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

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

Epidemiology of Hepatocellular Carcinoma in Egypt

Ranking of Most populous Countries

15 th Egypt

- The fifteenth-most populous nation in the world.
- Over 90 million inhabitants (2016 estimates).

Global Incidence of Hepatocellular carcinoma

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

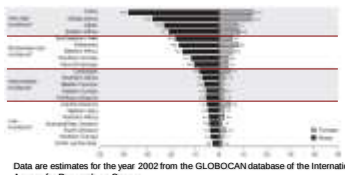
1. Perz JF, et al. J Hepatol. 2006;45:529-38. 2. Jelic S. Ann Oncol. 2009;Suppl 4:iv41-5.
3. Garcia M, et al. American Cancer Society. 2007. www.cancer.org. Accessed Jan 2010.
4. Llovet J, J Hepatol. 2000;33:423-9. 5. Marrero CR, Marrero JA. Arch Med Res. 2007;38:612-20.

Global Incidence of Hepatocellular carcinoma

- It is estimated that 82% of liver cancer occured in developing countries.
- China alone has 55% of total HCC worldwide.
- The highest rates are found in East-Asia and Subsaharan 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

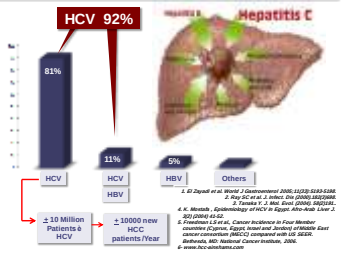
Global Variation in Liver Cancer Incidence



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.

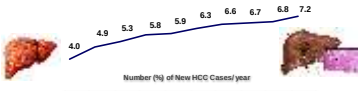
HCC in Egypt - Risk Factors and Incidence



1. El Zayadi et al. World J Gastroenterol 2005;11(33):5183-5189.
2. Ray SC et al. J. Infect. Dis (2009);182(2)698.
3. Tanaka Y. J. Med. Virol. (2006); 58(2)181.
4. K. Mostafa , Epidemiology of HCV in Egypt. Afro-Arab. Liver J. 3(2) (2006) 43-52.
5. Freedman LS et al, Cancer Incidence in Four Member countries (Cyprus, Egypt, Israel and Jordan) of Middle East cancer consortium (MECC) compared with US SEER. Bethesda, MD: National Cancer Institute, 2006.
6- www.hcc-aleshams.com

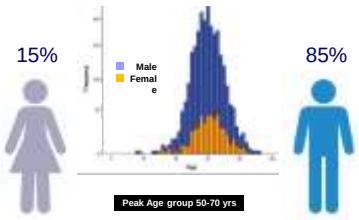
Epidemiology of Hepatocellular Carcinoma in Egypt

El-Zayadi et al., 2005 reported almost 2 folds increase in HCC among chronic liver disease patients over a decade.



Annual number and proportion of HCC among chronic liver diseased patients attending CLC during the period 1993-2002

Epidemiology of Hepatocellular Carcinoma in Egypt



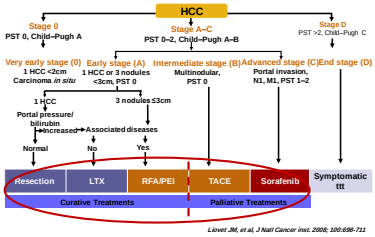
Risk factors for HCC are many and include viral hepatitis B (HBV) and C (HCV), cirrhosis, aflatoxins, alcohol, smoking, and male sex. These risk factors vary among countries, but chronic infection with HBV and HCV are the most important precursors for HCC development on a global scale, together accounting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

Alazawi W, et al; 2010

BCLC HCC Staging System



Llovet JM, et al, J Natl Cancer Inst. 2009; 101:698-711

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)

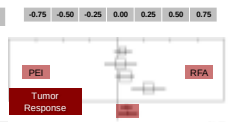
Therefore, when possible, **anatomical resection should be the treatment of choice** and considered as the reference surgical treatment when comparing it to other treatments .Moreover, when anatomical resection does not seem to be a possible, either because of the tumor location and/or the degree of 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. (Ryder, 2010)

Percutaneous Ethanol Injection (PEI)

