RESEARCH ARTICLE

Survival and Prognostic Factors for Hepatocellular Carcinoma: an Egyptian Multidisciplinary Clinic Experience

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Abstract

    <u>Background</u>: Hepatocellular carcinoma (HCC) is a dismal tumor with a high incidence, prevalence and poor prognosis and survival. Management of HCC necessitates multidisciplinary clinics due to the wide heterogeneity in its presentation, different therapeutic options, variable biologic behavior and background presence of chronic liver disease. We studied the different prognostic factors that affected survival of our patients to improve future HCC management and patient survival. <u>Materials and Methods</u>: This study is performed in a specialized multidisciplinary clinic for HCC in Kasr El Eini Hospital, Cairo University, Egypt. We retrospectively analyzed the different patient and tumor characteristics and the primary mode of management applied to our patients. Further analysis was performed using univariate and multivariate statistics. <u>Results</u>: During the period February 2009 till February 2013, 290 HCC patients presented to our multidisciplinary clinic. They were predominantly males and the mean age was 56.5±7.7years. All cases developed HCC on top of cirrhosis that was mainly due to HCV (71%). Most of our patients were Child-Pugh A (50%) or B (36.9%) and commonly presented with small single lesions. Transarterial chemoembolization was the most common line of treatment used (32.4%). The overall survival was 79.9% at 6 months, 54.5% at 1 year and 22.4% at 2 years. Serum bilirubin, site of the tumor and type of treatment were the significant independent prognostic factors for survival. <u>Conclusions</u>: Our main prognostic variables are the bilirubin level, the bilobar hepatic affection and the application of specific treatment (either curative or palliative). Multidisciplinary clinics enhance better HCC management.

Keywords: Hepatocellular carcinoma - multidisciplinary - prognosis - survival

Introduction

    Hepatocellular carcinoma (HCC) is considered as one of the most challenging tumors with high incidence, prevalence and mortality rates (Elbaz et al., 2013). It is the sixth most common cancer worldwide, accounting for 7% of all cancers and an estimated incidence that is almost identical to the mortality rate. Moreover, it represents the third cause of cancer related deaths (WHO, 2010).

    HCC used to be described as a tumor with an ultimately poor prognosis. This poor prognosis is related to its rapid progression and its aggressive biological behavior that leads usually to the diagnosis at an advanced stage (Lee et al., 2012). In addition, the majority of patients affected with HCC had a background of chronic liver diseases such as liver cirrhosis that can limit the possibilities of curative treatment Park (2002). Survival of HCC patients depends on several prognostic factors that are either patient related or tumor related (Esmat et al., 2013). Survival may also differ between regions and countries according to the different predisposing factors for HCC as well as the degree of standard of care that enables early diagnosis and management of the tumor. Recent focus on screening, surveillance and the improvement of the different modalities of HCC management tends to change the gloomy fact of short survival and bad prognosis (Elbaz et al., 2013).

    Nearly half of the data on HCC in Africa came from Egypt (Ezzat et al., 2005). Over the last decade, a considerable increase was observed in the proportion of chronic liver disease Egyptian patients with HCC (from 4.0% to 7.2%) (Freedman et al., 2006; National Cancer Registry of Egypt, 2010; Abdel-Hamid et al., 2011). HBV and HCV infections are the main causes of liver disease worldwide. The incidence of HCV infection is hard to quantify as large number of patients are asymptomatic and

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no vaccination is effective yet (Zekri et al., 2012). Due to the unique situation of HCC in Egypt, being plagued with the highest HCV prevalence in the world (Egyptian Ministry of Health Annual Report., 2007; Khattab et al., 2010), we performed an analysis for the different survival and prognostic factors that led to the development of HCC among Egyptian patients. The study is established in a specialized multidisciplinary clinic for HCC in Kasr El Eini Hospital, Cairo University, being a center of excellence and a referral point for the vast majority of Egyptian Governorates. This can represent a figure of the current situation and help the establishment of future plans to prevent and early manage HCC.

