HCC from diagnosis to treatment; 15 years of challenges and modification of resection strategies

By

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Abstract

Background: 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 especially with background of chronic liver disease.

Patients and Methods: This study is performed in a specialized clinic for HPB in Assuit university Hospital, Assuit University, and Sohag University hospital, Sohag University, Egypt. We studied different types of patient and tumor characteristics with evaluation of the surgical management applied to them. Further analysis was performed using univariate and multivariate statistics.

Results: During the period December 2000 till March 2014, 220 patients with HCC presented to our clinic. They were predominantly males and the mean age was 56.5±7.7years. Most of cases developed HCC on top of cirrhosis that was mainly due to HCV (71%). Most of our patients were Child-Pugh A (52%) or B (32%) and commonly presented with small single lesions. Trans arterial chemoembolization was the most common line of treatment used (32.4%), followed by local ablation therapy (27%). A major section of cases was palliatively treated due to delayed discovery and advanced stage of disease (63%), in the other hand, surgical resection was the gold standard in operable cases (25.4%). Non-anatomic open resection was the commonest procedure used in 58%, however other techniques were used as anatomic resection (27%), and laparoscopic non anatomic resection (15%), unfortunately, transplantation program does not started yet to be added in treatment. The overall survival was 80% at 6 months, 55% at 1 year and 20% at 2 years. Serum bilirubin, portal hypertension, site of the tumor and type of treatment were the significant independent prognostic factors for survival.

Conclusions: early discovery by surveillance protocols is very essential for better outcome of such cases, early interference weather by surgery or local ablation is a good substitute in absence of transplantation programs. Our main prognostic variables are the bilirubin level, portal hypertension, 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 the most common form of primary liver cancer.[1] Worldwide; liver cancer is the fifth and seventh most common cancer in men and women, respectively. Most of the burden lies in developing countries. The regions of high incidence include Eastern and South-Eastern Asia, Middle and Western Africa. It is the third most common cause of death from cancer. Its high fatality is reflected on high (0.93) mortality to incidence ratio.[2] In Egypt, liver cancer is the fourth most common cancer and is the second cause of cancer mortality in both sexes.[2] Risk factors for HCC are many and include viral hepatitis B (HBV) and C (HCV), cirrhosis, aflatoxins, alcohol, smoking, and male sex.[3] These risk factors vary among countries, but chronic infection with HBV and HCV are the most important precursors for HCC development on a global scale, together accounting for over 80% of liver cancer cases. Worldwide, HCV infection is one of the most serious health problems. HCV-related liver disease can progress over several decades in an insidious manner with liver cirrhosis and HCC in the advanced forms of the disease. About one quarter of subjects with HCV chronic infection are estimated to develop liver cirrhosis 15–25 years later. In those patients with compensated liver cirrhosis related to HCV, 1.8%–8.3% develop HCC each year.[4] In Egypt, HCV is the main risk factor for HCC where 71% of HCC cases are positive for anti-HCV antibodies.[5] As different treatment modalities of HCC may prolong survival in some cases, this will not accurately reflect the prognostic values of some factors.

The only proven potentially curative therapy for HCC remains surgical, either hepatic resection or liver transplantation (LT), and patients with single small HCC (<5 cm) or up to three lesions <3 cm should be referred as a candidates for these treatment modalities[6]. However, only 30% of patients with HCC are eligible for surgery, mainly because of the multiplicity of the lesions which often occurs on a background of chronic liver disease[7,8,9]. Over the past 10 years, there has been considerable progress in the diagnosis and surgical treatment of HCC. The tumors are more often identified at an early stage, in particular through the screening of high-risk patients[10-13]. Surgery is safer, with an acceptable overall mortality rate in cirrhotic patients (55%); also, good long-term survival, up to 45%, is achieved after adequate anatomical resections[14,15]. Partial resection is associated with a high incidence of tumor recurrence, mainly due to the presence of the chronic underlying liver disease which is a pre-neoplastic state[16]. Therefore, because LT removes the tumor(s) and the pre-neoplastic underlying chronic liver disease, LT appears to be the treatment of choice for small HCCs[8]. However, to avoid tumor recurrence, LT indications for HCC are restrictive and the limited availability of grafts and the cost of the LT represent the main potential limiting factors for its development[17]. In the vast majority of cases, HCC develops in the setting of cirrhosis, but 5–15% of patients have no underlying chronic liver disease[18]. Usually, the etiology of HCC development is undetermined, however, HCC tumors in patients with normal liver are often large (>10 cm) and diagnosed when tumors are symptomatic[19,20]. The only curative treatment is major hepatectomy, which is often well tolerated in the absence of underlying liver disease and the good regenerative capacity of the remnant liver. The long-term results of resection of HCC without chronic liver disease are much better than in patients with cirrhosis, with disease-free 5-year survival rates as high as 50%[21,22] . These favorable results observed in both

fibrolamellar and non-fibrolamellar HCC variants suggest that the absence of underlying liver disease is a major factor in short- and long-term prognosis[9,21].