Author	Year	PEI	RF
Lencioni	2003	46/50	51/52
Lin	2004	47/67	51/69
Lin	2005	67/76	75/78
Brunello	2008	25/69	46/70

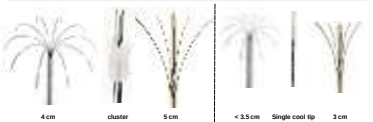


PEI - Egyptian Guidelines for HCC

- Small lesions ≤ 3 cm not suitable for RFA.
- (e.g. Close to main bile duct or intestinal loop)
- In combination with TACE for lesions 3-5 cm in diameters not suitable for RF ablation.

RFA – Egyptian Guidelines for HCC

- RFA is recommended for HCC ≤ 4 cm, away from main bile ducts or intestinal loops, without vascular invasion or extra-hepatic spread in Child-Pugh A or B patients neither candidate / ready for liver transplantation nor for surgery.
- Combined RFA + TACE is recommended for HCC between 4 – 6 cm,



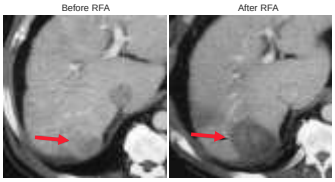
Large Conventional Electrodes

Small Conventional Electrodes

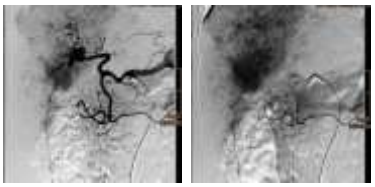
HCC THERAPY
RFA

Before RFA

After RFA



HCC THERAPY
TACE



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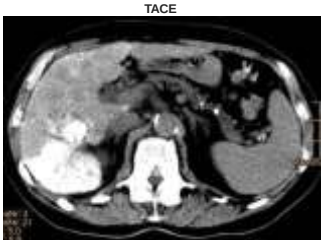

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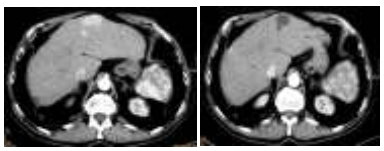


Patients and methods:

This retrospective study was conducted at Assuit University hospitals, and Sohag University hospitals; Egypt. These are the largest referral tertiary level centers allover 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

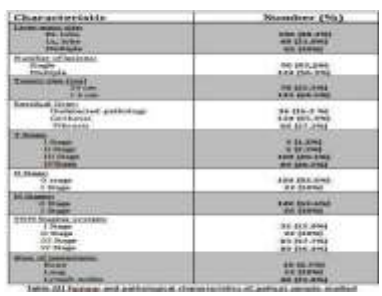
[ejs]:Decision on your article

Dear Prof. Radwan,

Yours sincerely,
The Editorial Team
The Egyptian Journal of Surgery

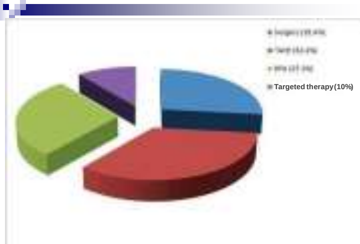
Characteristic	Number (%)
Demographics	
Age (Years) (mean ± SD)	[illegible]
Sex	
Male	185 (84.1%)
Female	35 (15.9%)
Risk Factors	
Smoking (No. of pt. assessed)	220
Yes	[illegible]
Hepatitis (No. of pt. assessed)	[illegible]
Yes	[illegible]
Known hepatitis C	[illegible]
Known hepatitis B	[illegible]
Known hepatitis B and C	[illegible]
Diagnosed Cirrhosis	[illegible]
Bilharziasis history	[illegible]
Clinical presentations	
Asymptomatic	[illegible]
Abdominal pain	[illegible]
Jaundice	[illegible]
Other e.g fatigue, ascites	[illegible]
Child Pugh Class	
Class A	115 (52.2%)
Class B	[illegible]
Class C	[illegible]

