

RESEARCH ARTICLE

Portal Vein Thrombosis in Unresectable Hcc Cases: a Single Center Study of Prognostic Factors and Management in 140 Patients

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Abstract

Objective: Hepatocellular carcinoma with portal vein thrombosis is considered a relative contraindication for transarterial chemoembolization (TACE). The aim of our study was to evaluate the prognostic factors and management in patients with hepatocellular carcinoma with portal vein thrombosis (PVT). **Methods:** Between February 2011 and February 2015, 140 patients presented to our specialized multidisciplinary HCC clinic. All were assessed by imaging at regular intervals for tumor response and the data compared with baseline laboratory and imaging characteristics obtained before treatment. **Results:** At the end of the follow up in February 2015, 78 (55.7%) of the 140 patients had died, 33.1% in the 1st year and 20.7% in the 2nd year. The overall median survival was 10 months from the date of diagnosis. Clinical progression was noted in 45 (32.1%). Univariate analysis revealed that, the Child-Pugh score, the performance states (Eastern Cooperative Oncology Group "ECOG" 0-1) and the presence of ascites exerted non-significant affects on survival. Similarly, the serum albumen level and AFP >400 ng/ml were without influence. However, patients with =>2 tumors, abdominal lymphadenopathy and serum bilirubin >2mg/dl had a significantly worse prognosis. Specific treatment significantly increased survival compared to patients left untreated (P value = 0.027). **Conclusion:** Application of specific treatments (curative or palliative) significantly increased survival in HCC patients with PVT. TACE can be considered as a promising procedure for unresectable PVT-associated HCCs. The main predictors of survival in our study were the serum bilirubin level and specific treatment application.

Keywords: Hepatocellular carcinoma- portal vein thrombosis- TACE- HCC prognosis

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Introduction

Hepatocellular carcinoma (HCC) is the commonest primary hepatic malignant tumor, the fifth common cancer in men and the seventh in women. It is the third common cause of deaths related to cancer all over the world (Wang et al., 2015). The survival of HCC patients depends on several prognostic factors that are either patient related such as the CHILD score, the liver function and the general performance status of the patient or tumor related as the tumor site, size and multiplicity (Esmat et al., 2013). Liver cirrhosis has been reported in many studies as the most predominant pathological lesion behind the development and progression of HCC.

Due to the hyper vascularity of HCC, it can show rapid progression, direct invasion of the surrounding tissues and vessels or spontaneous rupture (Zhang et al., 2015). Portal Vein Thrombosis (PVT) is present in up to

40% of HCC patients at the time of diagnosis, which is an adverse prognostic factor. Management of HCC associated with PVT is complex and needs an understanding of the different treatment options (Quirk et al., 2015).

Various treatment options are available to treat unresectable HCC. According to the AASLD guidelines, advanced HCC with PVT can only be treated with Sorafenib-targeted therapy. Trans-catheter intra-arterial therapies allow for selective delivery of the chemotherapeutic agent to hepatic tumors and protect against ischemic necrosis of the rest of the liver. Recent data revealed that highly selective approach may be safe in patients with portal vein thrombosis. Also a more recent study comparing the efficacy of combined TACE and Sorafenib in patients with advanced-stage HCC (Barcelona Clinic Liver Cancer (BCLC) stage C) suggested a promising outcome with Trans-arterial chemoembolization (TACE) (Ajit et al., 2014)

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The purpose of our study was to evaluate the prognostic factors and management in patients with hepatocellular carcinoma with portal vein thrombosis (PVT).

Materials and Methods

Between February 2011 and February 2015, 140 HCC patients presented to our multidisciplinary HCC clinic. They were diagnosed according to the EASL guidelines (Bruix et al., 2001) and the AASLD updated practice guidelines for management of HCC (Bruix & Sherman, 2011). Concerning management, we applied BCLC guidelines (Llovet, Brú, & Bruix, 1999) with case-by-case discussion.

Data collection

After the approval of the local ethical committee, collected parameters included: patient characteristics such as (age, sex, etiology of underlying chronic liver disease, presence of cirrhosis and its degree of decompensation using the Child score, HCC presentation at time of diagnosis and family history of any relatives diagnosed as HCC). Tumor characteristics such as the tumor site, size and number, the site and extent of portal vein thrombosis were documented. AFP level and presence of extrahepatic metastases, if any, were mentioned. Other ultrasonography findings such as the size of the liver and size of the spleen, the presence of abdominal lymphadenopathy and History of previous ablation were as well analyzed. We also looked for the primary mode of HCC management for each patient being curative, palliative or supportive. Exclusion criteria includes: HCC patients without PVT, Presence of extrahepatic metastasis, and Patients with tumors other than HCC.