The role of hepatic resection for treatment of multiple and bilobar HCCs is more controversial[23-26], bilobar HCCs may represent advanced disease with intrahepatic metastasis from one lobe to the other or may represent multifocal HCCs. However, in some selected patients with good liver function, the presence of a small solitary lesion in the contralateral lobe cases should not contraindicate the resection of the main tumor, and in selected cases major hepatic resection can be associated with wedge resection or local ablative therapy (if the lesion is not superficial)[27,28]. Therefore, when possible, anatomical resection should be the treatment of choice and considered as the reference surgical treatment when comparing it to other treatments. Moreover, when anatomical resection does not seem to be a possible, either because of the tumor location and/or the degree of the liver function, other therapeutic options such as LT and/or percutaneous treatment are considered[29].

Non-surgical therapy should only be used where surgical therapy is not possible as: percutaneous ethanol injection (PEI) to produce necrosis of small HCC, best suited to peripheral lesions, less than 3 cm in diameter. Radiofrequency ablation is a good alternative ablative therapy. Chemoembolization can produce tumor necrosis and has been shown to affect survival in highly selected patients with good liver reserve; using lipiodol is effective for pain or bleeding from HCC. Systemic chemotherapy with standard agents has a poor response rate and should only be offered in the context of trials of novel agents[6]

Patients and methods:

This retrospective study was conducted at Assuit University hospitals, and Sohag University hospitals; Assuit and Sohag Governorate, Egypt. These are the largest referral tertiary level centers allover Upper Egypt territory. It included a random sample of 220 patients encountered, studied, and treated with various treatment modalities except transplantation which was not feasible during that period.

Tumor characteristics, investigations, staging, treatment modalities, and follow up data were analyzed with evaluation of treatment protocols and its modification with time after introduction of new tactics, drugs, and surgical techniques and the resulting cumulative experience of the team.

Results:

This retrospective study included a random sample of 220 HCC cases who attended Assuit and Sohag University hospitals between December 2000 and March 2014. Age ranged between 29 and 72 years with a median of 50.5 years, with male predominance as male to female ratio was 5.6:1 **(table 1)**.

Preoperative assessment of patients: Almost two-thirds of the patients (142 patients about 64.5%) had a smoking history. Viral hepatitis markers status was done in 86 patients and was positive in 38%, with hepatitis C being the most predominant type among them (80%). Most of patients (84%) had some evidence of cirrhosis; by clinical, imaging or laboratory tools, with a history of schistosomiasis in 113 patients (51.3%). Routine follow up of cirrhotic patients led to the discovery of HCC among 50.9%

of our patients while symptomatic presentation accounted for the rest of them; the commonest presentation being abdominal pain (26.4%) followed by jaundice (13.6%), however minority presented with other symptoms as fatigue, or ascites (20 patients = 9.1%). Minority of the patients (9.7%) had a positive family history of HCC. Child-Pugh A patients was diagnosed in 115 patients (52.2%) and Child-Pugh B in 73 patients (33.1%) were more prevalent in our study than Child-Pugh C that was encountered in only 32 patients (14.5%).

Characteristic	Number (%)
Demographics	
Age (Years) (mean ± SD)	56.5±7.7
Sex:	
Male	185 (84.1%)
Female	35 (15.9%)
Risk Factors:	
Smooking (No. of pt. assessed)	220
Yes (+ve history)	142 (64.5%)
Hepatitis (No. of pt. assessed)	86
Yes (+ve patient)	67 (77.9%)
Known hepatitis C	39 (58.2%)
Known hepatitis B	11 (16.4%)
Known hepatitis B and C	17 (25.3%)
Diagnosed Cirrhosis (+ve)	184 (83,6%)
Bilharziasis history (+ve)	113 (51.4%)
Clinical presentations:	
Asymptomatic	112 (50.9%)
Abdominal pain	58 (26.4%)
Jaundice	30 (13.6%)
Other e.g fatigue, ascites	20 (9.1%)
Child-Pugh Class	
Class A	115 (52.2%)
Class B	73 (33.1%)
Class C	32 (14.5%)

Table (1): Clinical characteristics of the patient sample studied

Concerning the tumor characteristics **(table 2)**, 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 raised AFP tumor marker (cut off titer value of <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).

Treatment strategy: According to the Barcelona clinic liver cancer (BCLC) guidelines, different lines of treatment were offered to the patients **(fig. 1)**, as curative treatment including surgical resection in 56 patients (25.4%), or local curative radiofrequency ablation therapy in 18 patients (8.1%), while palliative radiofrequency ablation therapy was done in 42 patients (19%). Palliative treatment using trans arterial chemo-embolization (TACE) or Sorafenib was applied to 32.4% and 10% of patients

respectively. TACE was the most common line of treatment used (32.4%) followed by radiofrequency (27%) and surgery (25.4%) of patients.

