The significance of (*SERPINI1*, and *QP-C*) in the diagnosis of hepatocellula carcinoma in chronic HCV Egyptian patients.

Thesis

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and it is one of the major causes of death. HCC is now a rather common malignancy in Egypt which usually develops on top of liver cirrhosis secondary to viral infection.

AIM: To determine the expression profile of two candidate biomarkers (SERPINI1, and QP-C) in the liver biopsy in patients with primary HCC and to compare their expression in patients with HCV whether they are cirrhotic or not and in normal subjects

METHODS: This study was conducted on 21 patients with **HCC** using triphasic computerized tomography (CT) scan andhistopathologicalassessment (when needed) and **24**cirrhotic patients with noevidence of HCC; as well as **25 HCVnon**cirrhotic and **7**healthy subjects who served as control group.

We determined the level of(SERPINI1 and QP-C)for all cases together with full clinical assessment, liver biochemical profile, viral markers, conventionalultrasound (US), abdominal triphasic CT scan and guided liver biopsy forHCC cases with atypical CT pattern.

RESULTS: we found that SERPINI1 and QP-C is highly expressed in HCC group than cirrhotic group with sensitivity and specificity within 80% and 70% respectively for SERPINI1 and sensitivity and specificity within 65% and 79% respectively for QP-C

CONCLUSION:Tissue marker SERPINI1 and QP-C is highly expressed in HCC and so their use as independent tumor marker in the diagnosis of HCC is to beconsidered

Keywords:

- Hepatocellular carcinoma (HCC) – (SERPINI1)-(QP-C)-(HCV)

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LIST OF ABBREVIATION

AASLD	American Association for the Study of Liver Disease
Ab	Antibody
AFB1	Aflatoxin B1
AFP	Alpha fetoprotein
Ag	Antigen
AIH	Autoimmune hepatitis
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AR	Acyclic retinoid
AST	Aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
CEA	Carcinoembryonic antigen
CLD	Chronic liver disease
CLIP	Cancer of the Liver Italian Program
CT	Computerized tomography
CTA	Computerized tomography angiography
CTAP	Computerized tomography angioportography
CTHA	Computerized tomography hepatic angiography
DCP	Des-γ-carboxyprothrombine
FDA	Food & Drug Administration
FLC	Fibrolamellar carcinoma
GGT	Gamma glutamyltranspeptidase
HAP	Hepatic arterial phase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HFLs	Hepatic focal lesions
HGF	Hepatocyte growth factor
HGV	Hepatitis G virus
HIFU	High intensity focused ultrasound
IFN-α	Interferon-α
IGF-β	Insulin-like growth factor β
ILP	Interstitial laser photocoagulation
INR	International normalization ratio
IRS-1	Intracellular receptor substrate-1
LC	Liver cirrhosis

LTAE	Lipiodol trans arterial embolization
LTx	Liver transplantation
M	Mean
MRI	Magnetic resonance imaging
msAFP	Monosialyted alpha fetoprotein
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAI	Percutaneous acetic acid injection
PBC	Primary biliary cirrhosis
PC	Prothrombin concentration
PCR	Polymerase chain reaction
PDGF	Platelet derived growth factor
PEI	Percutaneous ethanol injection
PET	Positron emission tomography
PLTs	Platelets
PSI	Percutaneous hot saline injection
PT	Prothrombin time
PVP	Portal venous phase
RFA	Radiofrequency ablation
ROC	Receiver operating curve
SBP	Spontaneous bacterial peritonitis
SD	Standard deviation
TACE	Trans arterial chemoembolization
TAE	Trans arterial embolization
UCSF	University of California at San Francisco
US	Ultrasound

INTROUDUCTION

HCC is one of the most common and aggressive cancers worldwide. It has been the third cancer killer worldwide and the second cancer killer China since 1990s (**Yang et al., 2005).**

Globally, the 5-year survival rate of HCC is <5% and ~598,000 HCC patients die each year **(Parkin et al., 2005).**

The high mortality associated with this disease is mainly attributed to the inability to diagnose HCC patients at an early stage. In fact, most symptomatic HCC patients are diagnosed at an advanced stage, thus precluding their chance for surgical intervention **(Yuen et al., 2000).**

In contrast, HCC patients who were diagnosed at an early stage and received curative resection had a significantly improved survival time(**Poon et al ., 2oo2)**