At least two of the followings three criteria as a reference standard were used to diagnose malignant PVT: HCC size of more than 5 cm, Distance from HCC to PVT of less than 2 cm and Arterial enhancement of PVT with a sensitivity up to 100% and specificity of up to 90% of malignant PVT (Shah et al. 2007).

The treatment choice was selected for each patient with a case by case discussion depending on the financial support of the patient, availability of Sorafenib for Child A patients who do not have distant metastasis, the size of the tumor, extent of portal vein thrombosis whether it involves main portal vein trunk or a smaller division and aggressiveness of the tumor.

Statistical methods

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21.

Overall survivals were estimated using the methods of Kaplan and Meier. Differences between survival curves were assessed for statistical significance with the log-rank test. All significant prognostic factors in the univariate analyses were considered in a Cox proportional hazards regression model. Only the factors that independently affect overall survival were kept in the model. The hazard ratios (HRs) were estimated with their 95% confidence intervals, all p-values are two-sided. P-values < 0.05 were considered significant.

Results

This study was carried out on 140 patients, 123 of them (87.9%) were males. Ninety patients were at or below the age of 60 (56.7%). All cases developed HCC on top of cirrhosis that was mainly due to HCV (85%). We found a history of schistosomiasis in 75 patients (53.5%). The commonest presentation being jaundice in (21.4%) followed by weight loss (20%) while Palpable mass was felt in (4.3%) only. Minority of the patients (7.8%) had a positive family history of HCC (Table 1).

Concerning the tumor characteristics, single lesion found in 76 patients (54.2%), right lobe predominance (60%) and size larger than 3 cm observed in 127 patients (90.7%) were the predominant features. Near half of our patients (55.2%, n=69) had non-secreting AFP tumors (titer <400 ng/ml). The main PV was thrombosed in (76.45%, n= 107), the right branch in (17.9%, n=25) and the left branch in (5.7%, n=8), the extent of the thrombus was partial in (18.4%, n=19) and total in (81.6%, n=84). Features of more advanced HCC involvement like significant abdominal lymphadenopathy was evident in the minority of cases (10.7%, n=15).

According to the BCLC guidelines, different lines of treatment were offered to the patients. Decision of treatment in our study was Sorafenib in (19.3%, n=27), TACE in (25.8%, n=36), RFA in (1.4 %, n=2), microwave ablation in (2.9%, n=4), 3D radiotherapy in (0.7%, n=1) and combined therapy in (2.1%, n=3). Most of the patients were not treated (79.3%, n = 111) (Table 1).

At the end of the follow up in February 2015, 78 patients had died, 33.1% survived the 1st year and 20.7% the 2nd year. The overall median survival was 10 months from the date of diagnosis. Clinical progression was noted in 32.1% (n=45).

Univariate analysis revealed that Child-Pugh score, performance status (Eastern Cooperative Oncology Group "ECOG" 0-1), presence of ascites, serum albumin level and AFP >400 ng/ml didn't significantly affect survival. Patients having 2 or more tumors, abdominal lymphadenopathy, serum bilirubin >2mg/dl had significantly worse survival (Table 2) Multivariate analysis revealed that, the serum bilirubin (Figure 1) and receiving specific treatment (figure 2) were the only significant variables affecting survival, after controlling for the effect of the other prognostic factors, P value=0.031

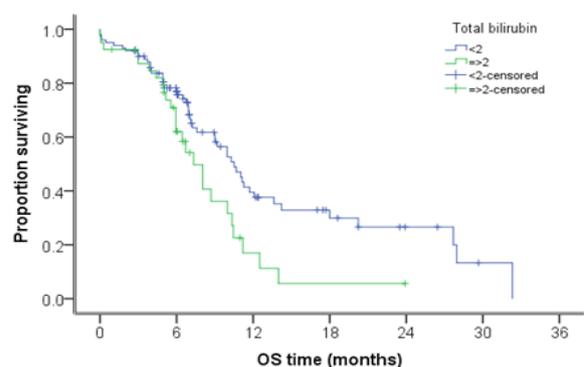


Figure 1. Kaplan-Meire Survival Analysis of the Studied Patients (Bilirubin)