Characteristic	Number (%)
Liver mass site:	
Rt. lobe	**106 (48.1%)**
Lt.. lobe	**48 (21.8%)**
Multiple	**66 (30%)**
Number of lesions:	
Single	**96 (43,2%)**
Multiple	**124 (56.3%)**
Tumor size (cm)	
≤5 cm	**78 (35.5%)**
> 5 cm	**142 (64.5%)**
Residual liver:	
Undetected pathology	**36 (16.3 %)**
Cirrhosis	**124 (65.3%)**
Fibrosis	**60 (27.2%)**
T Stage:	
I Stage	**3 (1.4%)**
II Stage	**5 (2.3%)**
III Stage	**109 (49.5%)**
IVStage	**89 (40.5%)**
N Stage:	
0 stage	**184 (83.6%)**
I Stage	**22 (10%)**
M Stages:	
0 Stage	**140 (63.6%)**
I Stage	**66 (30%)**
TNM Staging system:	
I Stage	**35 (15.9%)**
II Stage	**22 (10%)**
III Stage	**83 (37.7%)**
IV Stage	**80 (36.4%)**
Sites of metastasis:	
Bone	**10 (4.5%)**
Lung	**22 (10%)**
Lymph nodes	**48 (21.8%)**

Table (2) Tumour and pathological characteristics of patient sample studied

Surgery for HCC: Non-anatomic open resection was the commonest procedure used in 58%, however other techniques were used as anatomic resection (27%), and laparoscopic non anatomic resection (15%), unfortunately, transplantation program does not started yet to be added in treatment. The overall survival was 80% at 6 months, 55% at 1 year and 20% at 2 years.

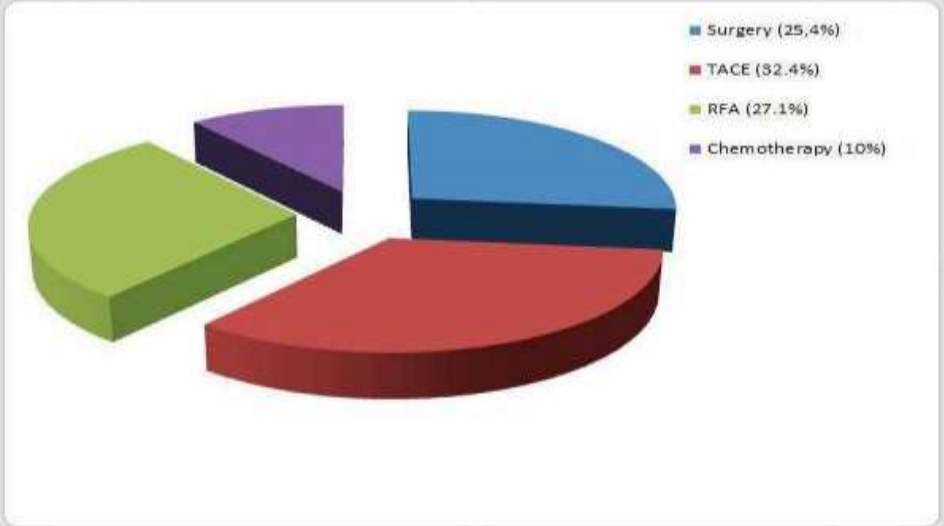

Fig. (1): Modes of Treatment of the 220 Patients

The main aims of hepatic resection, especially in cirrhotic liver is to resect all of the malignant tissue with effective clearance; and to leave enough non-tumorous liver parenchyma to prevent postoperative liver failure especially in patients with poor liver function.

Several techniques were used to improve the outcome of liver resection and minimize intra-operative bleeding as Inflow occlusion of portal triad, either continuous Pringle maneuver that can be safely applied to the normal liver under normothermic conditions for up to 60 minutes and up to 30 minutes in pathological (fatty or cirrhotic)[30], or intermittent inflow occlusion that can also be repeated safely for up to 90 minutes in cirrhotic patients with good liver function[29].

Finger-fracture (Digitoclasia) or clamp crushing (Kellyclasia) techniques were used for blunt transection when the liver parenchyma is crushed between the thumb and one finger or with Kelly clamps so that vessels and bile ducts stand out for proper haemostasis by diathermy, metal clips, or suture ligatures. Unipolar and bipolar cauteries are commonly employed for simultaneous haemostasis while transection is carried out[31]. Newer bipolar devices such as the Ligasure vessel sealing system has been used to seal off vessels up to 7mm in diameter[32], the liver tissue can be crushed between the blades of the device and then coagulation energy is applied to seal the vessels. Harmonic scalpel, an ultrasonically activated shear was also used for resection. It causes protein denaturation and coagulation by high frequency ultrasound vibration[33]. Vascular staplers were used for the division of hepatic veins and portal branches, moreover it were also used for transection of liver parenchyma after dividing the liver capsule by diathermy, followed by fracturing the liver tissue with a vascular clamp in a stepwise manner, and subsequently divided with endo-GIA vascular staplers[34].

Intra-operative ultrasound (IOUS) was very beneficial essential tool during hepatectomy procedure[35], and its role was much emphasized in our work

Laparoscopic resection of hepatic lesions was also used in some selected cases of accessible lesions[36.37], by the same surgical tools applied for open ones.

