Serum squamous cell carcinoma antigen as a novel biomarker for hepatocellular carcinoma

Thesis
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LIST OF ABBREVIATIONS

AFB١	Aflatoxin B١
ALT	Alanine aminotranseferase
AFU	Alpha-I-fucosidase
AFP	Alpha fetoprotein
AASLD	American Association for the study of Liver Disease
AHPBA	American Hepato-Pancreato-Biliary Association
AJCC	American Joint Committee on Cancer
AST	Aspartate aminotranseferase
BCLC	Barcelona Clinic Liver Cancer
CEA	Carcinoembryonic Antigen
CLIP	Cancer of the Liver Italian Program
CUPI	Chinese University Prognostic Index
CLD	Chronic Liver Disease
CT	Compeuterized Tomography
CYP٥٠	Cytochrome P٥٠
DCP	Des- gamma Carboxy Prothrombin
ESR	Erythrocytic Sedmentation Rate
EASL	Euoropian Assosiation for the Study of Liver
GGT	Gamma Glutamyl Transferase.
GPC-٣	Gypican-٣
Hb	Hemogloben
HBcAb	Hepatitis B core Antibody
HBcAg	Hepatitis B core Antigen
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCC	Hepatocellular Carcinoma

hTERT	Human telomerase reverse transcriptase
IGF-II	Insulin-like growth factor-II
IFN	Interferon
IL-٨	Interleukin-٨
INR	International normalized ratio
LCA	lectin lens culinaris agglutin
MRI	Magnatic Resonance Imaging
MAGE١	Melanoma-Associated Antigen
MELD	Model for End Stage Liver Disease
NS٣	non-structural HCV protein
NF-κB	nuclear factor κB
PEI	Percutaneous Ethanol Injection
PCR	Polemerase Chain Reaction
PIVKA-II	protein induced by vitamin K absence or antagonist II
PT	Prothrombine Time
RFA	Radio Frequancy Ablation
RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
s GPC٣	soluble GPC٣
SCCA	Squamous Cell Carcinoma Antigen
TACE	Transcatheter arterial chemoembolization
TGFβ١	Transforming growth factor-beta١
TA-٤	Tumor Associated Antigen
TSGF	Tumor Specific Growth Factor
US	Ultrasound
VEGR	Vascular endothelial growth factor

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequent cancer in the world and a common occurrence in patients with liver cirrhosis, although great differences exist according to geographic distribution (Colombo, ١٩٩٩).

Patients with advanced liver disease, particularly cirhrosis, are those at risk for HCC and should be screened every six months for its development. The risk of developing for a patient with HCV-related cirrhosis is approximately ٢-٦٪ per year (Sangiovanni et al., ٢٠٠٤).

Patients with chronic hepatitis B virus infection are known to be at risk for HCC even without cirrhosis, so all patients with chronic HBV (those who are HBsAg +ve) should be considered for screening for HCC (Lok et al., ٢٠٠١).

In patients with HCV, only those with advanced liver disease (particularly liver cirrhosis) are at risk for HCC so screening should be applied only to these patients. Other risk factors for HCC include inherited metabolic diseases such as hemochromatosis. Additional risk factors for HCC development include older age, alcohol abuse, and exposure to aflatoxin, particularly in developing countries (Ryder, ٢٠٠٣).

In Mediteranean countries, HCC develops on diseased liver, which represents the most important risk factor. Therefore, the number of cases is likely to undergo a further increase in coming years because of the spread of the hepatitis C virus (HCV) (Bruix and Llovet, ٢٠٠٢).

Worldwide there is a strong association between chronic HCV infection and HCC. There is a four times higher incidence of liver cancer among HCV Antibody positive patients than among HBsAg carriers (Sherlock and Dolley, ٢٠٠٢).

The clinical manifestations of HCC often overlaps with that of cirrhosis, therefore it is commonly diagnosed at asymptomatic phase by routine ultrasound tomography or because of a sudden worsening of underlying cirrhosis. In regard to serologic screening, alpha fetoprotein (AFP) still represents the only available test for HCC, despite its low sensitivity and reliability (Oka et al., ١٩٩٤).