Table 1. Basic Characteristics of Studied Patients

		(n=140)
Age	<=60	92
	>60	48
Sex	Female	17
	male	123
Family history	No	129
	yes	11
DM	No	108
	yes	32
smoking	No	79
	yes	61
Alcohol	No	138
	yes	2
Anti bilharzialttt	No	65
	yes	75
CHILD score	A	65
	B	53
	C	22
ECOG	0	57
	1	57
	2	20
	3	6
Splenomegly	No	60
	Yes	80
Ascites	No	82
	yes	58
Platelets	<100.000	41
	≥100.000	99
Bilirubin (mg/dl)	< 2	100
	≥ 2	40
Albumin (gm/dl)	< 3.5g/dl	91
	≥3.5g/dl	49
INR	< 1.7	109
	≥1.7	12
AFP (ng/ml)	< 400	69
	≥400	56
	missing	15
AST (IU/ml)	<=45	27
	>45	106
	missing	7
ALT (IU/ml)	<=40	40
	>40	92
	missing	8
HBsAg	-ve	139
	+ve	1
HCV Ab	-ve	21
	+ve	119

Table 1. Continued

		(n=140)
Number of tumors	1	76
	=>2	64
Site of tumor	Both	34
	Left	22
	right	84
Size of tumors	<3cm	13
	=>3cm	127
extent of main portal vein thrombosis	total thrombosis	84
	partially thrombosed	19
PVT extent	left	8
	main trunk	107
	right	25
Abdominal LN	No	125
	Yes	15
management	treated	29
	No ttt	111
Decision	3D radiotherapy	1
	Combined	11
	Microwave	4
	RFA	2
	Sorafenib	27
	BSC	67
	TACE	36

and 0.049, respectively (Table 3).

Discussion

Due to its wide heterogeneity in presentation, increasingly complex therapeutic options with diverse responses, highly variable biological behavior and a background of chronic liver disease in affected patients; HCC must be managed in multidisciplinary clinics. (Guy et al., 2012). PVT is present in up to 40% of HCC patients at the time of diagnosis and it is an adverse prognostic factor. Management of hepatocellular carcinoma (HCC) associated with portal vein thrombosis is complex and needs an understanding of the different treatment options (Quirk et al., 2015). Cheng et al. divided PVT into four types based on tumor site and extent: the segmental or sectoral portal vein branches (type I), the right or left portal vein (type II), the main portal vein trunk (type III), or the superior mesenteric vein (type IV) (Shuqun et al., 2007). The potentially radical treatment options for patients with HCC include surgical resection of the tumor, liver transplantation and loco-regional therapies depending on tumor staging and liver function. Both the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) guidelines consider hepatic resection the treatment of choice for patients with preserved hepatic function and resectable HCC. However, only 10- 30% of cases of HCC patients are eligible for surgical treatment

Table 2. Univariate Analysis for Different Factors Affecting Overall Survival of Studied Patients

Factors		Number of cases	Numbers of deahs	1 year	2 years	Median (months)	P-value
All		140	78	33.1	20.7	10.0	
Child score	A	65	33	45.8	21.4	11.0	
	B	53	32	19.4	15.5	8.0	
	C	22	13	30.0	30.0	10.4	0.372
ECOG	0	57	32	17.2	17.2	7.3	
	1	57	26	46.6	20.1	11.2	
	03-Feb	26	20	32.7	21.0	8.7	0.161
Ascites	No	82	46	32.2	17.9	10.0	
	Yes	58	32	35.6	25.4	10.0	0.687
T. Bilirubin	<2	100	52	39.5	26.6	10.5	
	=>2	40	26	16.9	5.6	7.3	0.014
Albumin	<3.5	91	52	29.2	18.5	10.0	
	=>3.5	49	26	39.8	24.8	11.0	0.572
AFP	<400	69	35	43.1	30.2	10.4	
	=>400	56	34	26.0	10.4	8.7	0.093
Number of tumors	1	76	34	40.7	28.6	10.3	
	=>2	64	44	25.7	13.9	8.7	0.048
Site	Both	34	24	22.1	11.8	7.0	
	Left	22	9	53.6	20.1	18.0	
	Right	84	45	32.7	23.8	10.2	0.114
Size	<3	13	8	33.0	33.0	10.0	
	=>3	127	70	33.2	19.0	10.0	0.633
LN	No	125	67	36.4	21.9	10.3	
	Yes	15	11	9.9	9.9	6.5	0.021
Management	Treated	29	14	53.9	38.4	12.5	

Table 3. Stepwise Cox Proportional Hazards Model for Independently Significant Factors

	95.0% CI for		HR	P-value
	HR	Lower		
Tbil (<2 vs =>2)	1.7	1.05	2.8	0.031
Treatment (yes vs no)	1.8	1.0	3.3	0.049

at the time of diagnosis (Brandi et al., 2014).

Trans-arterial radio-embolization (TARE) with yttrium-90 microspheres is emerging as a valuable treatment option. The wider range of patients with PVT is suitable for this procedure compared to TACE. TARE is as effective as TACE in HCC and has quality-of-life advantages (Lau et al., 2013). PVT remains one of the major contraindications to liver transplantation in patients with HCC due to the scarcity of organs and the high rate of tumor recurrence. Several studies show a high response rate after loco-regional treatment in patients with HCC and PVT, but their median survival time is <12 months (Brandi et al., 2014).