Post-operative data assessment: Data of our patients was analyzed using univariate analysis tools and it revealed that Child-Pugh A patients significantly survived more than Child-Pugh B and C patients (p value<0.001) **(fig. 2-3)**. Better performance states using the Eastern Cooperative Oncology Group "ECOG" 0-1 was associated with a significantly higher survival than presentation with lower performance states. It also showed that patients with single tumors, located in right lobe, and sized ≤ 3cm had significantly higher survivals than others. On the other hand, patients with portal hypertension, ascites, portal vein thrombosis, serum bilirubin >2mg/dl, serum albumin <3.5g/dl, INR >1.7 and AFP >400 ng/ml had significantly worse survivals than others. Specific treatment, either curative or palliative, significantly increased survival compared to patients receiving supportive or palliative symptomatic treatment only. Certainly, patients who got curative treatment showed significantly higher survivals **(fig. 4).** All significant factors in univariate analysis were further analyzed by a stepwise multivariate Cox proportional Hazard. As a result, serum bilirubin, site of the tumor and type of treatment were the significant independent prognostic factors affecting survival **(table 3)**.

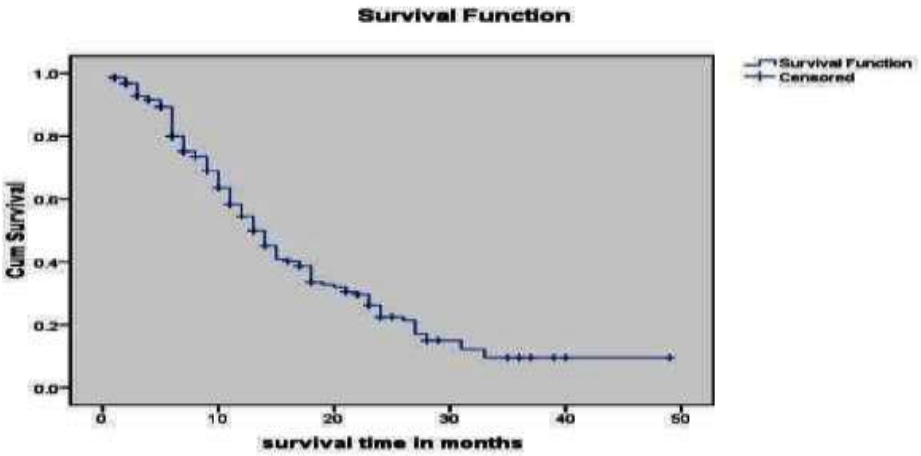

Fig. (2): Kaplan-Meier Survival Analysis of 220 Patients

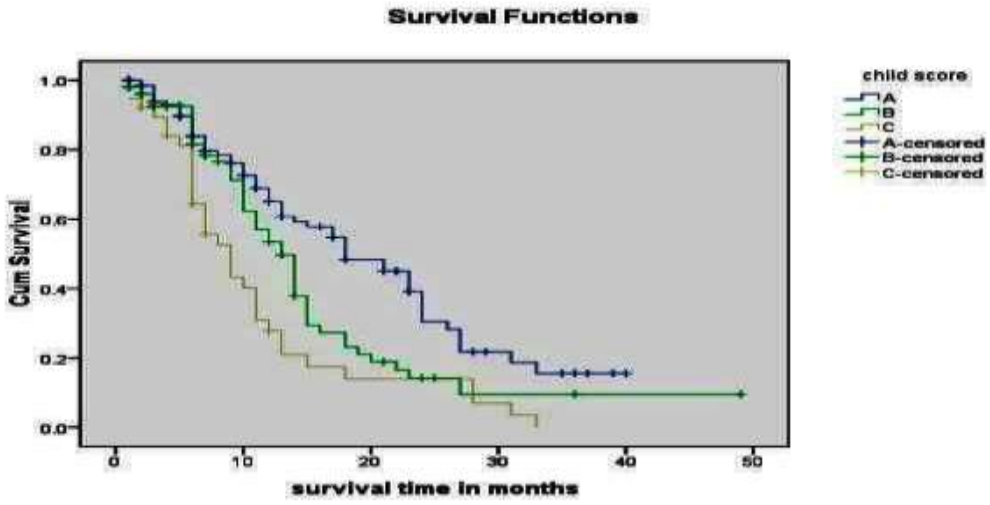

Fig. (3): Survival Analysis According to Child-Pugh Score

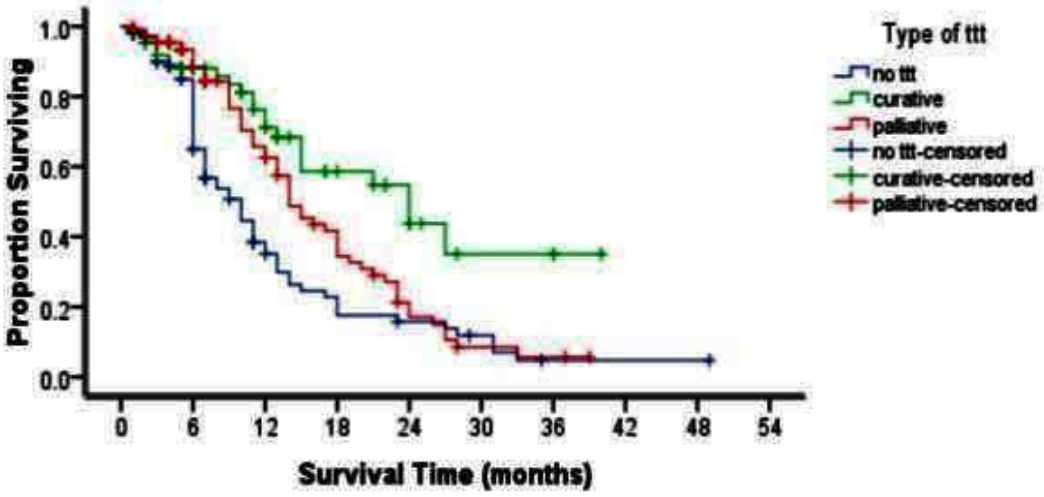

Fig. (4): Survival According to the Type of Treatment Used

	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 (Lt. vs. both)	**-0.332**	**0.31**	**0.285**	**1.39**	**0.76**	**2.56**
Site (Rt. Vs. both)	**-0.673**	**0.244**	**0.006**	**1.96**	**0,1.21**	**3.16**
Treatment			**0.002**			
Symptomatic vs. curative	**-0.863**	**0.262**	**0.001**	**2.37**	**1.42**	**3.96**
Symptomatic vs. paliative	**-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

Table (3): Multivariate Analysis for Prognostic Factors of HCC Survival in Studied Patients

Discussion:

HCC is a major health problem in Egypt and it carry a great concern from the health authority as many patients present with advanced disease beyond curative surgery or effective palliative local and regional therapies. Exceptionally certain group of patients with resectable disease and adequate liver reserve can benefit from resection or liver transplant, otherwise treatment of HCC remains palliative with minimal survival benefit[38,39].

Presentation of HCC are variable, and misleading, with unexpected biologic behavior counteracted by multiple complex therapeutic options for management with diverse responses documented in clinical practice, moreover the presence of endemic chronic liver disease in our locality evident in most of patients[40,41], that nictitates management of HCC 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 the cornerstone for managing HCC in our center as It is the most accepted and widely used systems approved by many liver management societies[42], moreover it was included in the HCC guidelines published by the Egyptian Society of Liver Cancer (ESLC)[43].

In our study, most of our patients (84%) 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[44]. In a similar study, liver cirrhosis accounted for 96% of HCC cases[45]. 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[46]. The highest prevalence of HCV in the world is reported in Egypt[47,48].

