

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

By

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Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer Worldwide, 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.

Poustchi H, Middle East J Dig Dis. 2013

Epidemiology of Hepatocellular Carcinoma in Egypt



- 6th largest country in the Middle East and the Arab world.
- The 3rd largest African country.

Epidemiology of Hepatocellular Carcinoma in Egypt



Global Incidence of Hepatocellular carcinoma



- HCC is the 3rd cancer related mortality worldwide.
- Its the 5th common malignancy in males, the 9th among females.
- Main cause of mortality in cirrhotic patients.
- Its annual incidence is ~ 749,000, and annual mortality of ~ 692,000.

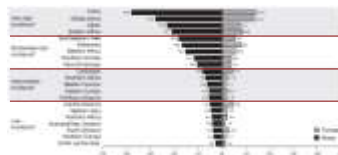
1. Pariz JF, et al. J Hepatol. 2006;45:529-38. 2. Jellu S, Ann Oncol. 2009; Suppl 4:441-5.
 3. Garcia M, et al. American Cancer Society. 2007. www.cancer.org. Accessed Jan 2010.
 4. Llovet J. J Hepatol. 2000;33:423-9. 5. Marrero DR, Marrero JA, Arch Med Res. 2007;38:612-20.

Global Incidence of Hepatocellular carcinoma

- It is estimated that 82% of liver cancer occurred in developing countries.
- China alone has 55% of total HCC worldwide.
- The highest rates are found in East-Asia and Sub-Saharan Africa where the rates of HBV ranges between 10-25%.

Incidence Rate	Annual Incidence	Areas
Low	1-3/100,000	South and Central America
Intermediate	3-10/100,000	Australia USA Europe
High	>10/100,000	South-East Asia Sub-Saharan Africa

Global Variation in Liver Cancer Incidence Rate

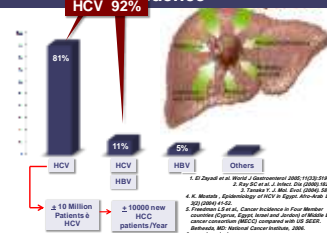


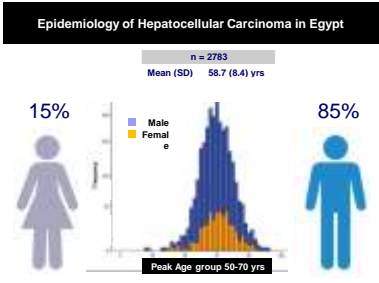
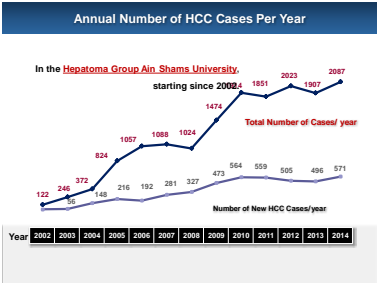
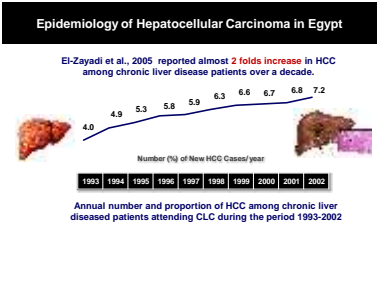
Data are estimates for the year 2002 from the GLOBOCAN database of the International Agency for Research on Cancer.

Classification of incidence was based on data in males.

- Very high rate: >20 per 100,000
- Moderate rate: 11-20 per 100,000
- Intermediate rate: 5-10 per 100,000
- Low rate: <5 per 100,000

HCC in Egypt - Risk Factors and Incidence



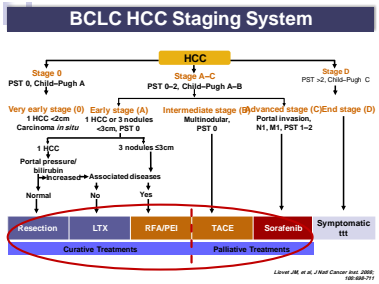


Risk factors for HCC are many and include viral hepatitis B (HBV) and C (HCV), cirrhosis, aflatoxins, alcohol, smoking, and male sex. These risk factors vary among countries, but chronic infection with HBV and HCV are the most important precursors for HCC development on a global scale, together accounting for over 80% of liver cancer cases worldwide.

Rabinovitz M., 2013

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. 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. In Egypt, HCV is the main risk factor for HCC where 71% of HCC cases are positive for anti-HCV antibodies.