Alpha fetoprotein may be elevated in chronic liver disease, especially in viral hepatitis, in the absence of HCC. It has been estimated that approximately ٢٠٪ of patients with chronic hepatitis (of any cause) and ٤٠٪ of patients with cirrhosis may have alpha fetoprotein levels between ١٠ and ٤٠٠ ng/ml. The differential diagnosis of elevated alpha fetoprotein levels also includes gastric, biliary, pancreatic cancers and germ cell tumors (Colombo, ٢٠٠١).

The relatively poor specificity of conventional alpha fetoproteins levels has led to a search for more sensitive and specific markers. Other tumor markers include serum Des-gamma-carboxy prothrombin (DCP) that has been used for screening of HCC. The failure of hepatoma cells to express prothrombin carboxylase leads to a higher DCP serum levels. The sensitivity of DCP is better than that of alpha fetoprotein only in larger tumors and hence is of limited benefit in clinical practice (Okuda et al., ١٩٩٩).

It has been reported that squamous cell carcinoma antigen (SCCA), a member of the high molecular weight family of serine protease inhibitor, is strongly expressed in a number of different epithelial cancers such as those of the cervix, lung, head and neck, and so can be used as a clinical marker of these malignancies (Kato et al., ١٩٩٧).

Squamous cell carcinoma antigen has been reported to be strongly expressed in HCC tissue hampering its extensive use in clinical practice (Potisso et al., ٢٠٠٤).

Giannelli et al. (٢٠٠٥) found that serum SCCA levels are significantly higher in patients with HCC than cirrhotic patients which could represent a useful marker for large scale screening of serum in patients at risk.

AIM OF THE WORK

The aim of this work was to evaluate the clinical usefulness of serum SCCA as marker for early detection of HCC among high risk patients and to compare it with alpha fetoprotein as a known biomarker for diagnosis of HCC.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the ten most common cancers worldwide (Comar and Clark, ٢٠٠٥). It is increasingly associated with prevalence of hepatitis B and hepatitis C (Sherlock and Dooley, ٢٠٠٢). The great variations in levels of carcinogenic factors in the environment account for the different incidences of the tumor (Ikai et al., ٢٠٠٤).

Epidemiology:

HCC is the fifth most common cancer in the world and the most common type of liver cancer (El Serag et al., ١٩٩٩). It is also the ٥th among men and ٨th among women; it is the ٢nd among cancers of the digestive tract after stomach cancer (Sangiovanni et al., ٢٠٠٤).

The higher prevelance of HCC in males may be at least in part explained by differences in exposure to risk factors. However, sex hormones and other x-linked genetic factors may also be important (Yu MC et al., ١٩٩١).

The estimated annual number of cases exceeds ٥٠٠,٠٠٠ (Bruix et al., ٢٠٠١), with a mean annual incidence of around ٣-٤٪ (Llovet and Beaugrand, ٢٠٠٣).

The incidence of HCC varies considerably with the geographic area because of differences in the major causative factors. The geographic areas at the highest

risk are located in Eastern Asia, with age-adjusted incidence rate (AAIR) ranging from ٢٧٫٦ to ٣٦٫٦ per ١٠٠،٠٠٠ in men; Middle Africa (AAIR ٢٠٫٨ – ٣١٫١/١٠٠،٠٠٠) and in some Western African countries (٣٠ – ٤٨/١٠٠،٠٠٠).The Geographic areas with the lowest risks are Northern Europe, Australia, New Zealand and Caucasian populations of North and Latin America (Bosch et al., ١٩٩٩).

The incidence of HCC in the United States is approximately ٢٫٤ per ١٠٠،٠٠٠ persons per year and rising (El Serag et al., ١٩٩٩).

In Egypt, about ٧٫٢٪ of chronic liver disease patients develop HCC. The development of HCC is mainly due to the high rate of hepatitis B and C infections among Egyptian patients (El Zayadi et al., ٢٠٠٥). According to the data from National Institute of Cancer, (٢٠٠٧), Gharbiah is Egypt first population based cancer registry. Liver cancer is the second most frequency for males after bladder cancer. It constitutes ١٣٪ of all cases. For females, it is the forth after cancer breast, NHL and leukemia. It constitutes ٤٫١٪of all cases.

The number of deaths per year from HCC exceeds ٢٥٠،٠٠٠, placing it as the sixth cause of death from cancer world-wide (Steel et al., ٢٠٠٤).

Time trends in the incidence of HCC:

An important epidemiological factor is the rising incidence of HCC in developed countries during the last two decades due to the increasing rate of hepatitis C