Although nearly half of HCC patients (52.2%) had a compensated liver cirrhotic condition (Child Pugh score A), curative treatment (surgery or radiofrequency therapy) was provided for only 33.5% of HCC cases (25.4% for surgery, and 8.1% for curative radiofrequency ablation), and 61.4.1% of cases received palliative therapy (19% for radiofrequency ablation, 32.4% for TACE therapy, and 10% for systemic chemotherapy treatment). 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[41]. These findings reflect the detection of HCCs at advanced stages even with compensated liver cirrhosis, and documented that these findings are not so much related to distant metastases but more related to locally advanced tumors and the consequences of cirrhosis[49].

Data of our patients were analyzed using univariate analysis tools documented that low burden disease (non-metastatic disease), absence of symptoms (ascites, or fatigue), good liver reserve (Child-Pugh A), and female sex are significantly associated with improved survival. Similar to our results, absence of ascites was associated with improved survival in the Italian group. But in contrast, factors affecting survival in their study were INR, bilirubin, portal hypertension, performance status (not assessed in our study), and low albumin reflecting different disease biology[50]. In previous studies with similar design, multivariate analyses showed many independent prognostic factors as AFP, bilirubin, performance status and disease stage being the most consistent between these trials. In agreement with Liovet et al[13], the current study showed that extra-hepatic spread was a predictor of poor survival as it is usually associated with high burden of the disease and it precludes local treatments. Extra-hepatic spread combined with the absence of effective systemic treatments is responsible for the dismal outcome in that advanced stage of the disease. Again, a higher Child-Pugh class and fatigue were independent factors of poor survival mostly because they reflect the underlying poor liver reserve. Fatigue may also reflect a bad performance status, consistent with Cabibbo et al[50], who concluded that PS was an independent prognostic factor.

Surgery was the main treatment strategy in early operable cases through non-anatomic resection in 58%, anatomic resection in 27%, and laparoscopic non anatomic resection in 15%. In contradistinction to several studies demonstrating that anatomical resections of small solitary HCC achieve a significant better overall and disease-free survival than limited resections, without increasing the postoperative risk[29,51,52]. Therefore, when possible, anatomical resection should be the treatment of choice and

considered as the reference surgical treatment when comparing it to other treatments. The main risk of limited resections is tumor recurrence by local metastasis and particularly by tumor cell seeding in the adjacent or distal liver segments through tumor portal venous territory[14,29,51]. Anatomical resections according to the architecture of the portal vein have the potential to remove undetected cancerous foci (portal vein metastases and satellite nodules) disseminated from the primary gross tumor. On the other hand, some authors found no difference detected in recurrence rates between the anatomic and the non-anatomic groups in either univariate or multivariate analysis, and the type of resection is not considered a distinct risk factor for early (2 year) tumor recurrence in patients with solitary HCC and preserved liver function[53]. Hence non-anatomical or wedge resection was the commonly used technique especially for peripheral or superficial lesions, when the lesion crosses the boundary of multiple segments, or in situations where the preservation of liver substance is of paramount importance[30].