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



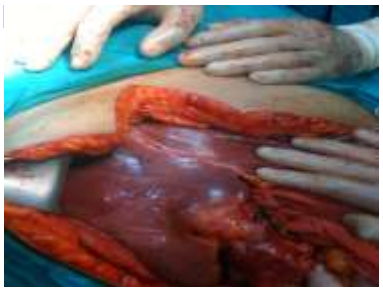
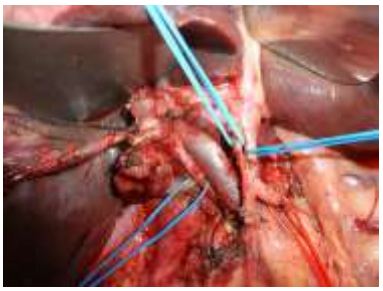
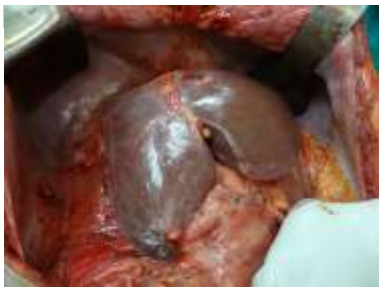
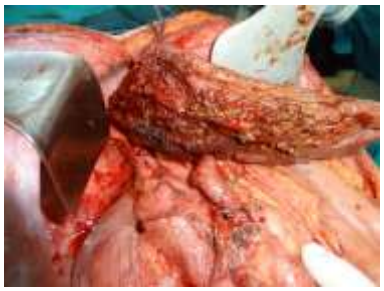
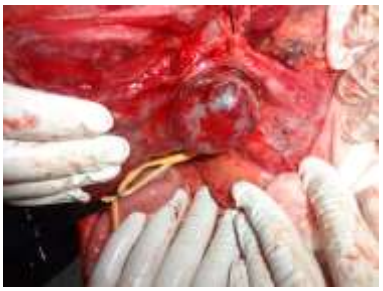
Characteristic	Number (%)
[illegible]	[illegible]

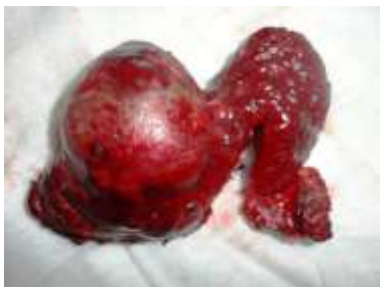
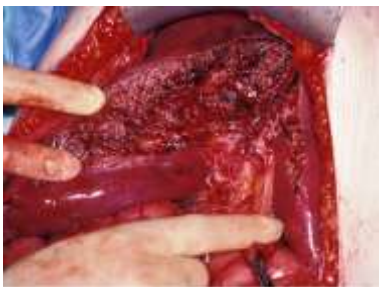
According to the Barcelona clinic liver cancer (BCLC) guidelines, different lines of treatment were offered to the patients, as curative treatment including surgical resection in 56 patients **(25.4%)**, or local PEI or radiofrequency ablation therapy in 60 patients **(27.1%)**, while palliative treatment 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%).



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 52.5% of cases (25.4% for surgery, and 27.1% for radiofrequency ablation),** 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.**

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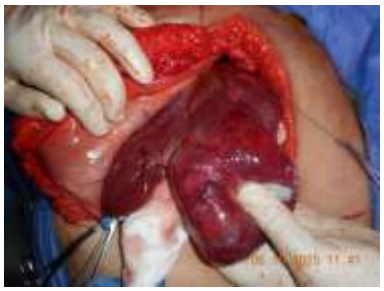

