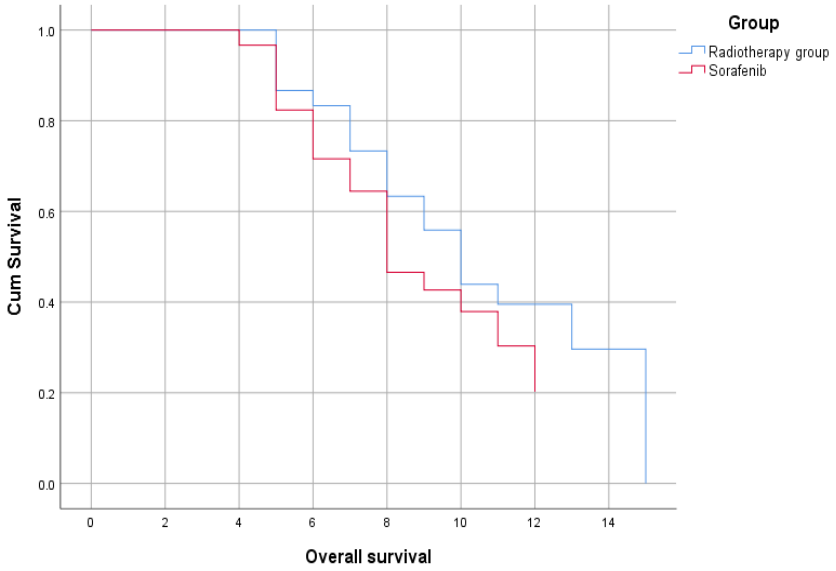


Figure 3 Kaplan-Meier curves for OS of the RT (blue line) and sorafenib (red line) groups.

Table 2: Comparison between both groups as regard clinical and treatment characteristics

		Group		
		Radiotherapy group N (%)	Sorafenib group N (%)	P value
Age group	<55 Year	11 (36.7%)	17 (56.7%)	0.121
	≥ 55 Year	19 (63.3%)	13 (43.3%)	
Gender	Male	26 (86.7%)	21 (70%)	0.117
	Female	4 (13.3%)	9 (30%)	
Child-Pugh score	Child-A	24 (80%)	24 (80%)	1.0
	Child-B	6 (20%)	6 (20%)	
Total bilirubin	<2	24 (80%)	25 (83.3%)	1.0**
(mg/dL)	2-3	5 (16.7%)	5 (16.7%)	
	>3	1 (3.3%)	0 (0%)	
Serum albumin	>3.5	21 (70%)	22 (73.3%)	1.0**
(g/dL)	2.8-3.5	8 (26.7%)	8 (26.7%)	
	<2.8	1 (3.3%)	0 (0%)	
INR	<1.7	28 (93.3%)	28 (93.3%)	1.0**
	1.7-2.3	2 (6.7%)	2 (6.7%)	
	>2.3	0 (0%)	0 (0%)	
ECOG Performance status (PS)	0	6 (20%)	15 (50%)	0.015*
	1	24 (80%)	15 (50%)	
HCV	Negative	4 (13.3%)	2 (6.7%)	0.671**
	Positive	26 (86.7%)	28 (93.3%)	
HBV	Negative	28 (93.3%)	29 (96.7%)	1.0**
	Positive	2 (6.7%)	1 (3.3%)	
Antiviral therapy	None	11 (36.7%)	16 (53.3%)	0.460**
	Sofosbuvir	17 (56.7%)	13 (43.3%)	
	Other	2 (6.7%)	1 (3.3%)	
Tumor size(cm)	<2	3 (10%)	0 (0%)	0.307**
	2-5	9 (30%)	10 (33.3%)	
	>5	18 (60%)	20 (66.7%)	
AFP(ng/mL, pre-therapy)	<400	16 (53.3%)	15 (50%)	0.796
	≥400	14 (46.7%)	15 (50%)	
Thrombus size(cm)	<2cm	7 (23.3%)	4 (13.3%)	0.317
	≥2cm	23 (76.7%)	26 (86.7%)	
Thrombus location	Main portal vein	13 (43.3%)	18 (60%)	.290*
	First branch portal vein	10 (33.3%)	5 (16.7%)	
	Bilateral	7 (23.3%)	7 (23.3%)	
AFP reduction	Yes	18 (60%)	14 (46.7%)	0.301*
	No	12 (40%)	16 (53.3%)	
Tumor response	CR	7 (23.3%)	2 (6.7%)	0.285*
	PR	9 (30%)	9 (30%)	
	SD	11 (36.7%)	16 (53.3%)	
	PD	3 (10%)	3 (10%)	
PVTT response	CR	11 (36.7%)	1 (3.3%)	0.012**
	PR	6 (20%)	10 (33.3%)	
	SD	10 (33.3%)	14 (46.7%)	
	PD	3 (10%)	5 (16.7%)	
Previous treatment lines	None	16 (53.3%)	9 (30%)	0.08**
	Surgery	5 (16.7%)	4 (13.3%)	
	RFA	8 (26.7%)	10 (33.3%)	
	TACE	1 (3.3%)	7 (23.3%)	