In order to perform liver resections safely and to minimize blood loss and need for blood transfusions, different hepatic vascular occlusion techniques were used based upon the type of resection to be performed, tumor size and location, and preoperative liver function[54]. The commonly used type was inflow occlusion (Pringle maneuver) either continuous or intermittent[55]. However the intermittent occlusion was more commonly used by clamped for 10 minutes and then unclamped for 3 minutes, allows for a longer total occlusion time of up to 2 hours in the normal liver, which can be useful for more prolonged complex liver resections[54], or with periods of 15 minutes of clamping and 5 minutes of unclamping can also be repeated safely for up to 90 minutes in cirrhotic patients with good liver function[29]. Sometimes, It involves inflow clamping for 15-20 minutes followed by unclamping for five minutes (mode 15/5 or 20/5), or five minutes clamping followed by one minute unclamping (mode 5/1)[30]; all techniques increases worm ischemia time of the liver allowing more time for major resection[29]. Ischaemic preconditioning (IP) of the liver was adopted by some authors and refers to an endogenous self-protective mechanism by which a short period of ischaemia followed by a brief period of reperfusion produces a state of protection against subsequent sustained ischaemia-reperfusion injury[30, 56].

Parenchymal dissection of liver tissue was done using finger fracture or clamp crushing technique in most of cases, as these methods are commonly practiced in many centers around the world[30,52], however other techniques were used as unipolar or bipolar diathermy[31], and the newer bipolar devices as Ligasure sealing that has been employed for liver transection with proven effectiveness[30,32], but it does not seem to work so well in cirrhotic livers compared with non-cirrhotic livers[32]. Harmonic scalpel ultrasonic dissector was used effectively for many cases[33], although it reduce operative time and blood loss, when compared with clamp crushing, it was shown to have an increased incidence of biliary fistulae[33]. A recent randomized controlled trial comparing different transection methods in liver resection showed that the clamp crushing method remained the most efficient device in terms of resection time, blood loss, and blood transfusion frequency, when compared with other methods and the dissecting sealer, and was also the least expensive[57]. Additionally, there are other important factors to be considered when choosing a particular method, such as operative time, availability and ease of use, extent of hepatic injury affected, and cost. The use of one tool over the other will also

vary according to the type of resection, and different techniques can be more advantageous in one setting than another. It is important to be familiar with many strategies and be able to apply them in the most appropriate setting[54]. Since these methods of transection involve quite a different set of skills, not only is it difficult to compare, it may well be a simple case of the surgeon's preference for one technique over another[30], taking in consideration that preservation of as much liver parenchyma is important since many patients will receive post-operative chemotherapy and risks of liver failure are much higher[54].

Vascular stapler devices were commonly used for division of hepatic veins and portal branches, moreover it was used for transection of liver parenchyma[34], although the technique appears attractive, the financial cost for the staplers is a serious drawback[30].

The role of intraoperative ultrasound was well emphasized in our work as it proved effectiveness as an essential tool for hepato-biliary surgeons[30], to locate known liver lesions, to detect further liver lesions on-table, to guide the line of transection and to mark important vascular patterns. It allows accomplishment of anatomical resections such as segmentectomy, and it also allows better tumour clearance in non-anatomical resections[30,35].

Laparoscopic hepatectomy procedures were recently evolved, but relatively slow due to concerns about haemorrhage, air embolism, tumour seeding (port site and peritoneal) and oncological clearance[30]. Although successful laparoscopic major hepatectomy have been reported, most authors agree that laparoscopic liver resection should be offered to selected patients[36,58], tumours located at segment II, III, IVb, V or VI, of size 5cm or less; lesions which are not close to major vascular trunks; and when there is no need for vascular or biliary reconstruction; were considered as favourable for laparoscopic resection[30]. It was associated with shorter hospital stay, less analgesic requirement and quicker resumption of oral intake, while complications and conversion rates were acceptable[37]. Without doubt, laparoscopic liver resection is technically demanding and can only be safely accomplished by liver surgeons with experience in both laparoscopic and open hepatic surgery[30].

Although there were common prognostic factors shared between trials, there were still several other factors associated with outcome in HCC. This may reflect the aggressive biology of the disease independent on certain single factor. So if we consider the aggressive biology of the disease, and the limited treatment options for HCC patients as well as the limited resources or access to effective treatment for most of Egyptian patients like sorafenib or liver transplant, we found that HCC is a fatal disease and constitutes a major national problem. So we have to find other effective treatment modalities or try to stress the importance of screening programs which can enable diagnosis at an early stage with the opportunity for treatment with curative intent. But the most valuable solution is to put more effort into a prevention program, whether through prevention of infection by viral hepatitis or treating it at early stages before causing cirrhosis which is the main risk factor for HCC in Egypt.

Conclusion:

HCC in Egypt is an aggressive disease and the overall survival in untreated HCC is very short. Many factors interact to produce this dismal survival. Our study reveals the different prognostic factors that affected the survival of our HCC patients. The main variables were bilirubin level, portal hypertension, 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. Till then, much effort should be put into the field of prevention and screening programs to get rid of the problem.