Materials and Methods

Patients

In February 2009, a multidisciplinary HCC clinic was established in Kasr El Eini Hospital, Cairo University, Egypt. This clinic includes hepatologists, surgeon hepatologists, radiologists, oncologists, pathologists and clinical pathologists. Between February 2009 and February 2013, 290 HCC patients presented to the clinic. They were diagnosed according to the EASL guidelines (Bruix et al., 2001) and the AASLD updated practice guidelines for management of HCC (Bruix and Sherman, 2011). Concerning management, we applied BCLC guidelines (Llovet et al., 1999) with case by case discussion and in compliance with the ethics principles of the Declaration of Helsinki with Good Clinical Practice Guidelines.

Data collection

Collected parameters included: patient characteristics (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, history of schistosomiasis affection and family history of any relatives diagnosed as HCC). Tumor characteristics such as the tumor site, size and number as well as the presence of portal vein thrombosis are documented. AFP level and presence of extrahepatic metastases, if any, are mentioned. Other ultrasonographic findings such as the size of the spleen, the presence of abdominal lymphadenopathy and the status of ascites are as well analyzed. We also looked for the primary mode of HCC management for each patient being curative, palliative or supportive.

Statistical analysis

Numerical data are reported as means±standard deviation (S.D) or median and range while categorical data are represented as counts and percentages. The Mann-Whitney U test and the Chi-square test are used when appropriate. Statistical significance is considered if the probability of occurrence by chance is 5% or less (p<0.05).

Survival analysis using the Kaplan-Meier method is performed from the date of primary diagnosis to the date of last follow up or death. All collected data variables are included in a univariate analysis. Statistically significant

parameters are further analyzed using multivariate regression analysis. Survival curves are compared using the Cox-Mantel log-rank test.

Results

Our retrospective study included 290 HCC patients. They were predominantly males (79.7%) and the mean age was 56.5±7.7years. All cases developed HCC on top of cirrhosis that was mainly due to HCV (71%) while HBV counted for 3.4% patients only. We found a history of schistosomiasis in 150 patients (51.7%). Routine follow up of cirrhotic patients led to the discovery of HCC among 51.4% of our patients while symptomatic presentation accounted for the rest of them; the commonest presentation being abdominal pain (26%) followed by jaundice (7.8%). Minority of the patients (9.7%) had a positive family history of HCC. Child-Pugh A patients (50%; n=145) and Child-Pugh B patients (36.9%; n=107) were more prevalent in our study than Child-Pugh C (13.1%, n=38) patients.

Concerning the tumor characteristics, single lesion (52.8%), right lobe predominance (65.5%) and smaller size than 3 cm were the predominant features. Most of our patients (67.2%) had non secreting AFP tumors (titer <400 ng/ml). Features of more advanced HCC involvement like portal vein thrombosis, significant abdominal lymphadenopathy and distant metastases were evident in the minority of cases (17.2%, 7.2% and 1.4% respectively).

According to the BCLC guidelines, different lines of treatment were offered to the patients (Figure 1); curative treatment (surgery, microwave therapy or radiofrequency therapy) was provided to 67 (23.1%) patients, palliative treatment (TACE or Sorafenib) was applied to 122 (42.1%) patients while supportive symptomatic care was provided to the rest of the patients. TACE was the most common line of treatment used (32.4%; n=94) followed
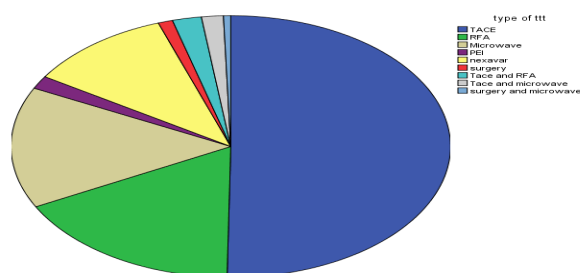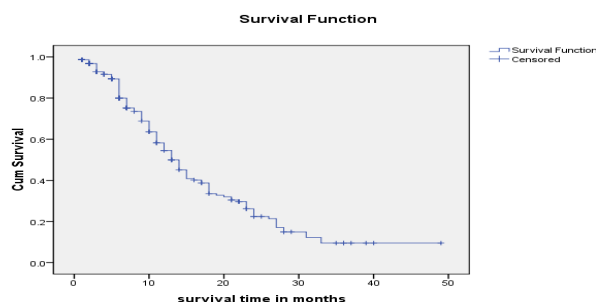