*Chi square test

**Fisher exact test

HCV: Hepatitis C virus, HBV: Hepatitis B virus, AFP: Alpha-Fetoprotein, PVTT: portal vein tumor thrombosis, RFA: Radiofrequency ablation, TACE: Transarterial chemoembolization.

Table 3: Relation of OS with clinical and treatment characteristics between both groups

		Radiotherapy group mOS (CI)	P	Sorafenib group mOS (CI)	P
Age group	<55 years	10 (7.655-12.345)	0.673	9(6.848-11.152)	0.681
	≥ 55 years	10 (6.619-13.381)		8(5.915-10.085)	
Gender	Male	10 (7.752-12.248)	0.697	8 (7.156-.844)	0.813
	Female	10 (2.515-17.485)		9 (1.679-16.321)	
Child-Pugh score	Child-A	10 (8.649-11.351)	0.956	8(6.461- 9.539)	0.438
	Child-B	6 (-)		6(3.913 8.087)	
Total bilirubin	<2	10(7.922-12.078)	0.937	8 (6.068 9.932)	0.412
	2-3	10(5.706-14.294)		6 (4.341 7.659)	
	>3	10 (-)		8(6.303- 9.697)	
Serum albumin	>3.5	10(8.599-11.401)	0.104	8(6.532- 9.468)	0.267
	2.8-3.5	11(0-22.562)		6(3.474- 8.526)	
	<2.8	6(-)		8(6.303- 9.697)	
INR	<1.7	10 (8.512-11.488)	0.994	8(7.015-8.985)	0.980
	1.7-2.3	5 (-)		10(-)	
ECOG Performance status (PS)	0	8 (-)	0.743	7(5.185- 8.815)	0.646
	1	10 (8.649-11.351)		10(6.596-13.404)	
HCV	Negative	10 (5.756-14.244)	0.725	5(-)	0.490
	Positive	10 (6.837-13.163)		9(6.975-11.025)	
HBV	Negative	10 (7.720-12.280)	0.589	8(6.331- 9.669)	0.040
	Positive	10 (-)		5(-)	
Received Antiviral therapy	No	11(8.226-13.774)	0.527	9(-)	0.290
	Yes	9(6.698-11.302)		8(6.858-9.142)	
Tumor size(cm)	<2	-	0.058	10(5.445-14.555)	0.315
	2-5	13 (8.973-17.027)		8(6.990-9.010)	
	>5	8 (5.441-10.559)		8(6.303-9.697)	
AFP (pre-therapy)	<400	10 (7.593-12.407)	0.586	9(-)	0.447
	≥400	9 (6.111-11.889)		8(6.760-9.240)	
Thrombus size (cm)	<2cm	NR	0.029	NR	0.060
	≥2cm	9 (7.480-10.520)		8(7.055-8.945)	
Thrombus location	Main portal vein	NR	<0.001	10(7.469-12.531)	0.130
	First branch portal vein	10 (8.554-11.446)		8(5.853- 10.147)	
	Bilateral	6 (3.434-8.566)		7(4.853-9.147)	
AFP reduction	Yes	13 (8.772-17.228)	<0.001	12(10.089-13.911)	<0.001
	No	7 (5.884-8.116)		6(4.799- 7.201)	
Tumor response	CR/PR	15	<0.001	NR	<0.001
	SD	8(6.749-9.251)		7(5.055-8.945)	
	PD	5		5	
PVTT response	CR/PR	15	<0.001	NR	<0.001
	SD	7(5.450-8.550)		7(5.778-8.222)	
	PD	5		5	
Previous treatment lines	None	10 (6.985-13.015)	0.809	8 (5.316-10.684)	0.571
	Surgery	9 (2.559-15.441)		6 (4.040-7.960)	
	RFA	9 (5.119-12.881)		11 (7.058-14.942)	
	TACE	11 (-)		8 (6.717 9.283)	