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References:

1) Poustchi H, Sepanlou S, Esmaili S, Mehrabi N, Ansarymoghadam A.: Hepatocellular carcinoma in the world and the Middle East. Middle East J Dig Dis. 2010; 2(1): 31 – 41.
2) globocan.iarc.fr [homepage on the Internet]. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No 10. Lyon, France: IARC; 2010. Available from: http://globocan.iarc.fr. Accessed October 16, 2014.
3) Ahmad J, Rabinovitz M. In: Carr I, editor. Etiology and Epidemiology of Hepatocellular Carcinoma in Current Clinical Oncology: Hepatocellular Cancer: Diagnosis and Treatment. Totowa: Humana Press Inc.; 2005:1–22.
4) Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment. Pharmacol. Ther. 2010; 32(3): 344 – 355.
5) Rahman El-Zayadi A, Abaza H, Shawky S, Mohamed MK, Selim OE, Badran HM.: Prevalence and epidemiological features of hepatocellular carcinoma in Egypt-a single center experience. Hepatol. Res. 2001; 19(2): 170 – 179.
6) Ryder SD.: Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults, Gut 2003; 52 (Suppl III): iii1 – iii8.
7) Lau WY. : Future perspectives for hepatocellular carcinoma. HBP 2003; 5: 206 – 13.
8) Llovet JM, Fuster J, Bruix J.: The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004; 10: S 115 – 20.
9) Bilimoria MM, Lauwers GY, Doherty DA, Nagomey DM, Belghiti J, Do KA, et al.: Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. Arch. Surg. 2001; 136: 528 – 35.

10) Tong MJ, Blatt LM, Kao VW. Surveillance for hepatocellular carcinoma in patients with chronic viral hepatitis in the United States of America. J. Gastroenterol. Hepatol. 2001; 16: 553 – 9.
11) Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, et al.: Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001; 48: 251 – 9.
12) Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al.: Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona – 2000, EASL conference. European Association for the Study of the Liver. J. Hepatol. 2001; 35: 421 – 30.
13) Llovet JM, Burroughs A, Bruix J.: Hepatocellular carcinoma. Lancet 2003; 362: 1907 – 17.
14) Makuuchi M, and Sano K.: The surgical approach to HCC: our progress and results in Japan. Liver Transpl. 2004; S10: 46 – 52.
15) Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, et al.: Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann. Surg. 2001; 234: 63 – 70.
16) Shimozawa N, Hanazaki K.: Longterm prognosis after hepatic resection for small hepatocellular carcinoma. J. Am. Coll. Surg. 2004; 198: 356 – 65.
17) Llovet JM,Mas X, Aponte JJ, Fuster J, Navasa M, Christensen C, et al.: Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. Gut 2002; 50: 123 – 8.
18) Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F, et al.: Hepatocellular carcinoma occurring in non-fibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. Hepatology 2000; 32: 200 – 4.
19) Poon RT, Fan ST, Wong J.: Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. J. Am. Coll. Surg. 2002; 194: 592 – 602.
20) Yeh CN, Lee WC, Chen MF.: Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung memorial hospital. Ann. Surg. Oncol. 2003; 10: 1070 – 6.
21) Belghiti J, Regimbeau JM, Durand F, Kianmanesh AR, Dondero F, Terris B, et al.: Resection of hepatocellular carcinoma: a European experience on 328 cases. Hepato-gastro-enterology 2002; 49: 41 – 6
22) Kianmanesh R, Regimbeau JM, Belghiti J.: Selective approach to major hepatic resection for hepatocellular carcinoma in chronic liver disease. Surg. Oncol. Clin. North. Am. 2003; 12: 51 – 63.
23) Chen WT, Chau GY, Lui WY, Tsay SH, King KL, Loong CC، et al.: Recurrent hepatocellular carcinoma after hepatic resection: prognostic factors and long-term outcome. Eur. J. Surg. Oncol. 2004; 30: 414 – 20.
24) Liu JH, Chen PW, Asch SM, Busuttil RW, Ko CY.: Surgery for hepatocellular carcinoma: does it improve survival? Ann. Surg. Oncol. 2004; 11: 298 – 303.