Alazzawi W, et al; 2010



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. 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

(Llovet et al; 2012)

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. Surgery is safe, with an acceptable overall mortality and morbidity rates; and good long-term survival is achieved after adequate anatomical resections. 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

(Tong et al; 2010), (Makuuchi & Sano; 2012)

Therefore, because LT removes the tumor(s) and the pre-neoplastic underlying chronic liver disease, LT is the treatment of choice for HCC. 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. In the vast majority of cases, HCC develops in the setting of cirrhosis, but 5–15% of patients have no underlying chronic liver disease.

(Llovet et al; 2012)

Usually, the etiology of HCC development is undetermined, however, in patients with normal liver HCC are often presented large (>10 cm) and usually symptomatic. 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%. 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.

(Kianmanesh et al,2013)

The role of hepatic resection for treatment of multiple and bilobar HCCs is more controversial, 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

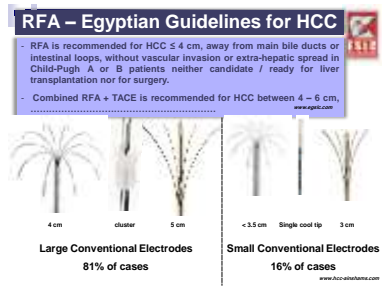
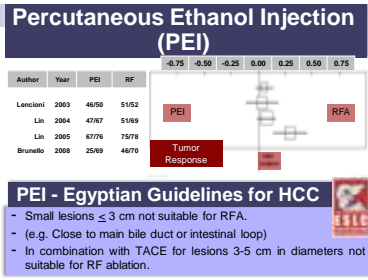
(Poon, and Fan; 2012)

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 local ablative therapy is considered.

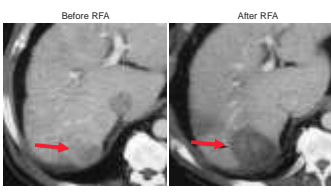
(BELGHITI, and KIANMANESH; 20012)

Non-surgical therapy should only be used where surgical therapy is not possible as: percutaneous ethanol injection (PEI) to produce necrosis of small HCC. 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. Systemic chemotherapy with standard agents has a poor response rate and should only be offered in the context of trials of novel agents

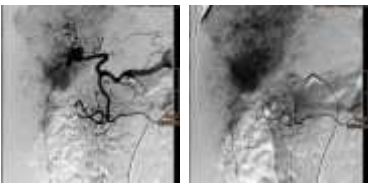
(Ryder, 2010)



**HCC THERAPY
RFA**



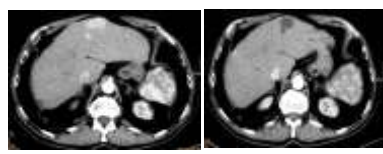
**HCC THERAPY
TACE**



**HCC THERAPY
TACE**



HCC THERAPY
TACE



Characteristic	Number (%)
Demographics	
Age (Mean) (range)	66.5 (27-77)
Sex	
Male	185 (88.1%)
Female	25 (11.9%)
Risk Factors	
Smoking (No. of pt. assessed)	720
Yes (yes history)	147 (20.5%)
Hepatitis (No. of pt. assessed)	98
Yes (yes patient)	67 (67.3%)
Screen Hepatitis C	80 (84.2%)
Screen Hepatitis B	31 (34.8%)
Screen Hepatitis B and C	37 (39.3%)
Diagnosed Cirrhosis (yes)	159 (84.2%)
EBH history (yes)	113 (61.6%)
Clinical presentation	
Asymptomatic	117 (56.8%)
Abdominal pain	58 (28.8%)
Jaundice	80 (41.8%)
Other (e.g. fatigue, weight loss)	22 (11.4%)
Child Pugh Class	
Class A	115 (57.2%)
Class B	53 (27.1%)
Class C	22 (11.3%)

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

Patients and methods:

This retrospective study was conducted at Assuit University hospitals, and Sohag University hospitals; Egypt. These are the largest referral tertiary level centers all over Upper Egypt territory. It included a random sample of 220 patients encountered with a single HPB team, studied, and treated with various treatment modalities by the same team 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

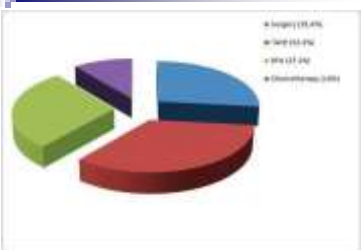
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Table (2): Baseline and pre-treatment characteristics of patient sample studied