Detection of, α-fetoprotein (AFP) in the serum of HCC patients in 1970s, has been the only serologic marker widely used for diagnosing HCC patients. This marker allows the identification of a small set of HCC patients with smaller tumors, and these patients have a relatively long-term survival rate following curative treatment(**Zhou et al ., 2000)**.)Thus, early detection and resection have been generally recognized as the most important factors to achieve long-term survival for HCC patients **(Poon et al ., 2oo2)**

Presently, the only approach to screen for the presence of HCC in high-risk populations is the combination of serum AFP and ultrasonography **(Nakakura and Choti., 2000).**

However, elevated serum AFP is only observed in about 60% to 70% of HCC patients and, to a lesser extent (33-65%), in patients with smaller HCCs **(Johnson., 2001**)

Moreover, nonspecific elevation of serum AFP has been found in 15% to 58% of patients with chronic hepatitis and 11% to 47% of patients with liver cirrhosis **(Kim et al., 2004).**

Therefore, it is necessary to identify new serologic HCC biomarkers that have a sufficient sensitivity and specificity for the diagnosis of HCC patients, especially in AFP-normal and/or smaller HCC cases. A significant increase in the expression of the candidate genes ((i.e**., SERPINI1, and QP-C,)** could be detected in most of the HCC samples, including those with normal serum AFP and small tumors.**(Jia., 2007)**

AIM OF THE WORK

To determine the expression profile of two candidate biomarkers (SERPINI1, and QP-C) in the liver biopsy in patients with HCC on top of liver cirrhocis and to compare their expression in patients with HCV whether they are cirrhotic or not as well as in normal subjects.

EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) represents approximately 85-90% of primary malignant tumors of the liver ***(El Serag and Rudolph, 2007).*** It is the fifth most common cancer worldwide and the third most common cancer in mortality ***(Parkin, 2001).***

- ***Global incidence of hepatocellular carcinoma*:**

Liver cancer burden is not distributed evenly throughout the world. Most HCC cases (more than 80%) occur in either sub-Saharan Africa or in Eastern Asia. China alone accounts for more than 50% of the world's cases**.** North and South America, Northern Europe, and Oceania are low-rate (less than 5.0/100,000) areas for liver cancer among most populations. ***(El Serag and Rudolph, 2007)***.

An exception to the predominance of HCC among primary liver cancer is the Khon-Kaen region of Thailand, which has one of the world's highest rates of liver cancer (annual age-standardized incidence rate during1993 to 1997 men, 88.0/100,000; women, 35.4/100,000) ***(Parkin, 2002)***. However, because of endemic infestation with liver flukes, the major type of liver cancer in this region is intrahepatic cholangiocarcinoma rather than HCC ***(Okuda et al., 2002).***

- ***Incidence of hepatocellular carcinoma in Egypt:***

HCC is now a rather common malignancy in Egypt, which usually develops on top of liver cirrhosis of viral origin. Both hepatitis C virus (HCV) & hepatitis B virus (HBV) infections increased the risk of HCC in

Egyptian patients. Because of the high prevalence rate of HCV in cirrhotic Egyptian patients, it accounts for most HCC cases in Egypt ***(Hassan et al., 2001).*** Over a decade (1993-2002), there was nearly a twofold increase of the proportion of HCC among chronic liver disease (CLD) patients in Egypt with a significant decline of HBV and slight increase of HCV as risk factors ***(El-Zayadi et al., 2005)***.

Sex distribution

In almost all populations, males have higher liver cancer rates than females, with male: female ratios usually averaging between 2:1 and 4:1. At present, the largest discrepancies in rates (more than 4:1) are found in medium-risk European populations ***(El Serag and Rudolph, 2007).***

The reasons for higher rates of liver cancer in males may be related to differences in exposure to risk factors. Men are more likely to be infected with HBV and HCV, consume alcohol, smoke cigarettes, and have increased iron stores. However, experiments show a 2- to 8-fold increase in HCC development in male mice; these data support the hypothesis that androgens influence HCC progression rather than sex-specific exposure to risk factors ***(Rudolph et al., 2000)***.

Age distribution

The global age distribution of HCC varies by region, incidence rate, sex, and, possibly, by etiology. In almost all areas, female rates peak in the age group 5 years older than the peak age group for males. In low-risk populations (e.g., United States, Canada, and United Kingdom), the highest age-specific rates occur among persons aged 75 and older. A similar pattern is seen among most high-risk Asian populations (e.g., Hong Kong