25) Regimbeau JM, Abdalla EK, Vauthey JN, Lauwers GY, Durand F, Nagomey DM, et al. : Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. J. Surg. Oncol. 2004, 85; 36.-.41.
26) Minagawa M, Makuuchi M, Takayama T, Kokudo N.: Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann. Surg. 2003; 238: 703 – 10.
27) Liu CL, Fan ST, Lo CM, Ng IO, Poon RT, Wong J. Hepatic resection for bilobar hepatocellular carcinoma: is it justified? Arch Surg 2003; 138 : 100 – 4.
28) Poon RT, and Fan ST.: Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transpl 2004; 10:S39–45.
29) JACQUES BELGHITI, and REZA KIANMANESH: Surgical treatment of hepatocellular carcinoma. HPB, 2005; 7: 42–49.
30) Mohsen Chowdhury M.D: Techniques for Liver Resection, BSMMU J. 2010; 3(2): 112-119
31) Nagano Y, Matsuo K, Kunisaki C, Ike H, Imada T, Tanaka K, et al. Practical usefulness of ultrasonic surgical aspirator with argon beam coagulation for hepatic parenchymal transection. World J Surg 2005; 29: 899-902.
32) Romano F, Franciosi C, Caprotti R, Uggeri F, Uggeri F. Hepatic surgery using the Ligasure vessel sealing system. World J Surg 2005; 29: 110-120.
33) Kim J, Ahmad SA, Lowy AM, Buell JF, Pennington LJ, Soldano DA, et al. Increased biliary fistulas after liver resection with the harmonic scalpel. Am Surg 2003; 69: 815-9.
34) Schemmer P, Friess H, Hinz U, Mehrabi A, Kraus TW، Z'graggen K, et al. Stapler hepatectomy is a safe dissection technique: Analysis of 300 patients. World J Surg 2006; 30: 419-30.
35) Torzilli G, Leoni P, Gendarini A, Calliada F, Olivari N, Makuuchi M. Ultrasound guided liver resections for hepatocellular carcinoma. Hepatogastroenterology 2002; 49: 21-7.
36) Vibert E, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B. Laparoscopic liver resection. Br J Surg 2006; 93:67-72.
37) Gagner M, Rogula T, Selzer D. Laparoscopic liver resection: Benefits and controversies. Surg Clin North Am 2004; 84 : 451-62.
38) Heidelbaugh JJ, and Bruderly M.: Cirrhosis and chronic liver failure: Part I. diagnosis and evaluation. Am Fam Physician. 2006; 74 (5):756–762.
39) Llovet JM.: Updated treatment approach to hepatocellular carcinoma. J Gastroenterol. 2005; 40(3):225–235.
40) Guy J, Kelley RK, Roberts J, Kerlan R, Yao F, Terrault N.: Multidisciplinary management of hepatocellular carcinoma. Clin Gastroenterol. Hepatol.; 2012; 10, 354-62.
41) Kaseb AO, Abaza YM, and Roses RE.: Multidisciplinary management of hepatocellular carcinoma. Recent Results Cancer Res, 2013; 190, 247-59.
42) Bruix J, and Sherman M: Practice Guidelines Committee، American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology, 2005; 42, 1208-36.
43) Bruix J, and Sherman M. : American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*, 2011; 53, 1020-2.

44) Xu J, Liu C, Zhou L, et al.: Distinctions between clinicopathological factors and prognosis of alphafetoprotein negative and positive hepatocelluar carcinoma patients. Asian Pac J Cancer Prev, 2012; 13, 559-62.
45) Lerose R, Molinari R, Rocchi E, Manenti F, Villa E.: Prognostic features and survival of hepatocellular carcinoma in Italy: impact of stage of disease. Eur J Cancer, 2001; 37, 239-45.
46) Raza SA, Clifford GM, Franceschi S.: Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. Br J Cancer, 2007; 96, 1127-34.
47) Egyptian Ministry of Health. Egyptian Ministry of Health. Annual Report (2007). Available from: http://www.mohp. gov.eg/Main.asp.
48) Khattab MA, Eslam M, Sharwae MA, Hamdy L.: Seroprevalence of hepatitis C and B among blood donors in Egypt: Minya Governorate, 2000-2008. Am J Infect Control, 2010; 38, 640-1.
49) Op den Winkel M, Nagel D, Sappl J, et al.: Prognosis of patients with hepatocellular carcinoma. Validation and ranking of established staging-systems in a large western HCC-cohort. PLoS One, 2012; 7, 45066.
50) Cabibbo G, Maida M, Genco C, et al. Natural history of untreatable hepatocellular carcinoma: A retrospective cohort study. World J Hepatol. 2012;4(9):256–261.
51) Regimbeau JM, Kianmanesh R, Farges O, Dondero F، Sauvanet A, Belghiti J. Extent of liver resection influences the outcome in patients with cirrhosis and small hepatocellular carcinoma. Surgery 2002;131:311–17.
52) Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y، Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198–206.
53) Karim M Eltawil, Mark Kidd1, Francesco Giovinazzo, Ahmed H Helmy and Ronald R Salem R: Differentiating the impact of anatomic and non-anatomic liver resection on early recurrence in patients with Hepatocellular Carcinoma; World Journal of Surgical Oncology 2010, 8:43
54) Robert J. Aragon, Naveenraj L. Solomon: Techniques of hepatic resection; Journal of Gastrointestinal Oncology, 2012;3 (1): 28-40. DOI: 10.3978/j.issn.2078-6891.2012.006.
55) Abdalla EK, Noun R, Belghiti J. Hepatic vascular occlusion: which technique? Surg Clin North Am 2004;84:563-85.
56) Capussotti L, Muratore A, Ferrero A, Massucco P, Ribero D، Polastri R. Randomized clinical trial of liver resection with and without hepatic pedicle clamping. Br J Surg 2006; 93: 685-9.
57) Lesurtel M, Selzner M, Petrowsky H, McCormack L, Clavien PA. How should transection of the liver be performed? Anprospective randomized study in 100 consecutive patients:nComparing four different transection strategies. Ann Surg 2005; 242: 814-23.
58) O'Rourke N, Fielding G. Laparoscopic right hepatectomy: Surgical technique. J Gastrointest Surg 2004; 8: 213-6.
59) kk