Figure 1. Modes of Treatment of the 290 Patients

Figure 2a. Kaplan-Meier Survival Analysis of 290 Patients

Table 1. Univariate Analysis for Prognostic Factors of HCC Survival in Studied Patients

					Survival (%)			
		Total N	N of Events	6 months	1 year	2years	Median	p-value
All		290	144	79.9	54.5	22.4	13	
Age (years)	<=65	258	129	79.8	55.3	24.9	13	
	>65	32	15	81.3	44.7	0	14	0.945
Sex	Female	59	28	83.4	52.8	19.2	14	
	Male	231	116	79	54.8	23	11	0.09
DM	No	228	111	76.2	46.7	15.2	12	
	Yes	62	26	83.5	63.6	15.4	16	0.168
Smoking	No	175	83	76	50	17.1	13	
	Yes	115	53	80.9	50	17.5	13	0.549
family history	No	249	112	77	53.5	18.6	13	
	Yes	41	25	80.8	34.6	11.5	11	0.33
Bilharziasis	No	140	62	76.1	51.3	16.8	13	
	Yes	150	73	79.6	49.2	17.7	12	0.88
child score	A	145	61	84	65	30.4	18	
	B	107	50	81.6	53.4	14.2	13	
	C	38	33	64.4	27.8	13.9	9	<0.001
ECOG	status 0-1	228	93	85.6	62.1	28	15	
	status 2-3	62	49	62.4	34.2	6.8	10	<0.001
Splenomegly	No	96	12	83.1	66.1	17.6	16	
	Yes	194	124	78	51.8	21.4	13	0.279
Ascites	No	228	95	83.9	59.9	26.2	15	
	Yes	62	49	67.5	39.9	12.6	10	0.001
Platelets	<100.000	117	47	83	53	12.1	13	
	≥100.000	173	70	76.5	51.1	20.9	13	0.428
Bilirubin (mg/dl)	< 2	198	87	84.4	63.9	24.6	15	
	≥ 2	90	50	72.2	34.5	12.9	10	0.001
Albumin (gm/dl)	< 3.5g/dl	187	107	77.4	45.4	15.3	11	
	≥3.5g/dl	103	36	84.4	71.8	37.1	23	<0.001
INR	< 1.7	248	110	82	61.1	24.1	15	
	≥1.7	42	33	68.1	23.8	11.9	10	0.001
AFP (ng/ml)	< 400	195	89	88.6	68.5	28	16	
	≥400	95	54	61.3	22	10.1	9	<0.001
number of tumors	Single	153	75	84.5	65.1	29	15	
	Two	54	22	85	50.2	17.6	14	
	multiple	83	47	69.4	34.4	9.4	10	<0.001
site of tumors	left lobe	35	21	75.8	48	21.3	12	
	right lobe	190	89	85.6	63.4	28.1	15	
	both lobes	65	33	66.9	31.6	0	9	<0.001
Size of tumors	≤3cm	120	30	90	74.7	35.7	21	
	>3-5cm	95	60	80.2	53.3	18.5	13	
	>5cm	75	50	71.3	41.3	19.2	11	0.003
PV thrombosis	No PVT	240	119	83.2	59.2	23	14	
	PVT	50	25	62.1	24.4	18.3	10	0.004
Abdominal LN	No LN	269	136	80.2	54.7	23.2	14	
	LN	21	7	84.7	56.4	14.1	13	0.614
Type of treatment	No treatment	101	64	65	35.1	15.8	10	
	palliative	122	58	88.4	62.4	17	14	
	curative	67	22	88.1	71.2	43.8	24	<0.001

by radiofrequency (11%, n=32) and microwave therapy (9.6%, n=28).

At the end of the follow up in February 2013, 144 (27.9%) patients had died. The causes of death were hepatic failure (55.5%), gastrointestinal hemorrhage (10.4%), spontaneous bacterial peritonitis (5.2%), as a complication of hepatic resection in 2 patients and pulmonary embolism in a single patient. The cause of death was unknown for the rest of the patients. The overall median survival was 13 months from the date of diagnosis. The overall actuarial probability of survival was 79.9% at 6 month, 54.5% at 1year and 22.4% at 2 years (Figure 2a).