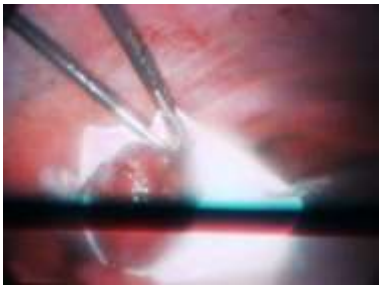
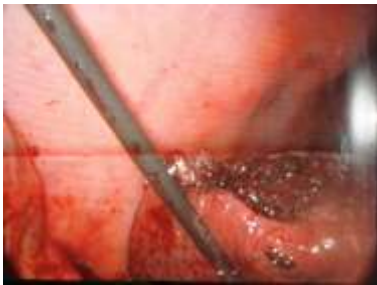
According to the Barcelona clinic liver cancer (BCLC) guidelines, different lines of treatment were offered to the patients, as curative treatment including surgical resection in 56 patients (25.4%), or local curative radiofrequency ablation therapy in 18 patients (8.1%), while palliative radiofrequency ablation therapy was done in 42 patients (19%). Palliative treatment using trans arterial chemoembolization (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.

Although nearly half of HCC patients (52.2%) had a compensated liver (Child Pugh score A), curative treatment (surgery or radiofrequency therapy) was provided for only 33.5% of cases (25.4% for surgery, and 8.1% for curative radiofrequency ablation), and 61.4% 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 and potentially curative treatment was applied for 24% only of patients. 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.

In our work; 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 was not added to treatment. The overall survival of treated cases was 80% at 6 months, 55% at 1 year and 20% at 2 years.







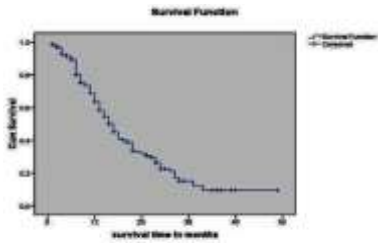
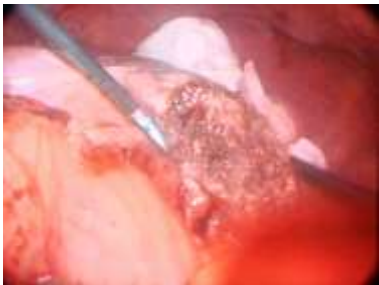
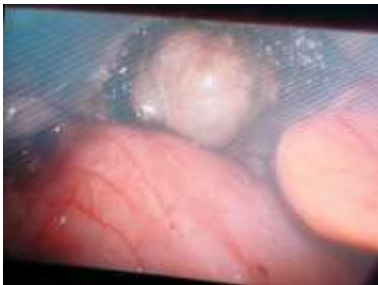
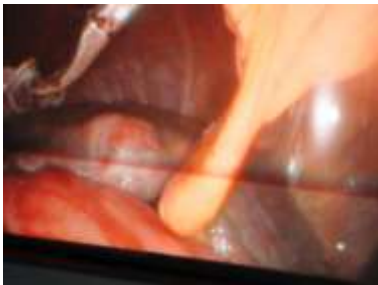


Fig. (2): Kaplan-Meier Survival Analysis of 220 Patients

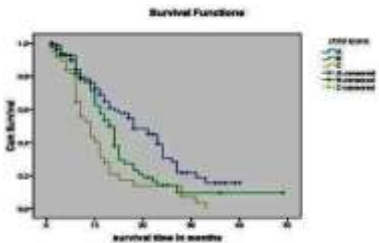


Fig. (3): Survival Analysis According to Child-Pugh Score

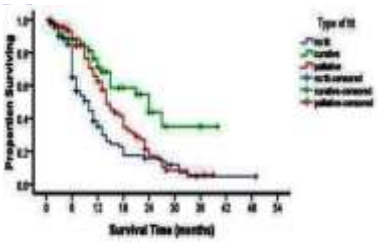


Fig. (4): Survival According to the Type of Treatment Used

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

	B	SE	Sig.	HR	95.0% CI for HR
					Lower Upper
Bilirubin	0.530	0.180	0.004	1.71	1.38 2.17
Size of lesion			0.016		
Size (Lr. vs. both)	-0.332	0.31	0.285	1.39	0.70 2.56
Size (Pr. vs. both)	-0.670	0.244	0.006	1.86	1.12 3.16
Treatment			0.002		
Symptomatic vs. curative	-0.863	0.262	0.001	2.07	1.42 3.06
Symptomatic vs. palliative	-0.448	0.186	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

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 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. 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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