Our study included 140 patients; all of them developed HCC on top of liver cirrhosis that was mainly caused by HCV. Liver cirrhosis has been previously reported in many studies as the most predominant pathological lesion behind the development and progression of HCC. We aimed to provide a clear view of the variable

options available for management of HCC with PVT in Egypt as sampled and represented by our specialized multidisciplinary clinic. The BCLC guideline represents our backbone for managing HCC. It is one of the most accepted and widely used systems as it includes variables related to the tumor specifications, liver profile and performance status of the patients.

We found that, specific treatment has significantly increased survival compared to patients left untreated. The median survival rate was 9 months in the untreated cases compared to 12.5 in the treated patients and this was similar to the results of the study done by (Abdelaziz et al., 2014) and found that the application of specific treatment is one of the main three prognostic factors that affected the survival of HCC patients. Also (Lau et al., 2013) found that systemic treatment with Sorafenib resulted in survival benefit in patients regardless of the presence of PVT. The same results are found by a study done by Yang and his colleagues on 2010, (Yang et al., 2010) as they found that Sorafenib combined with Hepatic arterial infusion chemotherapy (HAIC) and TACE subsequent to Sorafenib monotherapy resulted in further tumor response. They supposed that the antitumor effects of HAIC and TACE added to the effect of targeted Sorafenib therapy and doubled the tumor response.

In our study, there is no significant effect of the site and the extent of the portal vein thrombosis on the survival, to

be clarifying that, most of our patients (76.4%) had type III PVT (main stem PVT) and it was totally occluded in (81.6%) of the patients, while the type of PVTT was one of the independent predictors of survival in the study done by (Liu et al., 2014) as he found that Type of PVT, number of tumor lesions, liver function, and the metastasis are helpful for clinicians to predict the prognosis of these patients and select the candidates.

Our study revealed that, the Child-Pugh score, the performance states (Eastern Cooperative Oncology Group "ECOG" 0-1) and the presence of ascites are insignificantly affecting the survival, while the study done by (Ajit et al., 2014) found that, the response to chemoembolization, Child-Pugh class at diagnosis, and ascites at the time of presentation were the most important determining factors of survival rate. Also the median survival time was significantly longer in Child-Pugh A patients than in Child-Pugh B patients (7.5 months versus 3.8 months, $p < 0.001$) in the study done by (Liu et al., 2014).

Lei Liu, et al also found that, the median overall survival was significantly longer in patients with 1-2 tumor lesions than in those with 3 or more tumors (8.1 months versus 4.5 months, p value < 0.001). There is significant difference remained in Child- Pugh A patients (1-2 tumor lesions: 9.7 months, versus 3 or more tumor lesions: 5.3 months, p value < 0.001) but not in Child-Pugh class B patients (1-2 tumor lesions: 4.1 months, versus 3 or more tumor lesions: 3.7 months, p value = 0.65). In our study we found that, Patients with \Rightarrow 2 tumors, abdominal lymphadenopathy and serum bilirubin >2 mg/dl had significantly worse survivals, these results are similar to those of Lei Liu, et al 2014 that find that the total bilirubin , number of tumor lesions and metastasis were the independent predictors of survival.

Bilirubin level, bilobar hepatic affection and the application of specific treatment are the main three prognostic factors that affected the survival of HCC patients. Serum bilirubin is a well representative of hepatic condition. It is included in Child- Pugh and MELD scores. In addition, its level is critical to take decisions for surgical resection (together with absence of portal hypertension) and TACE procedures. Consequently, it was expected that bilirubin plays an integral role for HCC survival according to (Abdelaziz et al., 2014) in a large systematic review of 72 studies related to prognostic indicators of HCC, bilirubin proved to be one of the six most important prognostic parameters. As mentioned by op den Winkel and colleagues in 2012, these findings are not so much related to distant metastases but more related to locally advanced tumors and the consequences of cirrhosis. In our study, significant abdominal lymphadenopathy was evident in the minority of cases (10.7%) (op den Winkel et al., 2012).

Application of specific treatments (curative or palliative) has significantly increased survival in HCC patients with PVT. TACE is a promising procedure in unresectable hepatocellular carcinoma with PVT. The main predictors of survival in HCC with PVT in our study are the serum bilirubin and Specific treatment application.

Conflict of interest

All included authors declare absence of any financial or personal relationships with other people or organizations that could inappropriately influence and bias the work.

Submission declaration

This work has not been published previously, is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and, if accepted, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

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