Univariate analysis of the variables revealed that Child-Pugh A patients significantly survived more than Child-Pugh C patients (p value<0.001) (Figure 2b). Better performance states (Eastern Cooperative Oncology Group "ECOG" 0-1) carried a significantly higher survival than presentation with lower performance states. Similarly, patients with single tumors, right lobe location, size ≤ 3cm had significantly higher survivals. On the other hand, patients with ascites, portal vein thrombosis, serum bilirubin >2mg/dl, serum albumin <3.5g/dl, INR >1.7 and AFP >400 ng/ml had significantly
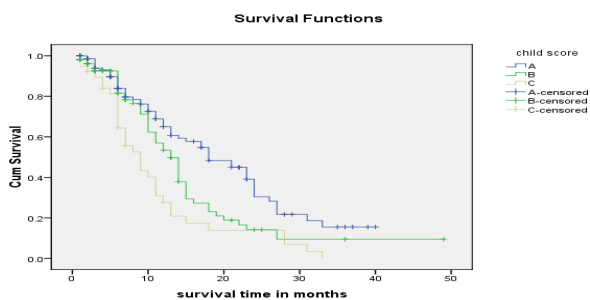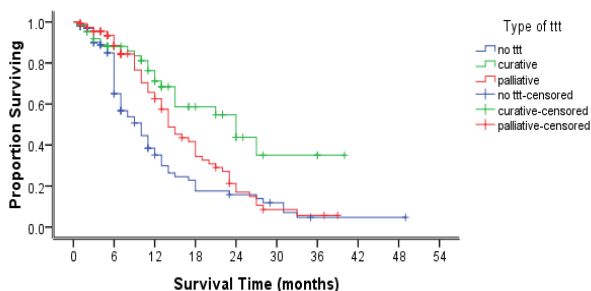
Figure 2b. Survival Analysis According to Child-Pugh Score

Figure 2c. Survival According to the Type of Treatment Used

Table 2. Multivariate Analysis for Prognostic Factors of HCC Survival in Studied Patients

	B	SE	Sig.	HR	95.0% CI for HR	
					Lower	Upper
Bilirubin	0.538	0.188	0.004	1.71	1.18	2.47
Site of lesion			0.016			
Site (Left vs Both)	-0.332	0.31	0.285	1.39	0.76	2.56
Site (Right vs Both)	-0.673	0.244	0.006	1.96	1.21	3.16
Treatment			0.002			
symptomatic vs curative	-0.863	0.262	0.001	2.37	1.42	3.96
symptomatic vs palliative	-0.446	0.196	0.023	1.56	1.06	2.29

B= regression coefficient, SE = standard error of the coefficient, HR = hazard ratio, CI= confidence interval

worse survivals. Specific treatment, either curative or palliative, significantly increased survival compared to patients receiving supportive symptomatic treatment only. Certainly, patients who got curative treatment showed significantly higher survivals (Table 1, Figure 2c).

All significant factors in univariate analysis were further analyzed by a stepwise multivariate Cox proportional Hazard (Table 2). As a result, serum bilirubin, site of the tumor and type of treatment were independent prognostic factors for survival. Patients with high bilirubin levels had 1.7 times more chance of dying than those with normal bilirubin. Patients with tumors in both lobes of the liver were 1.39 and 1.96 times more at risk of dying than those with tumors in left or right lobe respectively. Finally, patients who had symptomatic treatment were 2.37 and 1.56 times more likely to die than those who had curative or palliative treatment respectively.

Discussion

Due to its wide heterogeneity in presentation, increasingly complex therapeutic options with diverse responses in clinical practice, highly variable biological behavior and a background presence of chronic liver disease in affected patients (Guy et al., 2012; Kaseb et al., 2013), HCC must be managed in multidisciplinary clinics. In our study, we aimed to provide a clear view of the current situation of HCC in Egypt as sampled and represented by our specialized multidisciplinary clinic.