CI= 95% confidence interval; NR= not reached

Table 4: Comparison between both groups as regard side effects

		Group		P
		Radiotherapy group N (%)	Sorafenib N (%)	
Nausea & vomiting	None	5 (16.7%)	4 (13.3%)	0.718**
	Grade I	22 (73.3%)	20 (66.7%)	
	Grade II	3 (10%)	6 (20%)	
Elevated Liver enzymes	None	18 (60%)	15 (50%)	0.770**
	Grade I	8 (26.7%)	11 (36.7%)	
	Grade II	4 (13.3%)	4 (13.3%)	
Anemia	None	24 (80%)	26 (86.7%)	0.488*
	Grade I	6 (20%)	4 (13.3%)	
Hyperbilirubinaemia	None	23 (76.7%)	16 (53.3%)	0.169**
	Grade I	5 (16.7%)	12 (40%)	
	Grade II	1 (3.3%)	1 (3.3%)	
	Grade III-IV	1 (3.3%)	1 (3.3%)	
Leukopenia	None	18 (60%)	18 (60%)	0.661**
	Grade I	9 (30%)	11 (36.7%)	
	Grade II	3 (10%)	1 (3.3%)	
Thrombocytopenia	None	18 (60%)	12 (40%)	0.381**
	Grade I	10 (33.3%)	14 (46.7%)	
	Grade II	2 (6.7%)	4 (13.3%)	

*Chi square test
** Fisher exact test

Discussion:

Equipoise in outcome was the final conclusion reached in this retrospective analysis of IMRT vs. systemic therapy in unresectable HCC associated with PVTT. An established ominous sign, the association of PVTT to HCC requires structured multi-targeted approach. For example, systemic therapy alone or with TACE was explored by two studies whilst one showed an advantage in terms of time to progression (TTP) but not OS [16] whist the second one demonstrated a favorable survival.[17]

When incorporating RTH into the therapeutic equation Chu et al(18) found in a retrospective study of patients with advanced HCC with PVTT no significant difference in PFS and OS in those treated with TACE plus RT and TACE plus sorafenib.

Contrastingly a randomized controlled trial of 90 treatment-naive patients with non-metastatic HCC exhibiting macroscopic vascular invasion conducted at an academic tertiary care center were randomly allocated to receive sorafenib or TACE plus RT (within 3 weeks after the first TACE, maximum 45 Gy with the fraction size of 2.5 to 3 Gy). Significantly higher 12-week PFS and longer median OS were achieved with combined directed therapy compared to the sorafenib arm.[19]

All these previous trials displayed different outcomes, though not similar to the present study, making a comparison difficult. Having a different ethnic background, with all that may encompass genetically and culturally with its relation to the endemic diseases, the study population here displayed a strikingly high prevalence of HCV (90%) compared to HBV (5%) infection whereas other mainly Asian experience reported HBV to have the upper hand ranging from 76% [17], 84% [20] and 84.4% [19] whilst HCV as small as 1.1% representation [19], 15% [17] and 61%.[21] This distinct higher appreciation of HCV prevalence is recognized nationally compared to the regional vicinity as the African Network for Gastrointestinal and Liver Diseases consortium conducted an observational study comprising 2566 patients highlighting this characteristic.[22]

Furthermore, a subgroup analysis of the SHARP trial [23] reported a HR of 0.76 for OS in HBV-positive cases (95%CI: 0.38-1.50, P = insignificant) and 0.50 (95%CI: 0.32-0.77) in HCV-positive cases. The phase III randomized Asia Pacific trial [24] was comparable for HBV-positive HCC patients, with an OS HR of 0.74 (95%CI: 0.51-1.06, not significant) versus 0.57 (95%CI: 0.29-1.33) for HCC patients of other etiologies. In fact a combined analysis of the SHARP/Asia Pacific trial [25] demonstrated an absent HCV signal to be a potential prognostic factor for worse OS (HR = 0.7, P = 0.02). They did conclude in this meta-analysis that methodological issues and sample size must be considered foremost thus the available evidence renders a significant clinical benefit in patients

who are HBV-positive with sorafenib, yet this benefit may be even more in patients who are HCV-positive. These two viral etiologies may differ in systemic therapy response but it is not known if any have pursued to further examine this difference in the RTH setting.