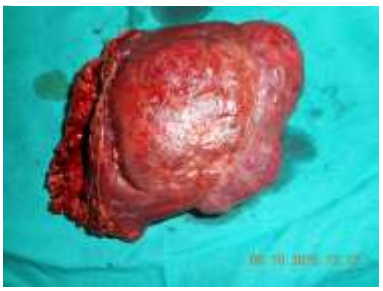

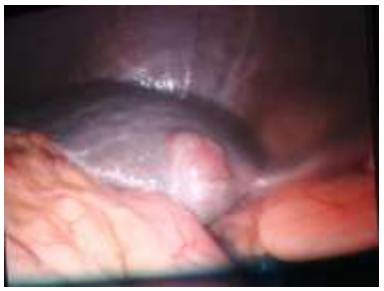

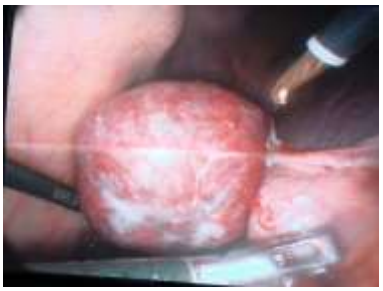

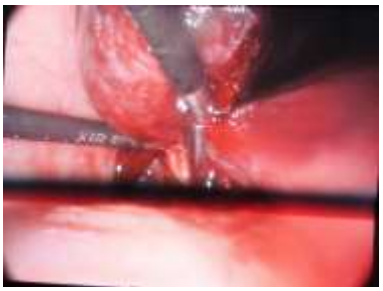

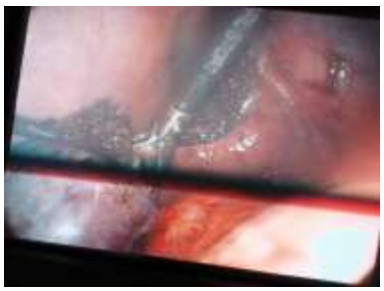

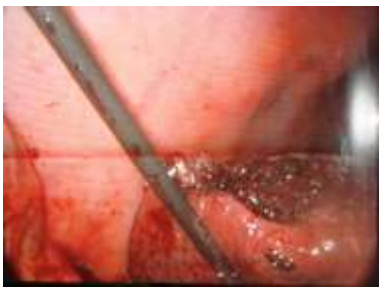

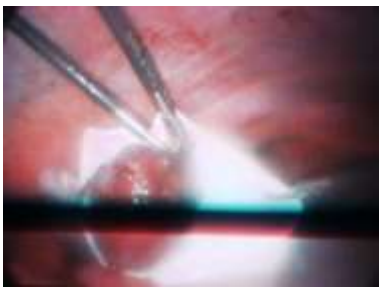

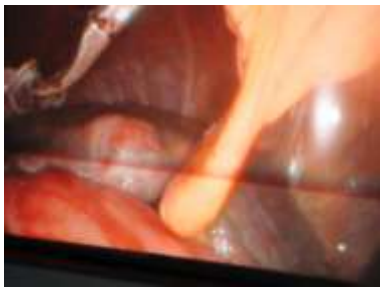

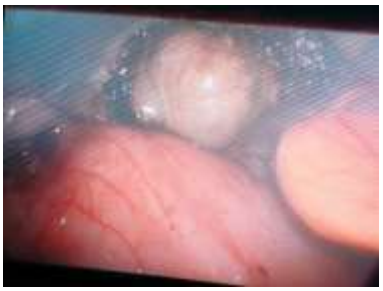

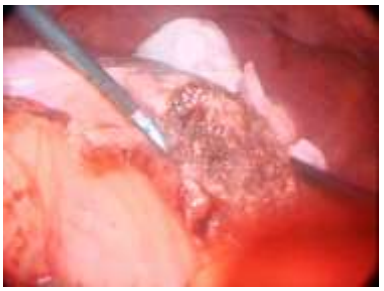

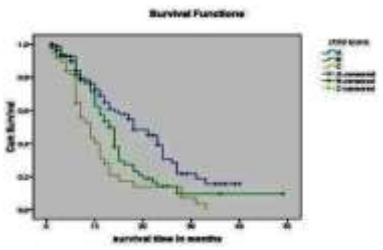

Fig. (3): Survival Analysis According to Child-Pugh Score

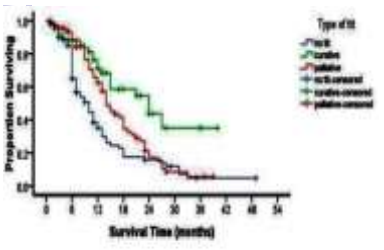

Fig. (4): Survival According to the Type of Treatment Used

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. 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 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% Lower	CI for HR 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)	-0.873	0.244	0.006	1.95	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. palliative	-0.446	0.186	0.023	1.56	1.09	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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