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 (Llovet et al., 1999). It has been approved by the EASL and the AASLD (Bruix and Sherman, 2005) and was recently included in the HCC guidelines published by the Egyptian Society of Liver Cancer (ESLC) (The Egyptian Guidelines for Management of Hepatocellular Carcinoma, 2011).

In our study, all patients (290 cases) 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 (Xu et al., 2012). In a similar study for prognostic factors of HCC in Italy, liver cirrhosis accounted for 96% of HCC cases (Lerose et al., 2001). As for hepatitis seroprevalence among HCC cases, a recent worldwide systematic review documented a predominance of HBsAg among HCCs from most Asian, African and Latin American countries while anti HCV predominated in Japan, Pakistan, Mongolia and Egypt (Raza et al., 2007). The highest prevalence of HCV in the world is reported in Egypt (Egyptian Ministry of Health Annual Report., 2007; Khattab et al., 2010).

Although nearly half of HCC patients (50%) had a compensated liver cirrhotic condition (Child Pugh score A), curative treatment (surgery, microwave therapy or radiofrequency therapy) was provided for 23.1% only of HCC cases and 42.1% received palliative therapy. In a recent study applied on a large Western HCC cohort, 53.7% had compensated liver cirrhosis and potentially curative treatment was applied for 24% only of patients (Op den Winkel et al., 2012). These findings reflect the detection of HCCs at advanced stages even with compensated liver cirrhosis. As mentioned by op den Winkel and colleagues, 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, just 1.4% of patients had distant organ metastases and 7.2% presented with significant abdominal lymphadenopathy (Op den Winkel et al., 2012).

Overall median survival of our studied patients was 13 months. Overall probability of survival was close to 80% at 6months, 54.5% at one year and 22.4% at two years. Overall survival varied greatly between different studies. Some papers recorded considerably low survivals as 3.5 months (El-Serag et al., 2006) and 1.9 months in Malaysia (Norsa'adah and Nurhazalini-Zayani, 2013) while other papers reported rates as high as 25.7 and 26.8 months in Italy and Taiwan respectively (Yeh et al., 2002; Grieco et al., 2005). Many factors can explain this discrepancy such as the biological behavior of the tumor, the underlying state of chronic liver disease and cirrhosis, the sum of predisposing risk factors and the

available therapeutic options. In addition, the application of screening and surveillance to early detect HCC can provide higher survival rates (Della Corte and Colombo, 2012; Forner et al., 2012). Researches to early predict HCC development are still needed and our overall survival rate is still considered sub-optimal.

Univariate analysis provided many variables that are either patient related or tumor related. These variables were further studied by multivariate analysis and three variables only proved to be independent prognostic factors for survival. These factors are bilirubin level, bilobar hepatic affection and the application of specific treatment (curative and palliative). 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 is expected that bilirubin plays an integral role for HCC survival. 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 (Tandon and Garcia-Tsao, 2009). Concerning the second factor, the bilobar hepatic affection may represent an aggressive behavior of the tumor that shows itself as multicenteric with a locally invasive pattern. As a consequence, this will greatly limit the therapeutic options and the overall survival rates. In Lerose et al study (Lerose et al., 2001), tumor location proved to be a statistically significant factor in univariate analysis. Another recent study for HCC prognostic indicators demonstrated that multifocal HCC was a significant factor, both in univariate and multivariate analyses (Kirchner et al., 2010). Dogan et al also reported that the median overall survival was significantly longer in uninodular HCC than multinodular and diffuse HCC (Dogan et al., 2012).

Finally, the third factor is the type of treatment provided. Curative treatment is superior to palliative treatment that is also superior to supportive treatment. As expected, the curative treatment provides the highest survival rates. Palliative treatment represented mainly by TACE succeeded to provide a higher survival rate than no treatment application. This is similarly reported in other studies using TACE and concluded a higher survival benefit in unresectable HCC cases (Takayasu et al., 2006; Lee et al., 2012).

In summary, our study reveals the different prognostic factors that affected the survival of our HCC patients. The main three variables were the bilirubin level, the bilobar hepatic affection and the application of specific treatment (either curative or palliative). We hope that these findings will ameliorate future early detection and management of HCC to gain a higher survival benefit.

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