The current patient population considerably received previous liver directed therapies (46.7% and 70% in each group) and surgery whilst most studies recruited treatment naïve patients having a Child-Pugh A score only [19,20]. Additionally, a single approach was utilized to therapy whereas upfront combined treatments were offered to the other participants in the aforementioned trials.[19,20]

This last point raises a valid conundrum often facing treating oncologists whether to follow the sequential approach and offer all options in an orderly manner or possibly combine all weapons upfront? Of course this is easier said than done knowing the restriction imposed by an already ailing cirrhotic liver paired by the constraints imposed by each modality, in the case of RTH the organs at risk (OAR) in the gastrointestinal area. This concurrent approach has limited data a prudent approach is advised to circumvent unwarranted toxicity.[26]

Yet the available data exploring this approach have combined liver directed therapies such as TACE/RTH [19,27] found it to be a positive choice and some have gone even further to endorse a new sub-classification of the Barcelona Clinic Liver Cancer stage C with MVI as a first-line treatment option based on these results.[28] Eagerly awaited data from randomized controlled trials (eg, Radiation Therapy Oncology Group 1112 [NCT01730937]) will definitely clarify if combining systemic therapy to stereotactic RTH is beneficial and further shed light on the adverse events encountered therefore aiding patient selection.

Reporting of radiation-induced liver disease (RILD) may be confusing as various toxicity definitions exist, are affected by EBRT regimens used, the baseline liver function, and previous therapies. Despite SBRT taking the center stage with dose escalated ultra- or moderately hypofractionated regimens yet the ASTRO task force recently based a consensus that current evidence supports conformal techniques (either IMRT or proton therapy) according to location of the tumor, technique, baseline liver function and available technology.[6]

Moreover the ASTRO Clinical Practice Guideline [6] recommended a dose range from 5040 cGy/28 fx to 7700 cGy/35 fx when implementing standard fractionation based on retrospective analyses.[29,30] Patients in the current review received 4500cGy, this may seem a substandard dose in light of this new guidance but it has been executed by others (19), and sometimes with variable ranges that encompass a median dose of 39Gy [28] and 48.7Gy. [31]

The dose received in the current study may serve as an explanation for the equality in outcome between both arms as a higher dose intuitively should translate to better response and survival. This dose was felt to be adequate as many of the current patient population were pretreated, some were CP B7 (20%) plus they differed from other studies in being a predominantly HCV driven malignancy. Kim et al. [28] supported adequacy of dosage given here by reporting a radiation dose ≤40 Gy as a significant predictor for poor overall survival. Contrastingly, two other studies found 45Gy to be the pivotal mark above which a positive survival was appreciated.[31,32]

The current study of HCV–related HCC, to the best of our knowledge, may be the first report of RTH administration in this poor prognostic subset of PVTT patients in comparison to the accepted systemic standard, as previous accounts have highlighted this in HBV subjects.[31] Therefore, it is worthy of recognition as it deepens our understanding of the different disease processes involved in carcinogenesis whilst opening new channels to explore local therapies and even molecular mechanisms further.

Not without limitations the retrospective nature of the study poses as a bias for data collection surely in addition to the small sample size studied. Some may consider the dosage inadequate though a precisely clear dose may not exist for every case as one is always governed by the target coverage with respect to OAR tolerance dose constraints and the hepatic reserve. VMAT with conventional fractionation compared to the newer SBRT/ hypofractionated and ultra-hypofractionated schedules may seem somewhat old, may be considered a disadvantage in the sense of not using the ”latest” in the technological field however using what we know how to implement best and availability are also basic requirements in most radiation facilities. Also this account comes from a region known to be plagued by HCC describes a unique population, mainly HCV driven, opening a new therapy for these cases that with better refinement in dose, technique or combination therapy upfront may substantially improve the prospects of survival for this dismal prognostic condition.

Conclusion:

This study demonstrated that RTH vs. sorafenib treatment provided a comparable survival benefit in unresectable liver-confined HCC with PVTT in a mainly HCV population with acceptable toxicity profile. These results provide an alternative non-invasive therapeutic option when other locoregional therapies are contraindicated and encourage further pursuance in enhancing RTH techniques, dose and adding systemic agents to improve outcomes in future trials.

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